

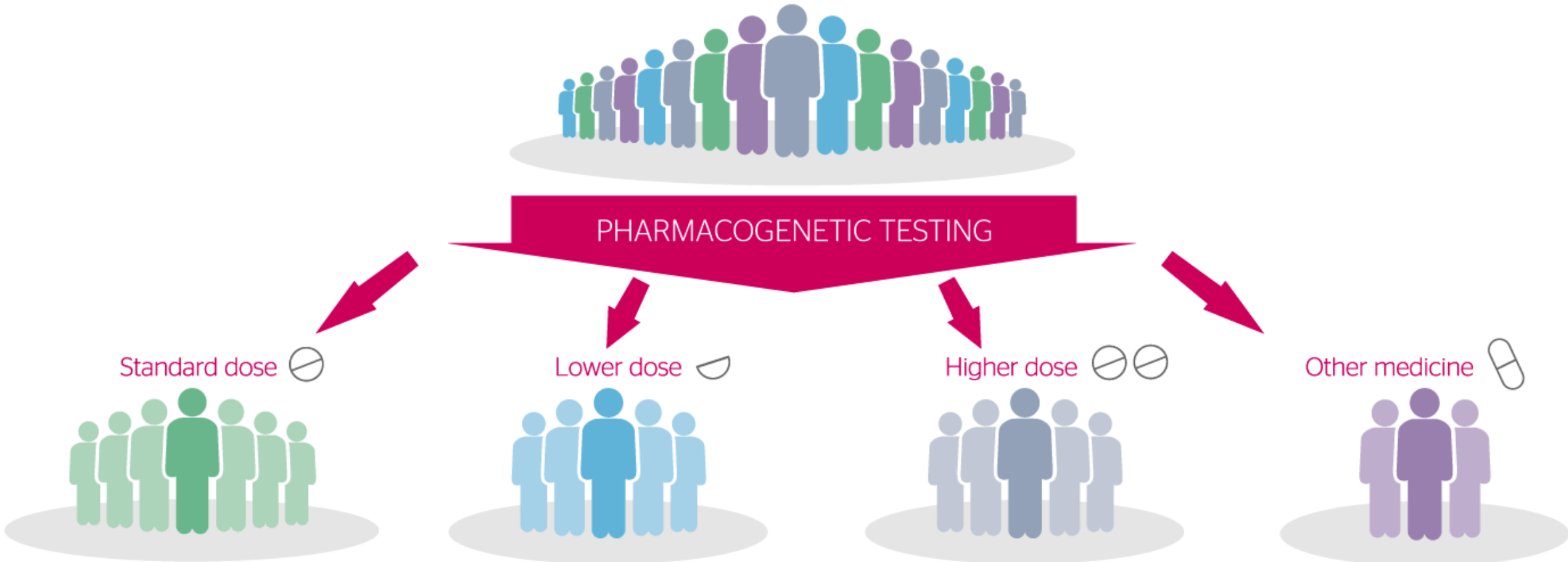
Using pharmacogenetic testing in psychiatry

Jari Forsström, Chief Medical Officer, Abomics Oy

The same dose does not work for all

ABOMICS

USING PHARMACOGENETICS FOR PERSONALISING MEDICATION



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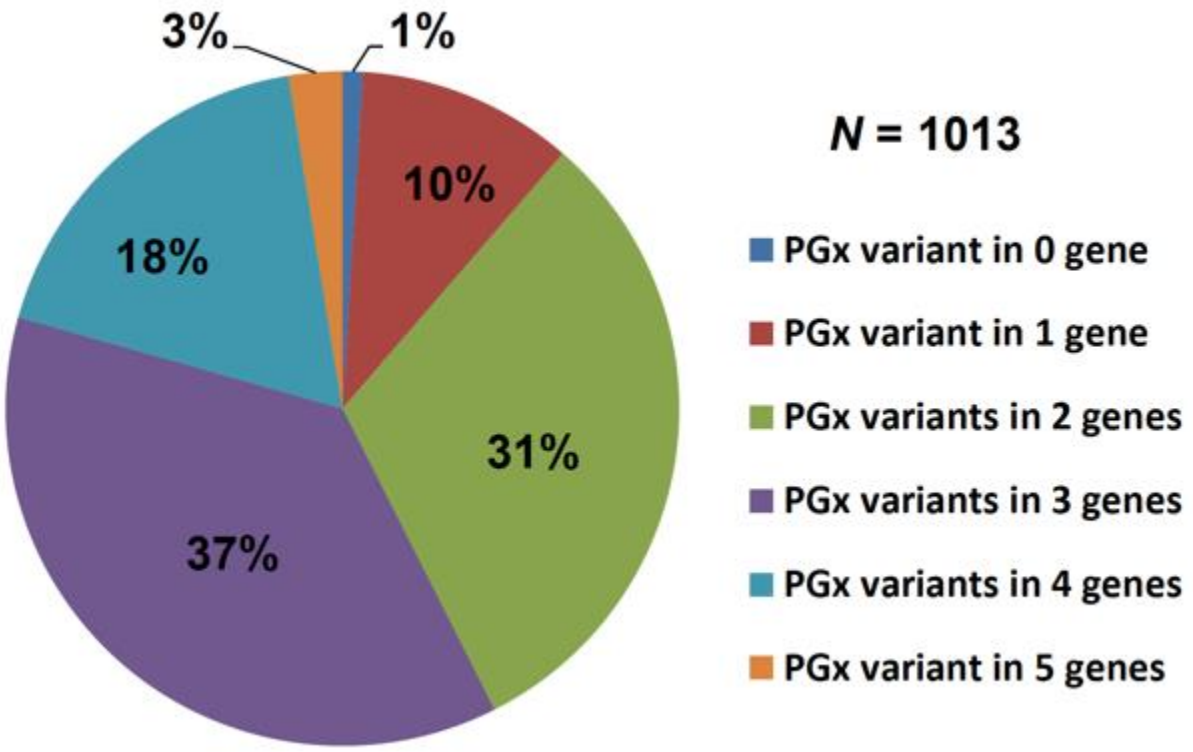
How many patients have a differing drug response because of pharmacogenetics?

99% of patients tested in a study by the Mayo Clinic in the USA have at least one pharmacogenetic variant that impacts medication decisions.[Ji]



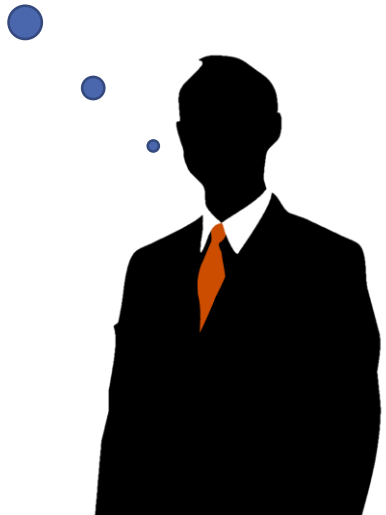
[Ji] Ji, Y., Skierka, J. M., Blommel, J. H., Moore, B. E., VanCuyk, D. L., Bruflat, J. K., ... & Black III, J. L. (2016). Preemptive pharmacogenomic testing for precision medicine: a comprehensive analysis of five actionable pharmacogenomic genes using next-generation DNA sequencing and a customized CYP2D6 genotyping cascade. The Journal of Molecular Diagnostics, 18(3), 438-445., 95(4), 423-431. http://dx.doi.org/10.1016/j.jmoldx.2016.01.003

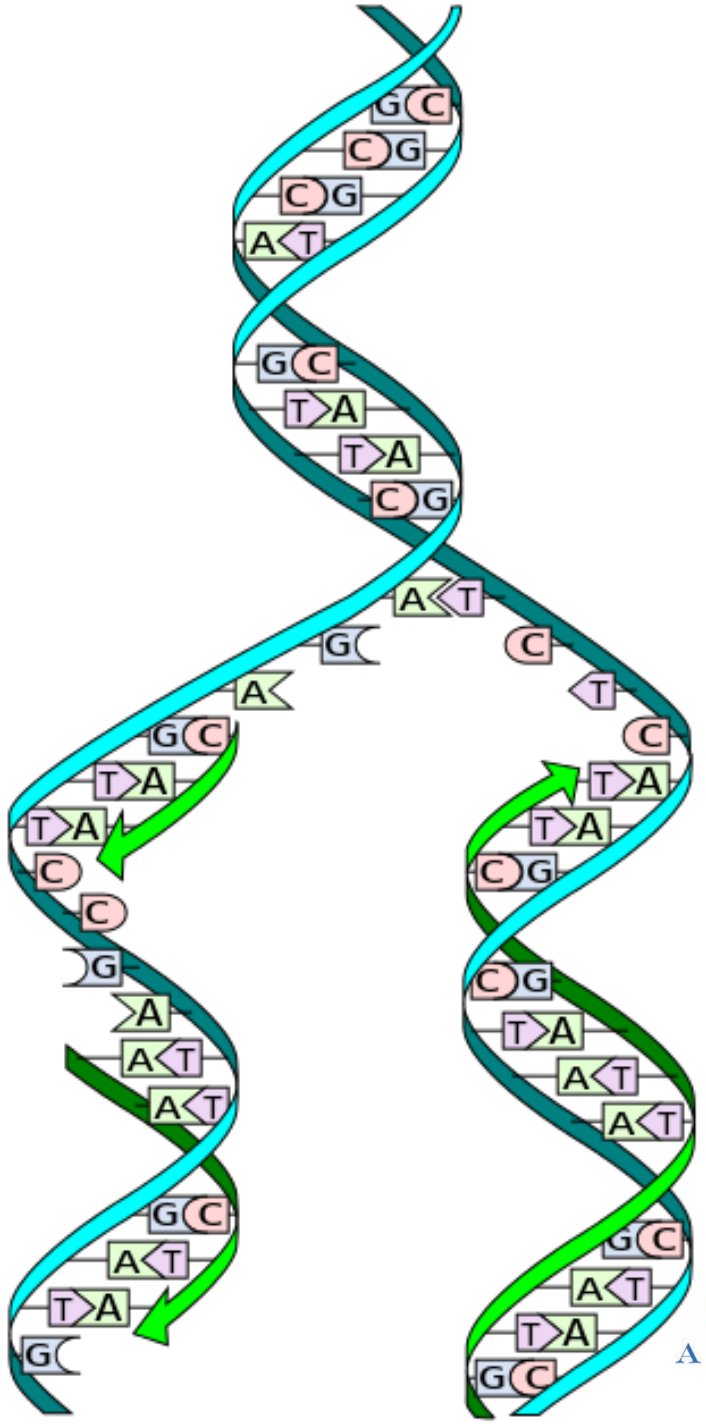
ABOMICS

Pharmacogenetics

Pharmacgenetics is a field of pharmacology, which studies the effects of hereditary factors in the metabolism and effects of drugs in patients.

"I don't have any allergies, but I am a poor CYP2D6 metabolizer"





ABOMICS

Classifying the metabolism in groups

- Based on PGx testing, metabolism is classified in 2-5 groups depending on the gene
    - Ultrarapid metabolizer
    - Normal metabolizer (ent. Extensive metabolizer)
    - Intermediate metabolizer
    - Poor metabolizer
- Clinical Pharmacogenetics Implementation Consortium (CPIC)
    - Publishes practice guidelines in pharmacogenetics
    - Standardized terminology is important, since same terms are used in dosing instructions in drug information.

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In many new drug the genotype information is needed to be able to use the drug properly

E.g. RXULTI ™ (brexpiprazole)

Factors	**Adjusted dose**
CYP2D6 poor metabolisers	
Known CYP2D6 poor metabolisers	Administer half of the recommended dose
Known CYP2D6 poor metabolisers taking strong/moderate CYP3A4 inhibitors	Administer a quarter of the recommended dose
Patients taking CYP2D6 inhibitors and/or CYP3A4 inhibitors	
Strong CYP2D6 inhibitors	Administer half of the recommended dose
Strong CYP3A4 inhibitors	Administer half of the recommended dose
Strong/moderate CYP2D6 inhibitors with strong/moderate CYP3A4 inhibitors	Administer a quarter of the recommended dose

ABOMICS

Pharmacogenetic test panel

Important in psychiatry:

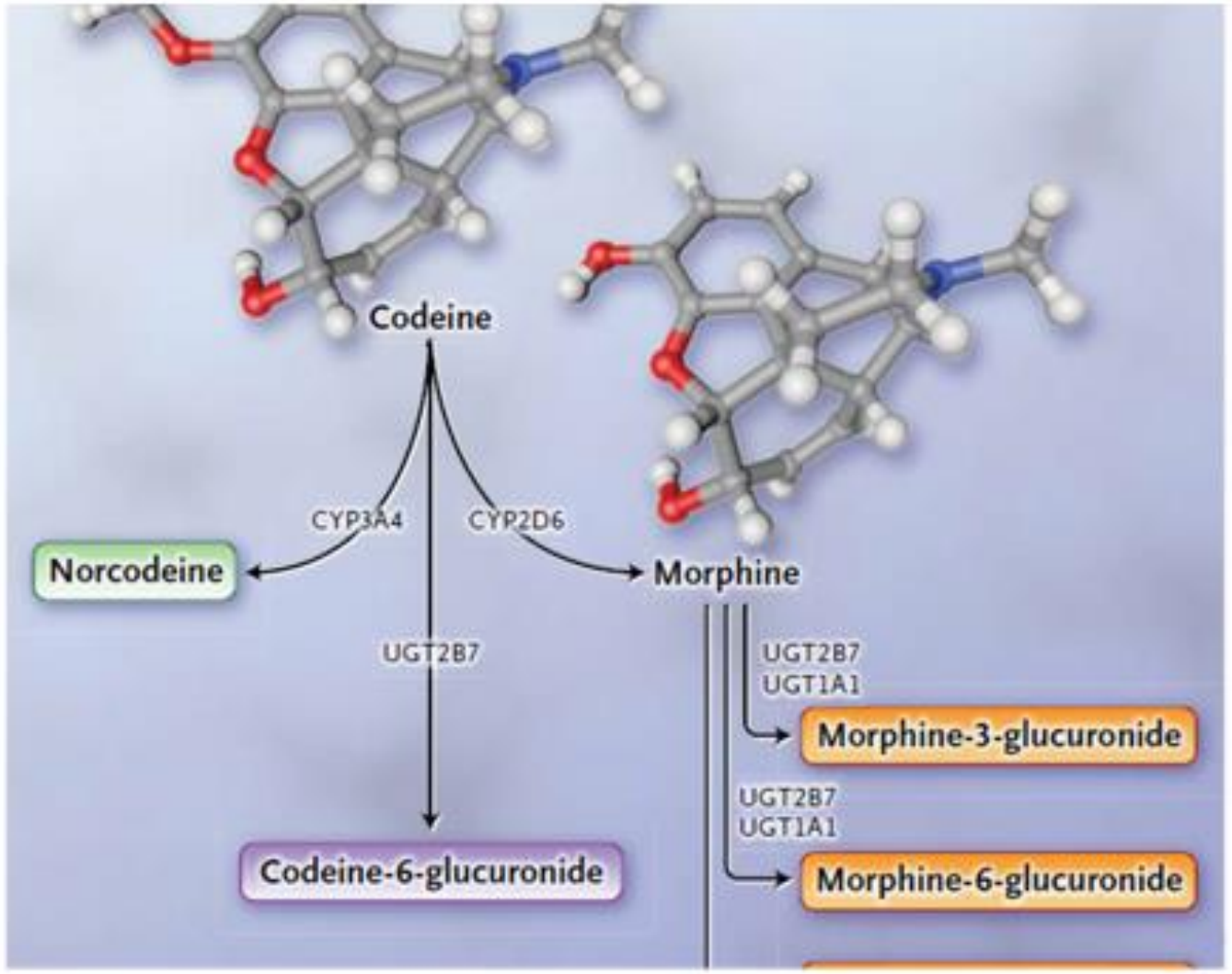
- **CYP2D6**
- **CYP2C19**
- **CYP1A2**
- **CYP2B6**
- CYP2C9
- CYP3A4
- CYP3A5

Others:

- CYP4F2
- SLCO1B1
- VKORC1
- F2 protrombiini
- F5 Leiden
- ABCB1
- DPYD
- G6PD
- TPMT
- UGT1A1
- ALDH2
- BCHE
- IFNL3

ABOMICS

Codeine and CYP2D6



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Codeine warnings

Codeine is also contraindicated in the following:

- In all paediatric patients (0-18 years of age) who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome due to an increased risk of developing serious and life-threatening adverse reactions (see section 4.4)
- In women during breastfeeding (see section 4.6)
- In patients for whom it is known they are CYP2D6 ultra-rapid metabolisers

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Clinical significance

A	Pharmacogenetic factors do not have significant effect on drug effectiveness or adverse reactions.
B	Drug effectiveness or adverse reactions may have pharmacogenetic variation, but the clinical significance is low for most patients. Monitor drug response and possible adverse reactions. If genetic test result is available, consider changing drug or dosing based on result.
C	Drug effectiveness or adverse reactions are having pharmacogenetic variation with intermediate relevance. If genetic test result is available, consider changing drug or dosing based on result. If genetic test has not been conducted, consider ordering test.
D	Drug effectiveness or adverse reactions are having pharmacogenetic variation with significant relevance. Order genetic test, or check existing test result before prescribing drug. Check dosing and administration based on test result.

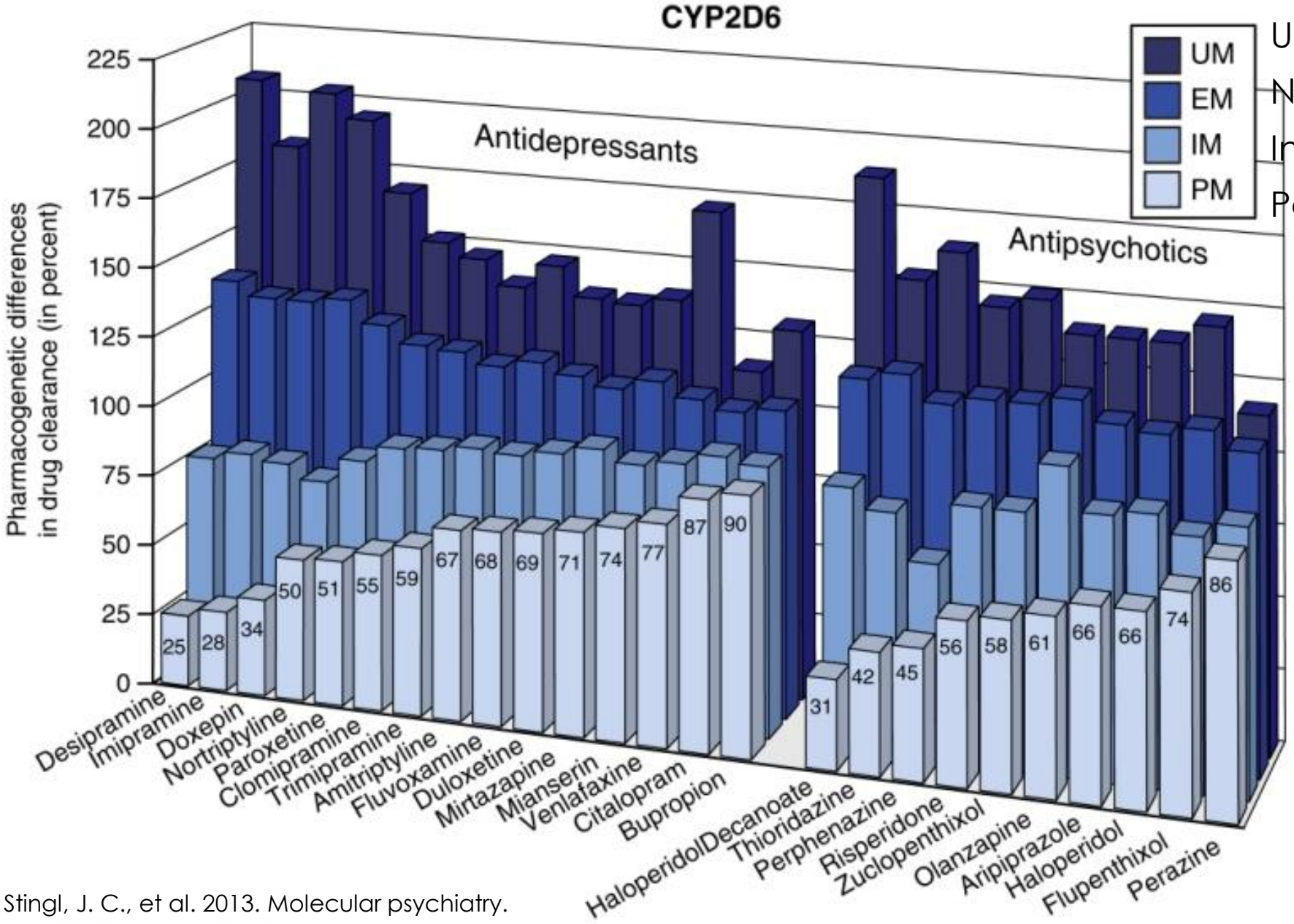
ABOMICS

CYP2D6 drugs DDD/1000 inhabitant/day

• D metoprolol	11,01	• C oxycodone	1,63
• C venlafaxine	10,07	• D tamoxifen	1,06
• D codeine	7,21	• D metoclopramide	1,01
• D amitriptyline	2,96	• D nortriptyline	0,53
• C tramadol	2,76	• D doxepin	0,49
• D paroxetine	2,33	• C haloperidol	0,44
• D aripiprazole	2,17	• C ondansetron	0,14
• D risperidone	1,87	• D atomoxetine	0,13
• D vortioxetine	1,68		

Source: Kela prescription statistics in Finland 2017

ABOMICS



Ultrarapid metabolism

Normal metabolism

Intermediate metabolism

Poor metabolism

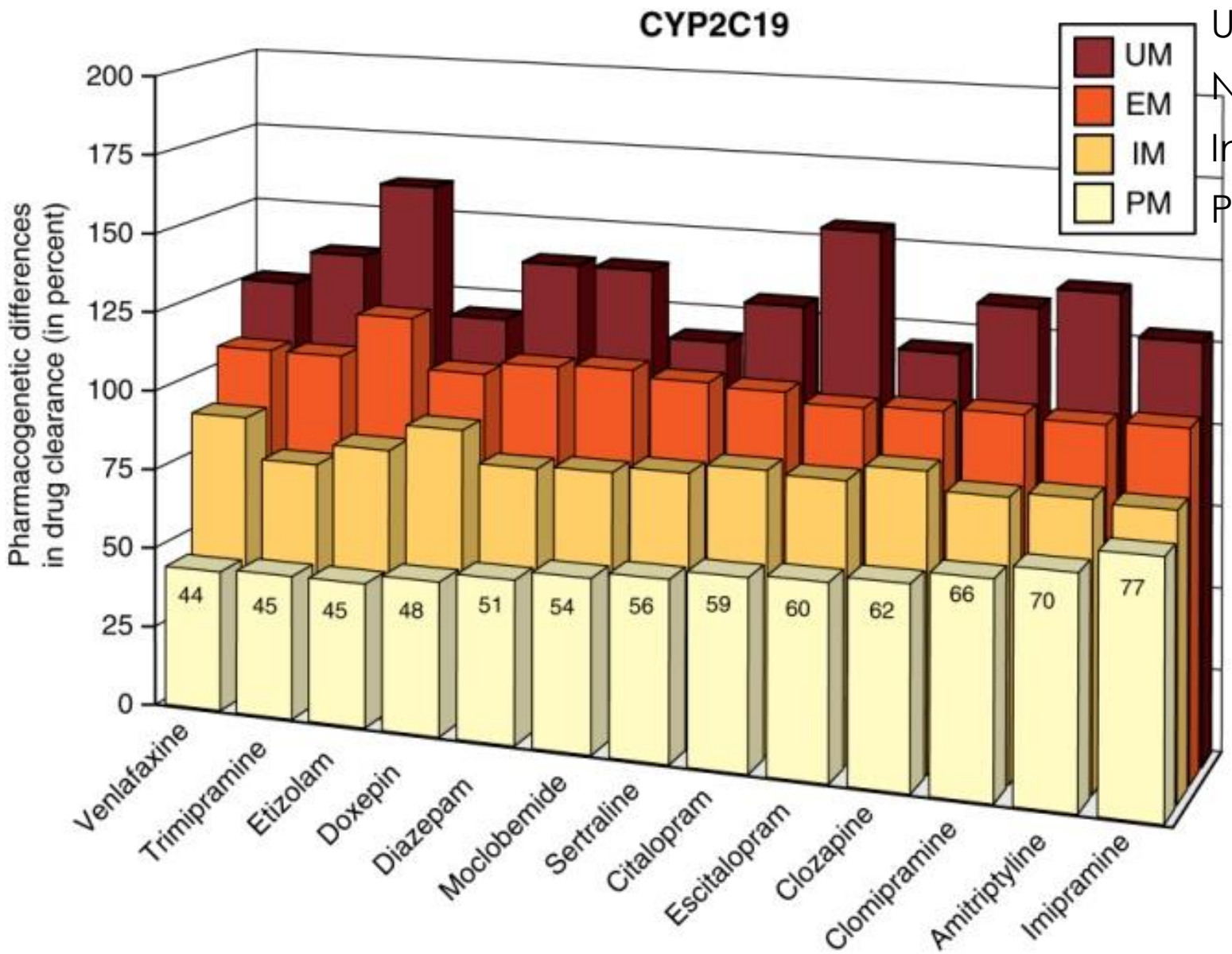
Stingl, J. C., et al. 2013. Molecular psychiatry.

ABOMICS

CYP2C19 drugs DDD/1000 inhabitant/day

• B pantoprazol	32,19
• C escitalopram	15,31
• B esomeprazol	13,82
• B omeprazol	9,94
• C citalopram	9,93
• B sertraline	7,78
• D clopidogrel	7,79
• B lansoprazol	6,64
• B diazepam	5,10
• C amitriptyline	2,96
• D doxepin	0,49
• B lacosamide	0,36
• B moclobemide	0,35
• D clobazam	0,34
• B phenytoin	0,20
• B clomipramine	0,20
• B trimipramine	0,10
• C voriconazole	0,01

ABOMICS



Ultrarapid metabolism

Normal metabolism

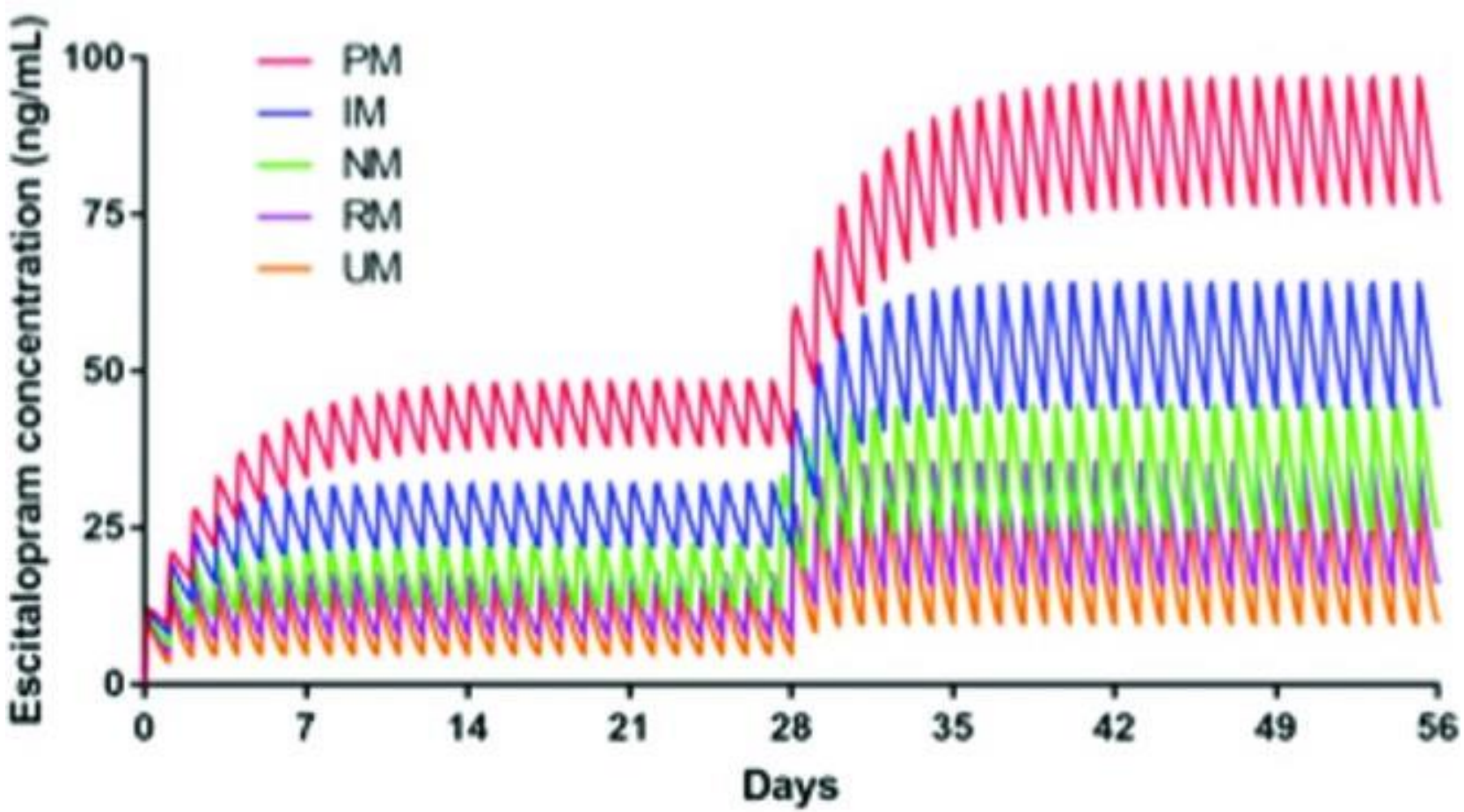
Intermediate metabolism

Poor metabolism

Stingl, J. C., et al. 2013. Molecular psychiatry.

ABOMICS

Practical example: Escitalopram without using pharmacogenetics

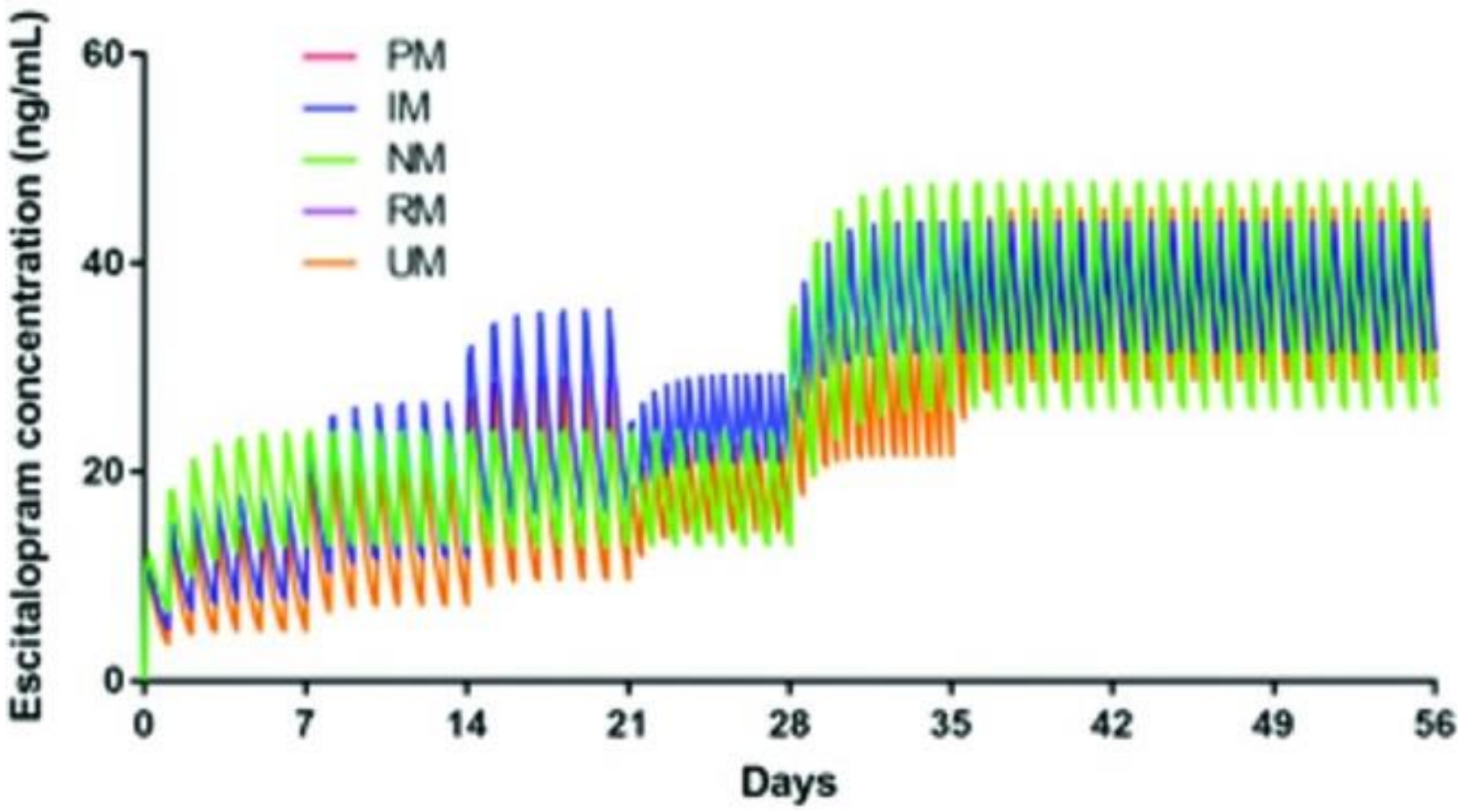


Treatment initiated at 10mg daily and increased to 20mg daily at week 4.

Figure: Strawn, Jeffrey R., Ethan A. Poweleit, and Laura B. Ramsey. "CYP2C19-guided escitalopram and sertraline dosing in pediatric patients: a pharmacokinetic modeling study." *Journal of child and adolescent psychopharmacology* 29.5 (2019): 340-347. https://doi.org/10.1089/cap.2018.0160

ABOMICS

Practical example: Escitalopram dosage adjusted based on pharmacogenetics



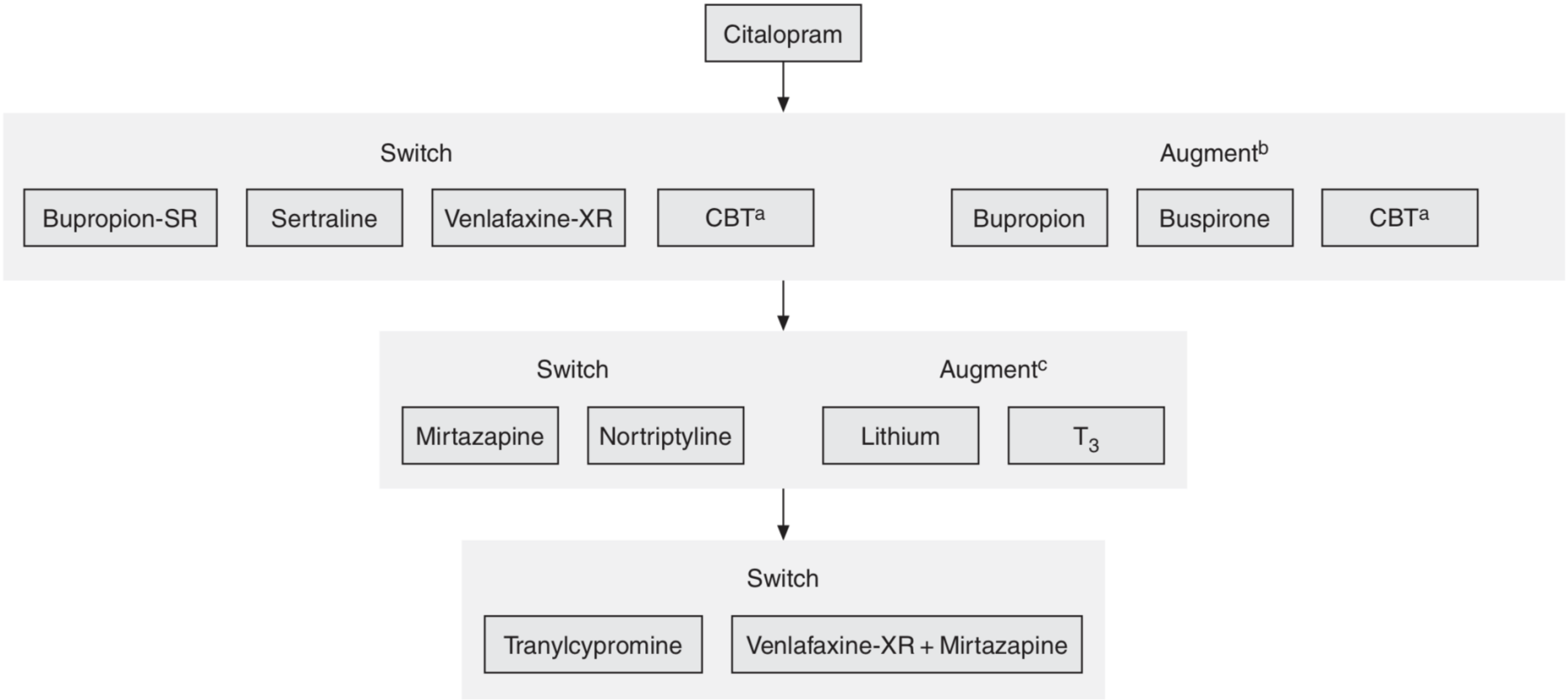
CYP2C19-guided dosing model.

Figure: Strawn, Jeffrey R., Ethan A. Poweleit, and Laura B. Ramsey. "CYP2C19-guided escitalopram and sertraline dosing in pediatric patients: a pharmacokinetic modeling study." *Journal of child and adolescent psychopharmacology* 29.5 (2019): 340-347. https://doi.org/10.1089/cap.2018.0160

ABOMICS

MDD:n hoito – Star*D study

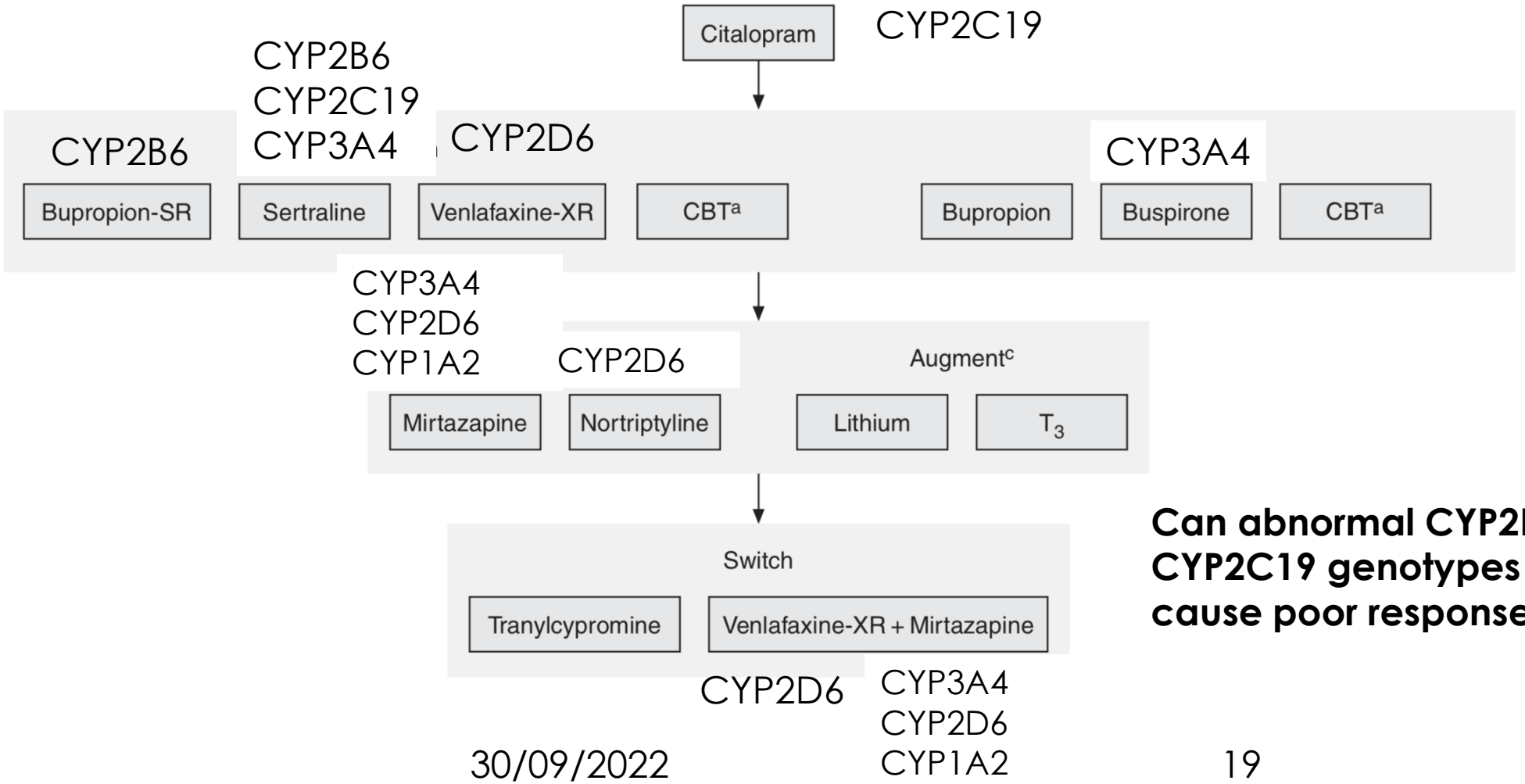
Figure 1. Sequential Therapies Evaluated in the STAR*D Trial



Huynh et al. J. Clinical Psychiatry 2008

STAR*D-tulosten pohdintaa

Figure 1. Sequential Therapies Evaluated in the STAR*D Trial



Can abnormal CYP2D6 + CYP2C19 genotypes cause poor response?

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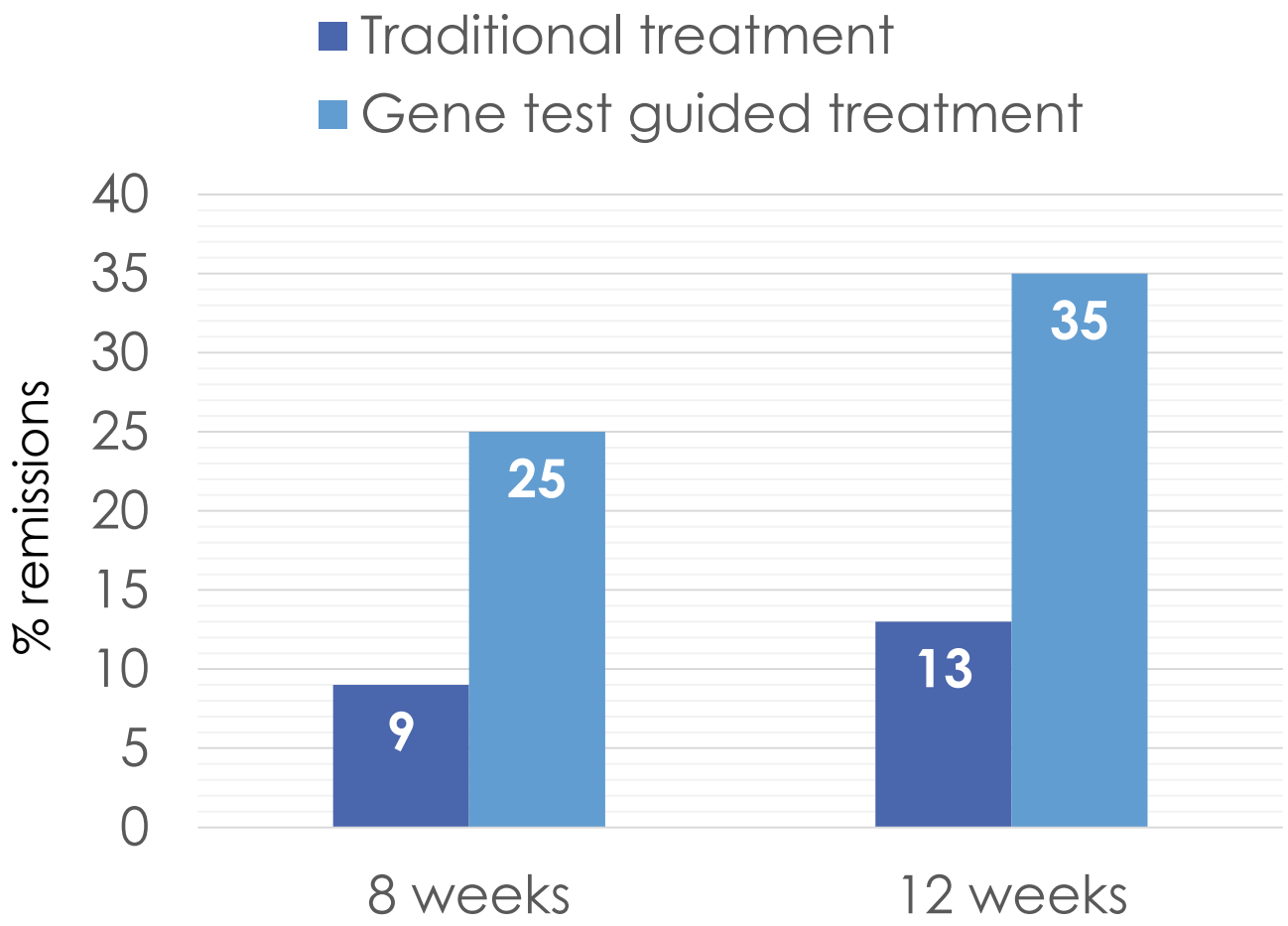
Treatment of depression



Bradley et al. J Psychiatr Res. 2018

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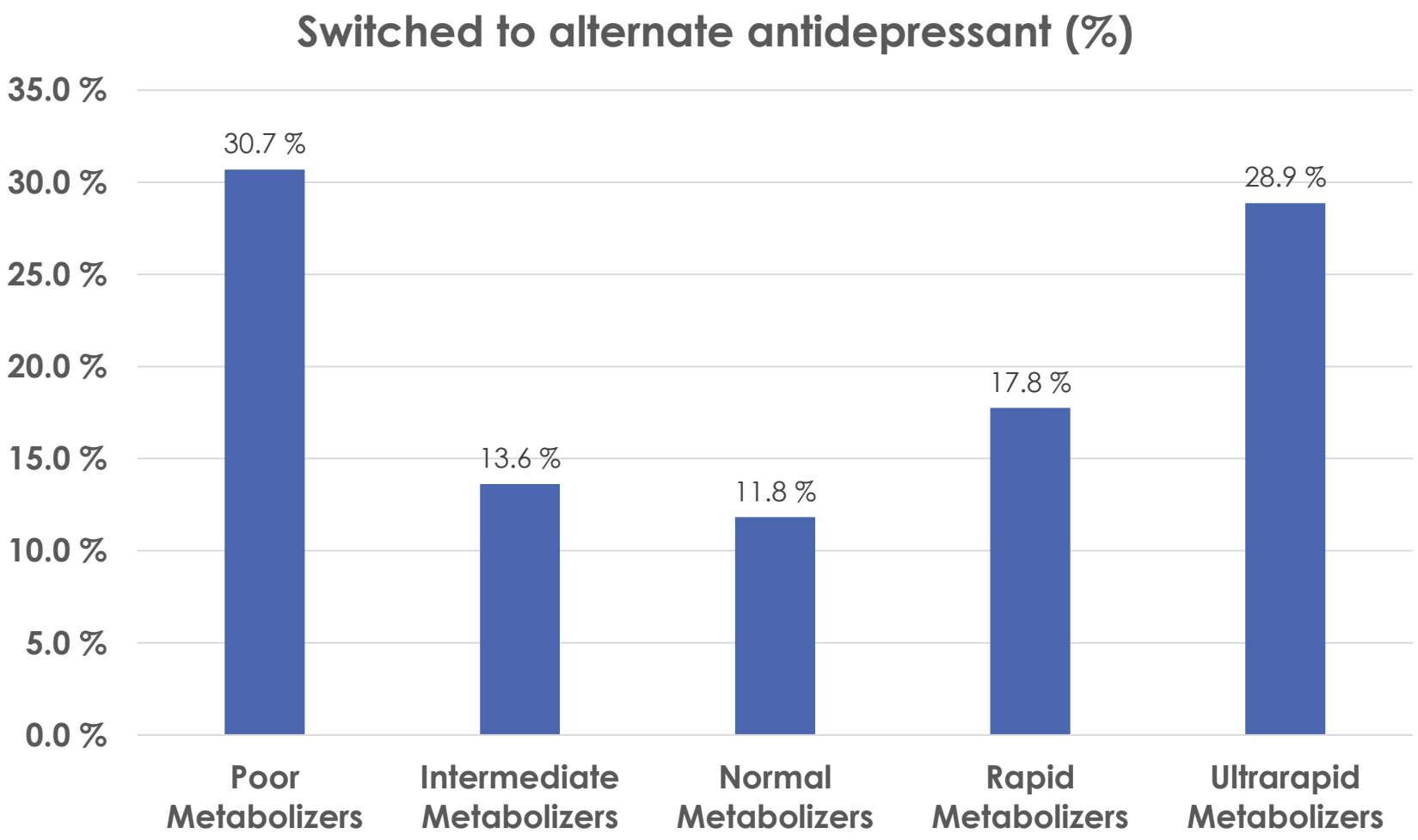
Impact of CYP2C19 Metabolism on Therapeutic Failure



CYP2C19 metabolism has a substantial impact on the risk of therapeutic failure of escitalopram, as measured by switching of antidepressant.

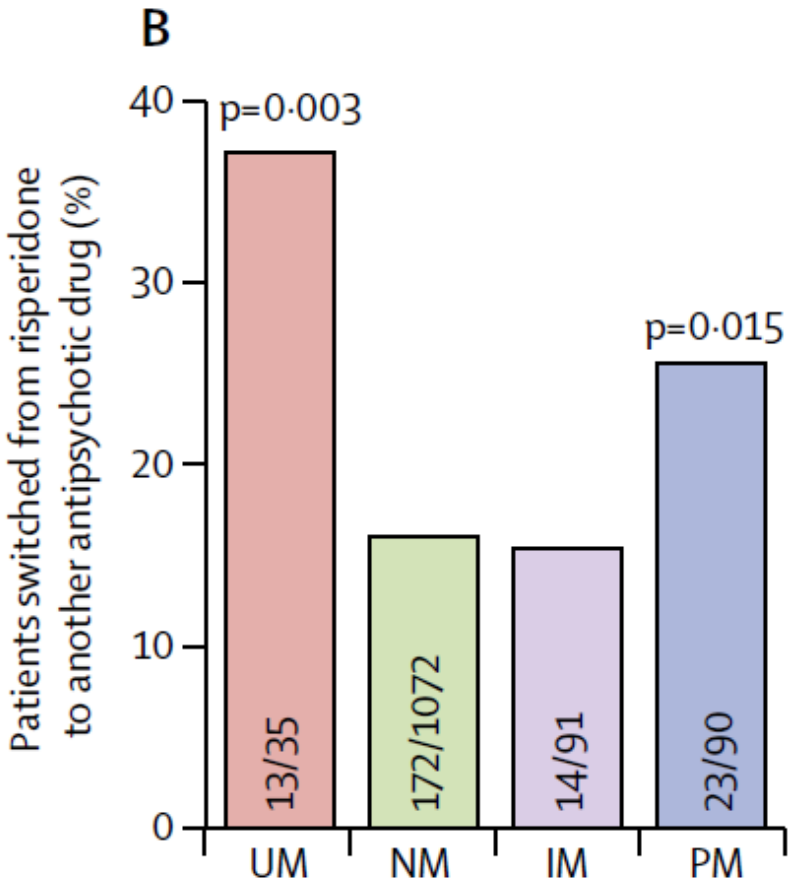
Jukić, M. M., Haslemo, T., Molden, E., & Ingelman-Sundberg, M. (2018). Impact of CYP2C19 genotype on escitalopram exposure and therapeutic failure: a retrospective study based on 2,087 patients. American Journal of Psychiatry, 175(5), 463-470.

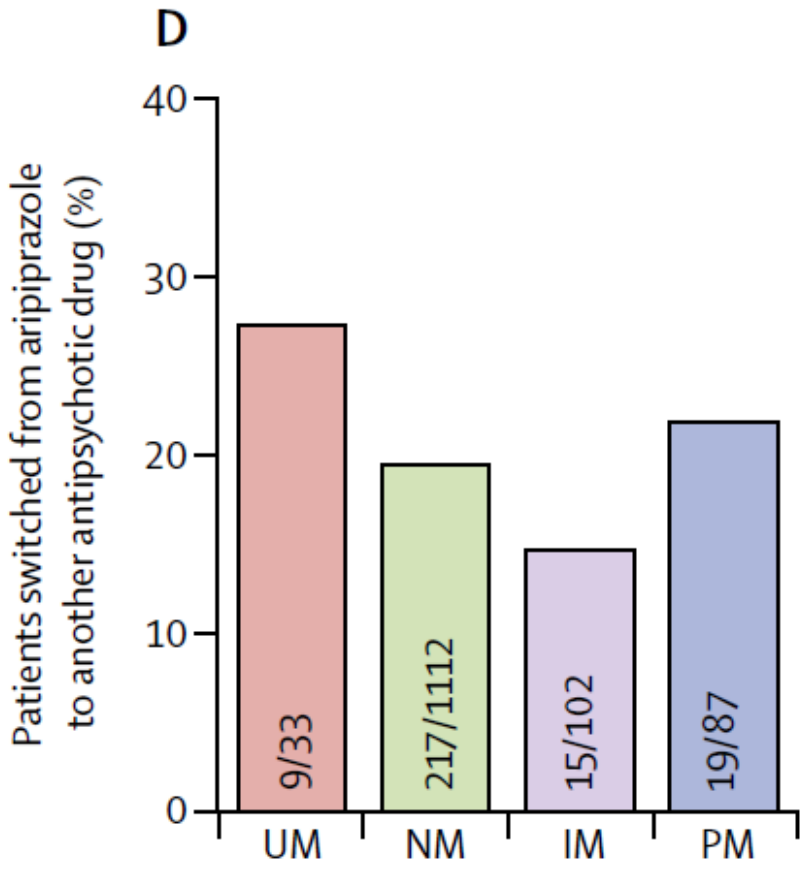
https://doi.org/10.1176/appi.ajp.2017.17050550

(Data from TABLE 2. “Impact of CYP2C19 Genotype on Escitalopram Exposure and Therapeutic Failure” adapted based on current CPIC diplotype/phenotype tables)

ABOMICS

Psyhosis treatment(aripiprazole ja risperidone)



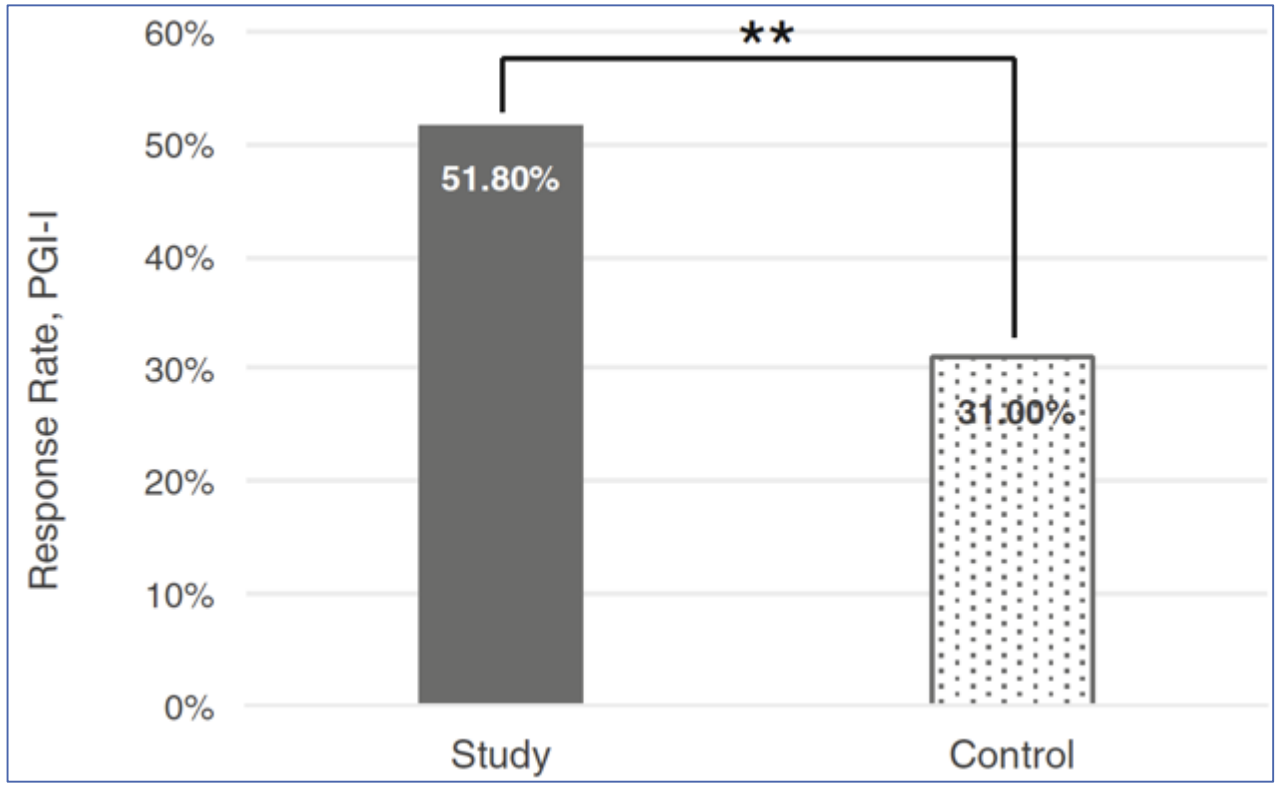


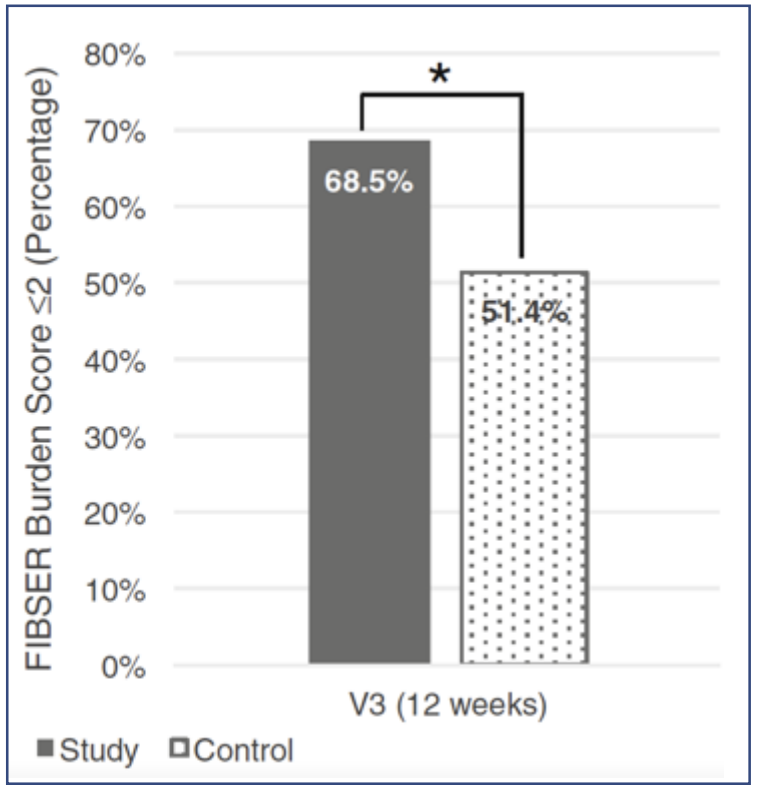
Jukic et al. Lancet Psychiatry 2019:6:418-26

ABOMICS

Clinical Outcomes of Pharmacogenetics in Treatment of Depression

According to an RCT (n = 280) including 18 public hospitals in Spain, the response rate and tolerability of pharmacogenetically tested patients diagnosed with major depression disorder are remarkably better after 12 weeks compared to untested patients.[Pérez]





[Pérez]. Pérez, V., Salavert, A., Espadaler, J., Tuson, M., Saiz-Ruiz, J., Sáez-Navarro, C., ... & Menchón, J. M. (2017). Efficacy of prospective pharmacogenetic testing in the treatment of major depressive disorder: results of a randomized, double-blind clinical trial. *BMC psychiatry*, *17*(1), 1-13. https://doi.org/10.1186/s12888-017-1412-1

ABOMICS

Clinical Outcomes of Pharmacogenetics in Treatment of Depression

A systematic review and meta-analysis showed that individuals with major depressive disorder receiving pharmacogenetic-guided therapy were 1.71 (p = 0.005) times more likely to achieve symptom remission relative to individuals who received treatment as usual.[Bousman]

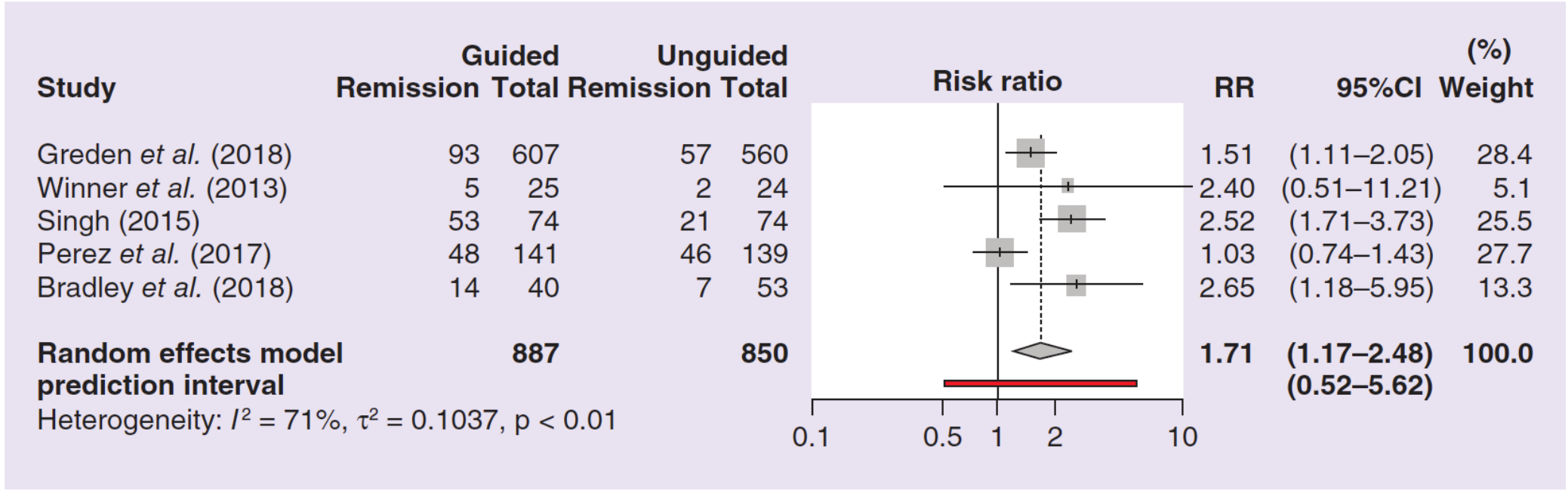


Figure 2. Forest plot of random-effects meta-analyses of five prospective, randomized controlled trials that examined the effect of pharmacogenetic-guided therapy on remission in major depressive disorder.
RR: Relative risk.

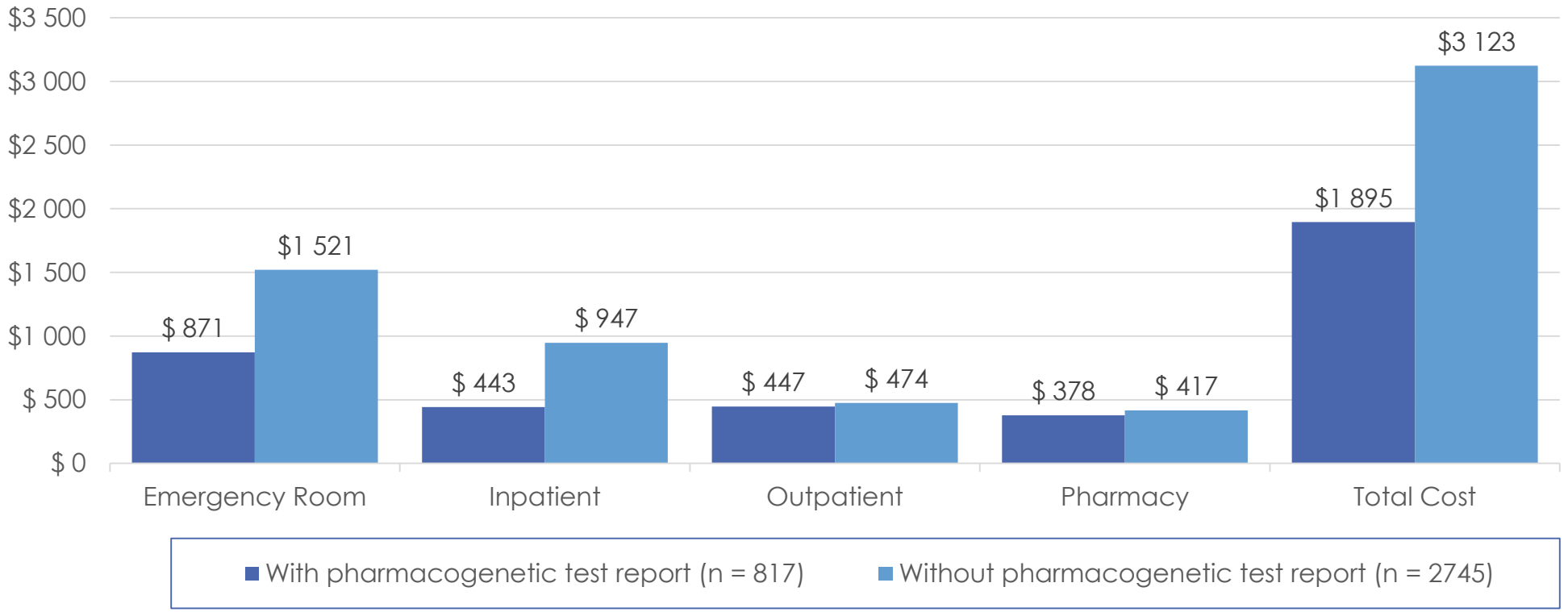
[Bousman] Bousman, C. A., Arandjelovic, K., Mancuso, S. G., Eyre, H. A., & Dunlop, B. W. (2019). Pharmacogenetic tests and depressive symptom remission: a meta-analysis of randomized controlled trials. *Pharmacogenomics*, *20*(01), 37-47.

https://doi.org/10.2217/pgs-2018-0142

ABOMICS

Cost Outcomes of Pharmacogenetics in Treatment of Depression

According to a propensity-score matched study in the USA, the health care costs of pharmacogenetically tested mental health patients are remarkably lower compared to untested patients. The cost savings per patient is approx. $1,948 during the 6-month follow-up period.[Perlis]

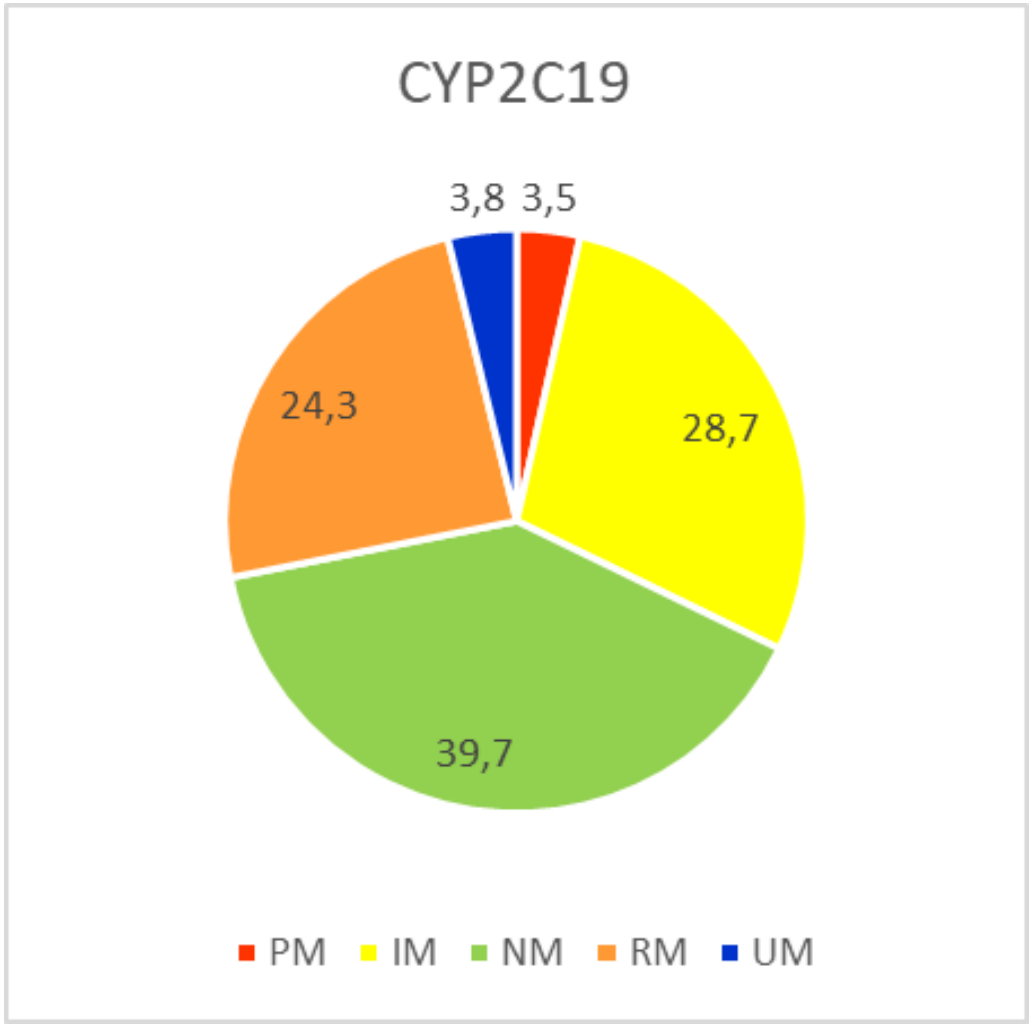


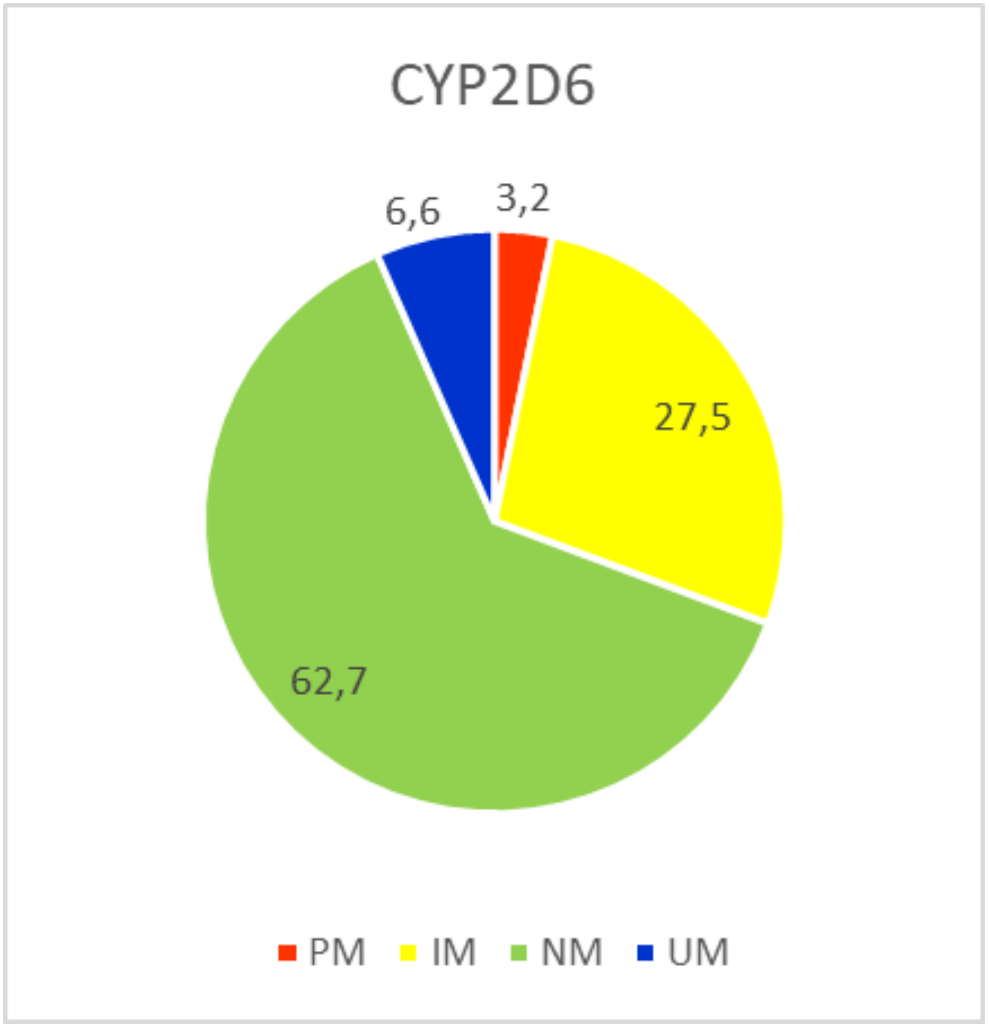
[Perlis] Perlis, R. H., Mehta, R., Edwards, A. M., Tiwari, A., & Imbens, G. W. (2018). Pharmacogenetic testing among patients with mood and anxiety disorders is associated with decreased utilization and cost: A propensity-score matched study. *Depression and anxiety*, *35*(10), 946-952.

https://doi.org/10.1002/da.22742

ABOMICS

CYP2D6 and CYP2C19 phenotypes in Finland





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Genes CYP2D6 and CYP2C19 are independent

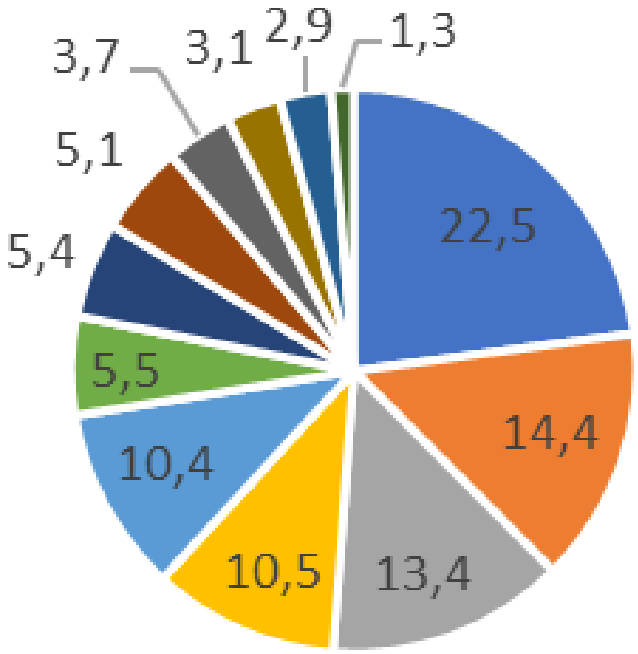
- CYP2D6 normal metabolism in 62,7 % of patients
- CYP2C19 normal metabolism in 39,7 % of patients
- Likelihood that both are normal is:

  0,627 * 0,397 * 100 % = **24,9 %**

- In **75,1 %** of patients either CYP2D6 or CYP2C19 is abnormal.

ABOMICS

Most used antidepressants in Finland 2020



escitalopram
venlafaxine
sertraline
citalopram
mirtazapine
fluoxetine
vortioxetine
duloxetine
amitriptyline
bupropion
paroxetine
agomelatine

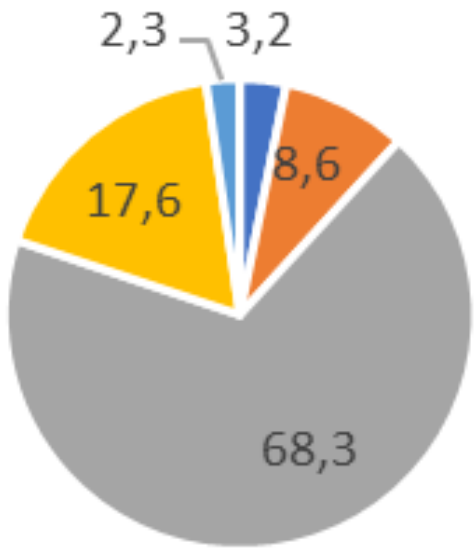
ABOMICS

Importance of CYP enzymes in the metabolism

	CYP2D6	CYP2C19	CYP2B6	CYP1A2
escitalopram	B3	C4		
venlafaxine	C4	B3		
sertraline		B3		
citalopram	B3	C4		
mirtazapine	B3			
fluoxetine	B4			
vortioxetine	D3			
duloxetine	B0			
amitriptyline	D4	C3		
bupropion			B3	
paroxetine	D4			B2

ABOMICS

Probability to succeed in the drug treatment of depression with a standard dose



- no effect
- possibly poor response
- good response
- possibly adverse reactions
- most porbably adverse reactions

ABOMICS

Selecting primary drug for depression if PGx result is available

CYP2D6 abnormal

Avoid:

- venlafaxine
- vortioxetine
- paroxetine
- nortripityline
- amitriptyline

CYP2C19 abnormal

Avoid:

- escitalopram
- citalopram
- amitriptyline

ABOMICS

Oulu University hospital guidelines draft: when to order PGx test?

In depression:

- When a first antidepressaat is started for a patient (CYP2D6 and CYP2C19 should be known)
- When a patient is referred to a secondary care due to depression, the test should be done before the visit.
- If sick leave is written to patient due to depression.
- When adverse reactions to antidepressants are strong and atypical and occur in small doses.
- When no effective drugs have been found with trial and error.
- When the physician plans to prescribe an antidepressant where PGx is clinically very significant (amitriptyline, nortiptyline, trimipramine, paroxetine and vortioxetine) or significant (escitalopram, citalopram, venlafaxine)

In psychosis:

- When the physician plans to prescibe a drug where PGx is clinically very significant (risperidone, aripiprazole, brekspiprazole)
- If the patient using clozapine has big changes in blood concentrations of clozapine (abnormal CYP1A2)

ABOMICS

GeneAccount

You were tested for 22 genes, out of which 6 may affect the efficacy or safety of your medication: **CYP2C19, CYP2C9, CYP2D6, IFNL3, UGT1A1, VKORC1**

Your genetic factors may affect the efficacy or safety of 106 drugs.

TEST SUMMARY

TABLE OF CONTENTS

This is the report of your pharmacogenetic test results. The report contains information on the tested genetic variants and their effects on the safety and efficacy of medications. **This report should not be used to change medications without guidance from a physician. Always consult your physician before making any changes to your medications.**

First, here is a short list of terms to understand the report better:

- variant = a genetic alteration which deviates from the common form
- genotype = the composition of your genetic variants for a gene
- phenotype = a property or function caused by a genotype, e.g. "rapid metabolizer" or "increased risk"

The report is divided into three major sections: gene-specific recommendations for medications, detailed genotype results and the raw data of your variants.

It is vital to remember that drug responses may be affected by other genetic variants not included in this report. Additionally, many other individual factors,

ABOMICS

HIGHLY AFFECTED MEDICATIONS ORDERED BY THERAPEUTIC AREA

Therapeutic area		Active ingredient	Phenotype	Classification
Alimentary Tract And Metabolism	Antiemetics And Antinauseants	ondansetron	CYP2D6 UM Ultrarapid Metabolizer	C
	Other Alimentary Tract And Metabolism Products	eliglustat	CYP2D6 UM Ultrarapid Metabolizer	D
Blood And Blood Forming Organs	Antithrombotic Agents	clopidogrel	CYP2C19 IM Intermediate Metabolizer	C
		warfarin	CYP2C9 NM Normal Metabolizer	C
		warfarin	VKORC1 Reduced expression of the enzyme	C
Cardiovascular System	Beta Blocking Agents, Plain	metoprolol	CYP2D6 UM Ultrarapid Metabolizer	D
	Beta Blocking Agents And Thiazides	metoprolol	CYP2D6 UM Ultrarapid Metabolizer	D
	Beta Blocking Agents And Other Antihypertensives	metoprolol	CYP2D6 UM Ultrarapid Metabolizer	D
General Antiinfectives For Systemic Use	Antimycotics For Systemic Use	voriconazole	CYP2C19 IM Intermediate Metabolizer	C
Antineoplastic And Immunomodulating Agents	Other Cytostatics	irinotecan	UGT1A1 IM Intermediate Metabolizer	C
	Immunostimulating Agents	peginterferon alfa-2a	IFNL3 Unfavorable response genotype	D

Nervous System	Opioids	codeine	CYP2D6 UM Ultrarapid Metabolizer	D
		tramadol	CYP2D6 UM Ultrarapid Metabolizer	D
	Antipsychotics	haloperidol	CYP2D6 UM Ultrarapid Metabolizer	C
		risperidone	CYP2D6 UM Ultrarapid Metabolizer	C
	Antidepressants	amitriptyline	CYP2D6 UM Ultrarapid Metabolizer	D
		citalopram	CYP2C19 IM Intermediate Metabolizer	C
		clomipramine	CYP2D6 UM Ultrarapid Metabolizer	D
		doxepin	CYP2D6 UM Ultrarapid Metabolizer	D
		escitalopram	CYP2C19 IM Intermediate Metabolizer	C
		nortriptyline	CYP2D6 UM Ultrarapid Metabolizer	D
		paroxetine	CYP2D6 UM Ultrarapid Metabolizer	D
		trimipramine	CYP2D6 UM Ultrarapid Metabolizer	D
	Psychostimulants	atomoxetine	CYP2D6 UM Ultrarapid Metabolizer	C
	Psycholeptics And Psychoanaleptics In Combination	amitriptyline	CYP2D6 UM Ultrarapid Metabolizer	D

citalopram

C

With this genotype the metabolism of citalopram is reduced. Recommendation by a Dutch board of experts (Dutch Pharmacogenetics Working Group): The risk of QT prolongation and therefore also the theoretical risk of torsades de pointes is increased as the gene variation leads to an increased citalopram plasma concentration. If you follow the dose recommendation below, the increased plasma concentration and the increased risk of QT prolongation will be offset. Do not exceed the following daily doses (50% of the standard maximum dose): 1. Adults up to 65 years: 20 mg as tablets or 16 mg as drops. 2. Adults 65 years or older: 10 mg as tablets or 8 mg as drops.

CYP2C19: IM Intermediate Metabolizer

ABOMICS

Patient case 1

- Middle-aged woman with prolonged depression. Difficulties in finding effective treatment for depression.
- In the pharmacogenetic panel:
  - CYP2D6 ultrarapid metabolism
  - CYP2C19 ultrarapid metabolism
- Citalopram was changed to sertraline and vortioxetine combination
- The patient returned to work within one month.

Lack of effect in depression drugs is often due to abnormalities in CYP2D6 or CYP2C19

ABOMICS

Patient case 2

- Female university student visited university health care due to depression
- Pharmacogenetic panel was done
- Results:
  - poor metabolism in CYP2C19
  - heterozygote for F5 (Factor Leiden mutation)
- Treatments:
  - Vortioxetine with a normal dose was started for depression.
  - P-pills were changed to progesterone pills to reduce the risk of thromboembolic complications.

CYP2C19 metabolism was abnormal. Escitalopram or citalopram was not started, since the dosing would be complicated. The other finding was F5, which is quite common in the European population (5%). Combination p-pills are contraindicated for carriers of hereditary risks of thromboembolic complications.

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Thank you !

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