Foppe Memorial Lecture 2025

14th PCNE Working Conference, Innsbruck, 05.02.2025

1	**EVOLUTION OF PHARMACEUTICAL CARE & RESEARCH**
2	GENOTYPING PATIENTS WITH ADVERSE DRUG REACTION OR THERAPY FAILURE: **DATABASE ANALYSIS OF A PHARMACOGENETIC CASE SERIES**

Kurt Hersberger & Anna Bollinger
Pharmaceutical Care Research Group, University of Basel

FOPPE MEMORIAL LECTURE 2025

J.W. Foppe van Mil (16-07-1950 – 18-07-2020)

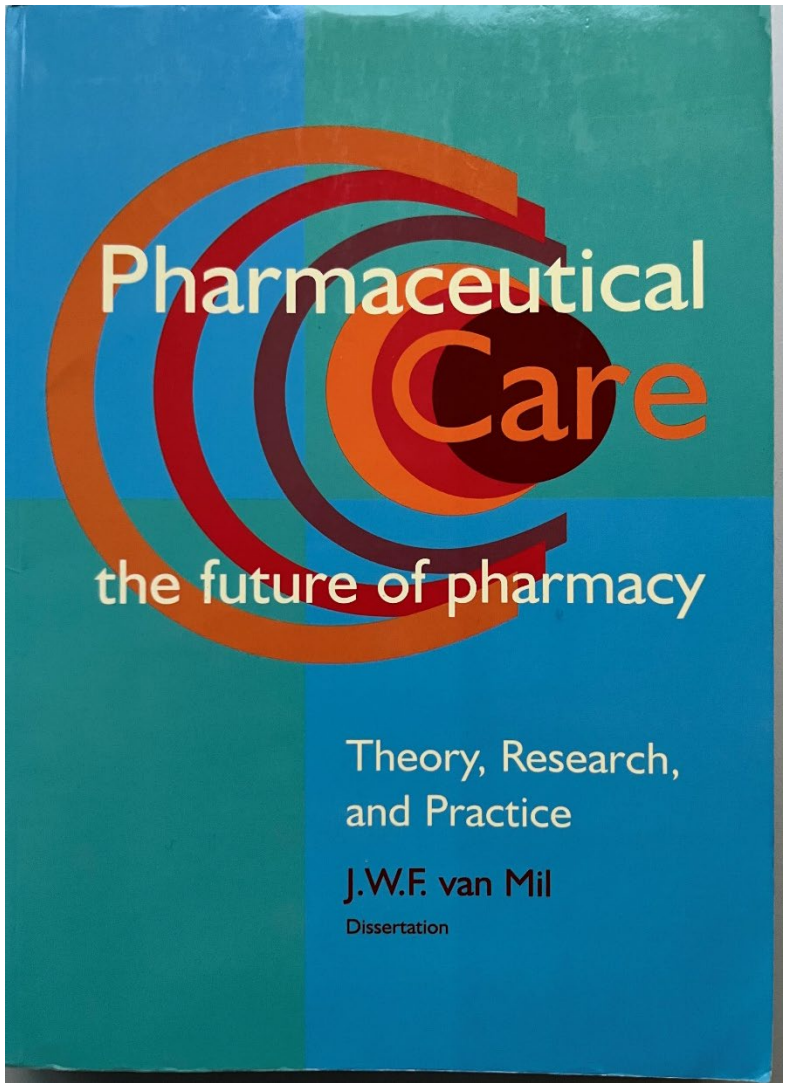
“Memory is the only paradise from which we cannot be driven away”

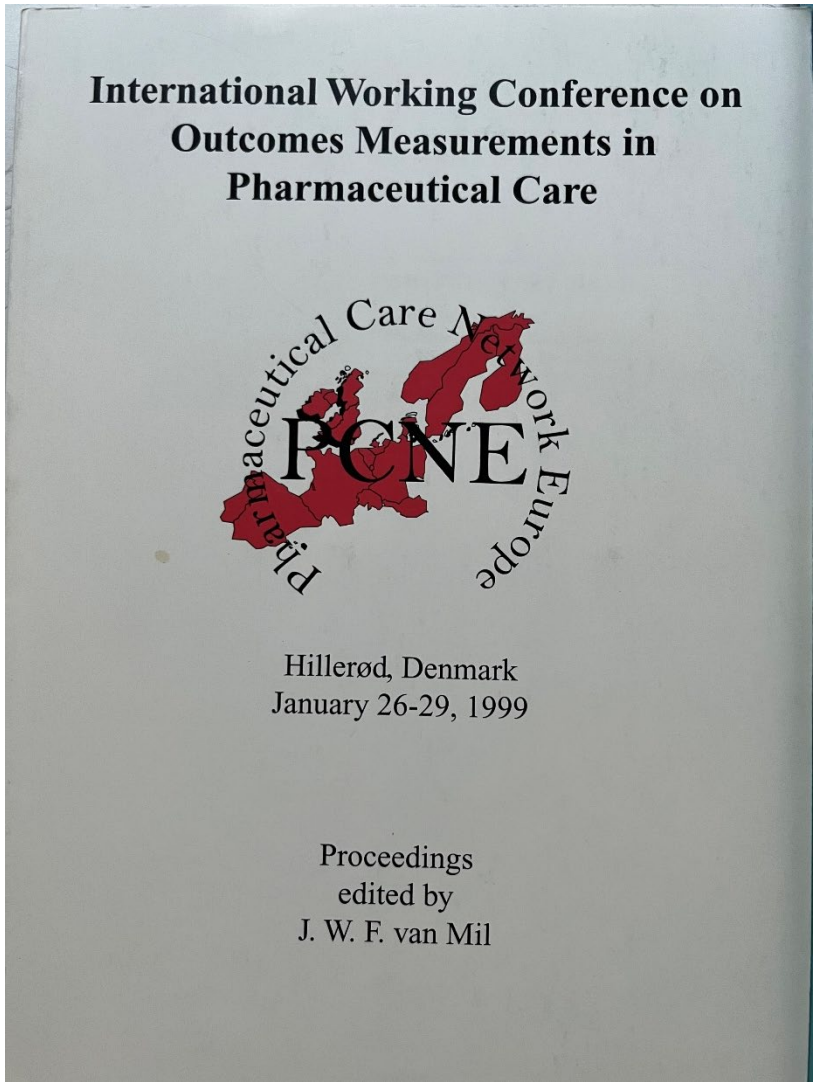
Jean Paul (1816):

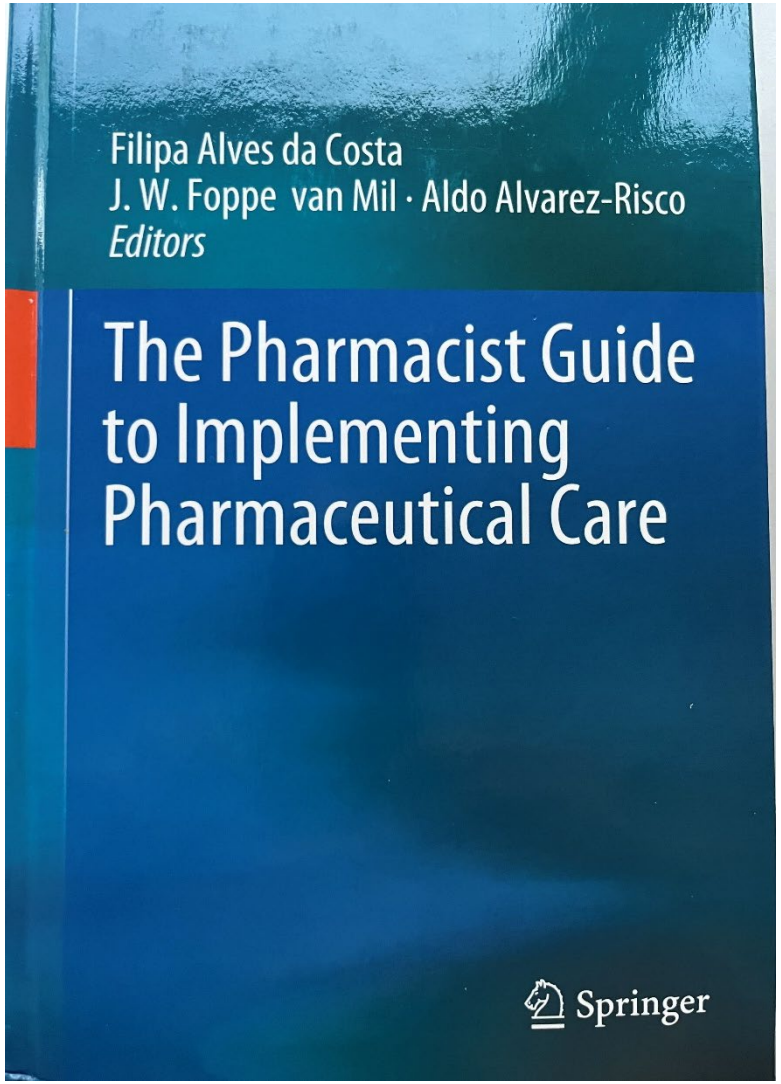
Co-founder of PCNE,
former chair and professional secretary

A global leader in pharmaceutical care as researcher, teacher, networker, editor and last but not least a practicing community pharmacist.

In my library







Pharmaceutical Care is the pharmacist's contribution to the care of individuals, in order to optimize medicines use and improve health outcomes.

Int J Clin Pharm (2014) 36:544–555
DOI 10.1007/s11096-014-9933-x

RESEARCH ARTICLE

Pharmaceutical Care: the PCNE definition 2013

Samuel S. Allemann · J. W. Foppe van Mil · Lea Botermann · Karin Berger · Nina Griese · Kurt E. Hersberger

Global burden of preventable medication-related harm in health care: a systematic review

Meta-analysis of the 100 studies (487’162 total patients) showed that the overall prevalence of preventable medication-related harm was 5% (1 in 20 patients receiving health care)

Global burden of preventable medication-related harm in health care: a systematic review.
Geneva: World Health Organization; 2023.
www.who.int/publications/i/item/9789240088887

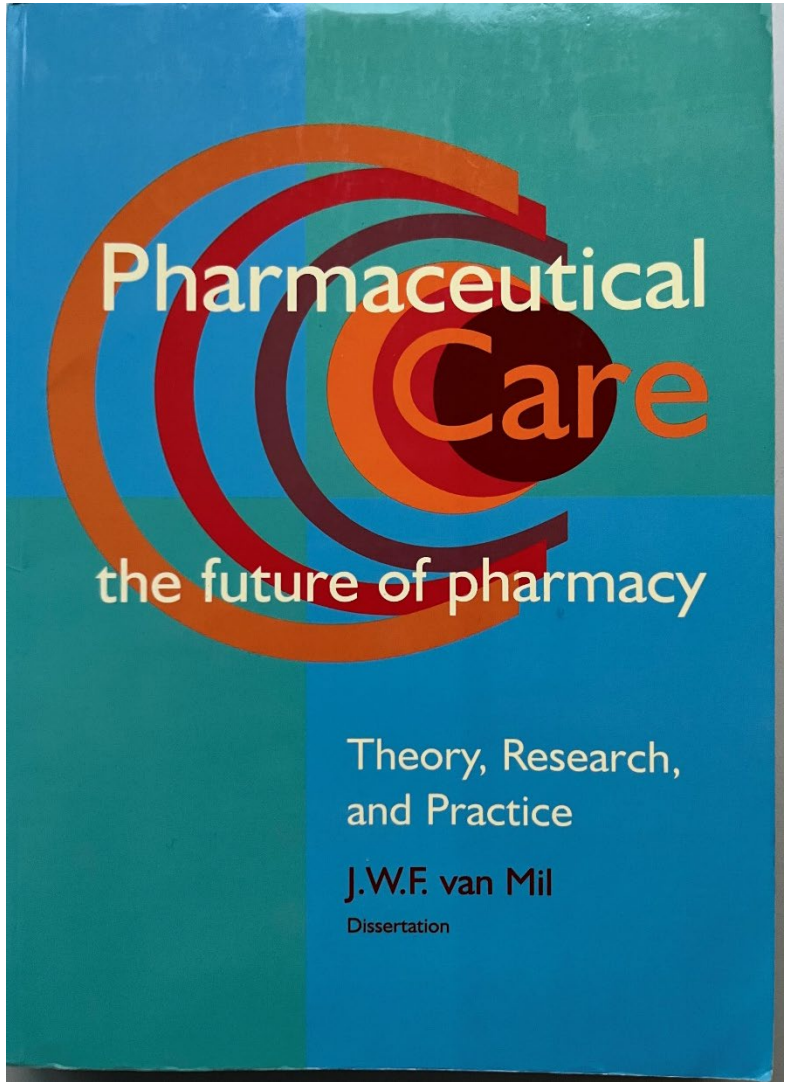
Stages of medication use at which most medication-related harm occurs in 70 studies from high-income countries (HICs)

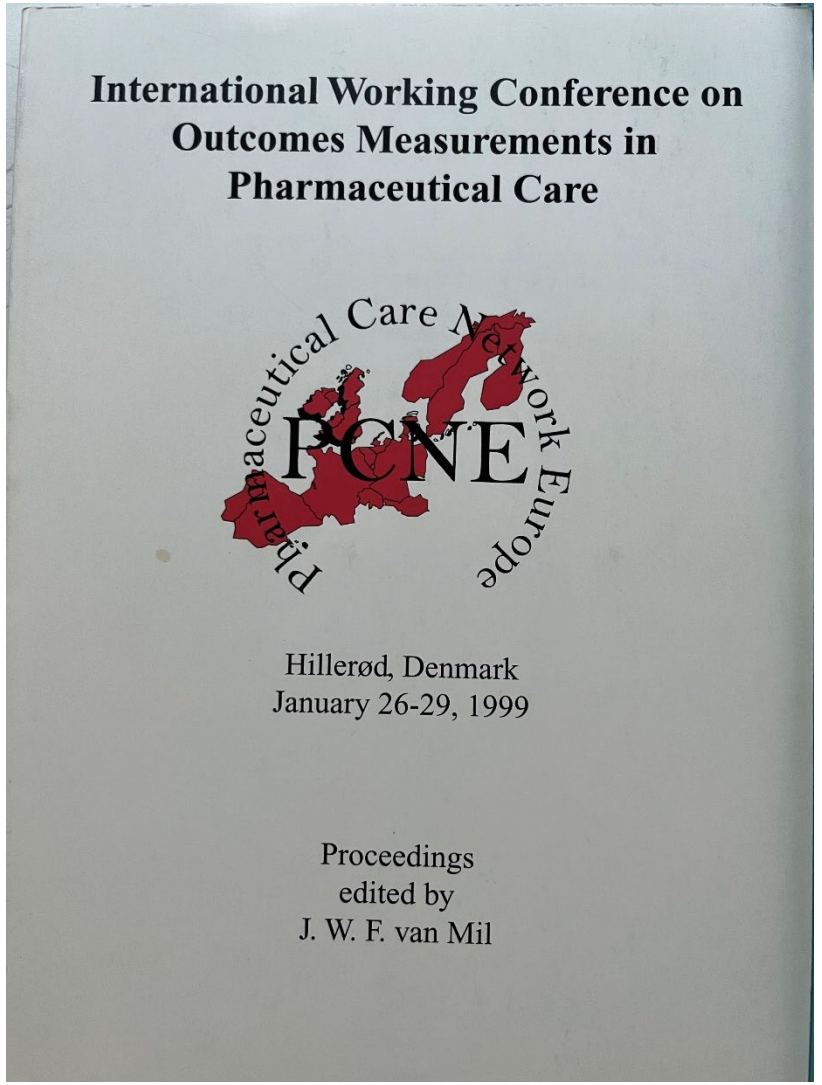
Stage of medication	No. of studies	Prevalence (%)
		HICs
Ordering/prescribing	15	47.00
Transcribing and verifying	6	5.63
Administering	13	22.14
Monitoring and reporting	10	39.66
Dispensing and delivering	4	4.30

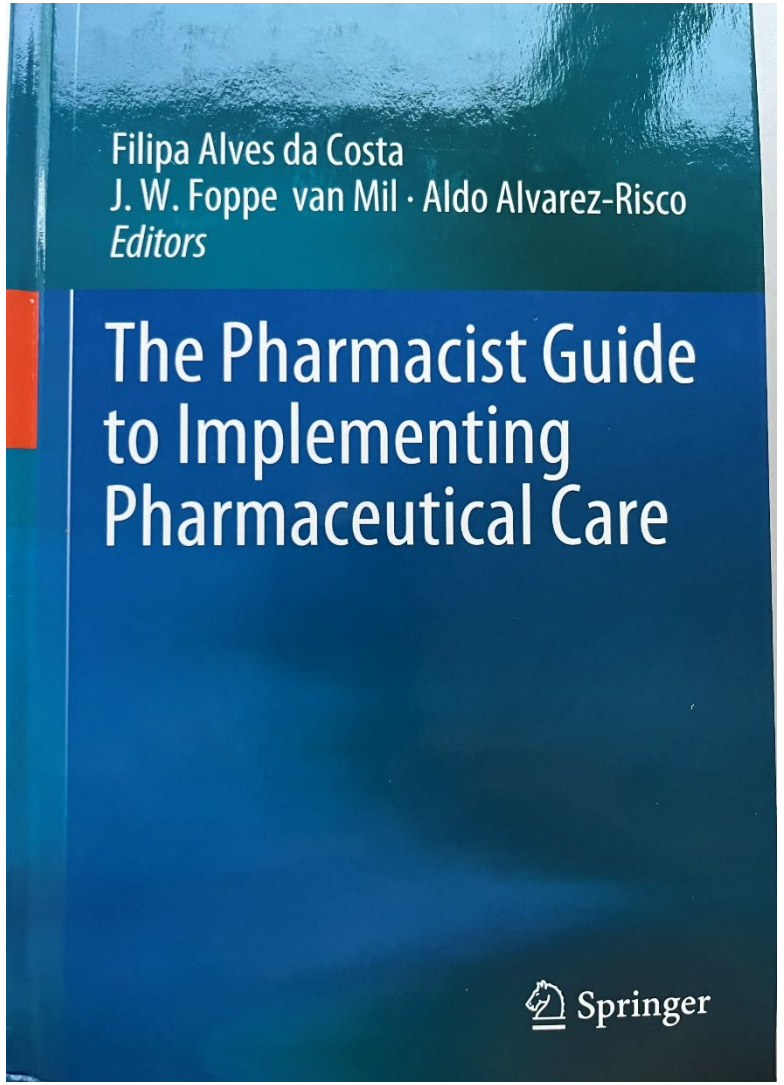
Within the sphere of influence of a pharmacist:

Pharmaceutical Care

In my library







Outcomes Measurements in Pharmaceutical Care

Review > Ann Pharmacother. 2004 May;38(5):859-67. doi: 10.1345/aph.1D182.
Epub 2004 Mar 30.

Drug-related problem classification systems

J W Foppe van Mil [1], L O Tommy Westerlund, Kurt E Hersberger, Marion A Schaefer

Outcomes Measurements in Pharmaceutical Care

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Drug-related problem classification systems

J W Foppe van Mil [1], L O Tommy Westerlund, Kurt E Hersberger, Marion A Schaefer

PCNE Classification for Drug-Related Problems V9.1

	Code V9.1	Primary domains
Problems (also potential)	**P1**	**Treatment effectiveness** There is a (potential) problem with the (lack of) effect of the pharmacotherapy
	P2	**Treatment safety** Patient suffers, or could suffer, from an adverse drug event
	P3	**Other**
Causes (including possible causes for potential problems)	**C1**	**Drug selection** The cause of the DRP can be related to the selection of the drug
	C2	**Drug form** The cause of the DRP is related to the selection of the drug form
	C3	**Dose selection** The cause of the DRP can be related to the selection of the dosage schedule
	C4	**Treatment duration** The cause of the DRP is related to the duration of treatment
	C5	**Dispensing** The cause of the DRP can be related to the logistics of the prescribing and dispensing process
	C6	**Drug use process** The cause of the DRP is related to the way the patient gets the drug administered by a health professional or carer, in spite of proper instructions (on the label)
	C7	**Patient related** The cause of the DRP can be related to the patient and his behaviour (intentional or non-intentional)
	C8	**Patient transfer related** The cause of the DRP can be related to the transfer of patients between primary, secondary and tertiary care, or transfer within one care institution.
	C9	**Other**
Planned Interventions	**I0**	**No intervention**
	I1	**At prescriber level**
	I2	**At patient level**
	I3	**At drug level**
	I4	**Other**
Intervention Acceptance	**A1**	**Intervention accepted**
	A2	**Intervention not accepted**
	A3	**Other**
Status of the DRP	**O0**	**Problem status unknown**
	O1	**Problem solved**
	O2	**Problem partially solved**
	O3	**Problem not solved**

Outcomes Measurements in Pharmaceutical Care

Planned Interventions	**I0**	**No intervention**
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Cor Outcome Sets, COS

"COS should be developed and used in all clinical trials testing the effectiveness of an intervention for a specific health condition or area of healthcare".

The COMET Handbook: version 1.0
Trials, 18 (Jun 20 2017), p. 280, 10.1186/s13063-017-1978-4

Pharmaceutical Care Network Europe definition of quality indicators for pharmaceutical care: a systematic literature review and international consensus development

Kenji Fujita[1] · Kjell H. Halvorsen[2] · Noriko Sato[3] · Janja Jazbar[4] · Pilar Modamio[5] · Isabel Waltering[6] · Isabelle De Wulf[7] · Tommy Westerlund[8] · Timothy F. Chen[3] · Martina Teichert[9]

International Journal of Clinical Pharmacy (2024) 46:70–79

Research | Open access | Published: 24 January 2025

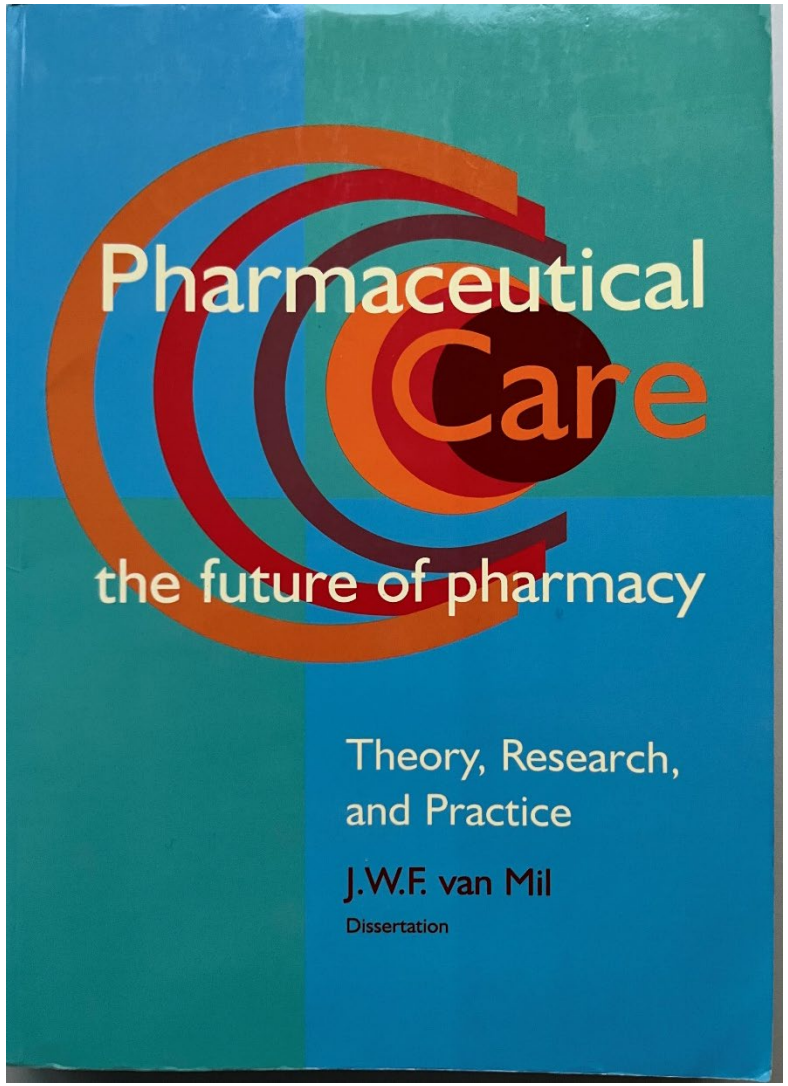
A systematic review of outcomes reported in studies to optimise the medication use of patients at hospital discharge

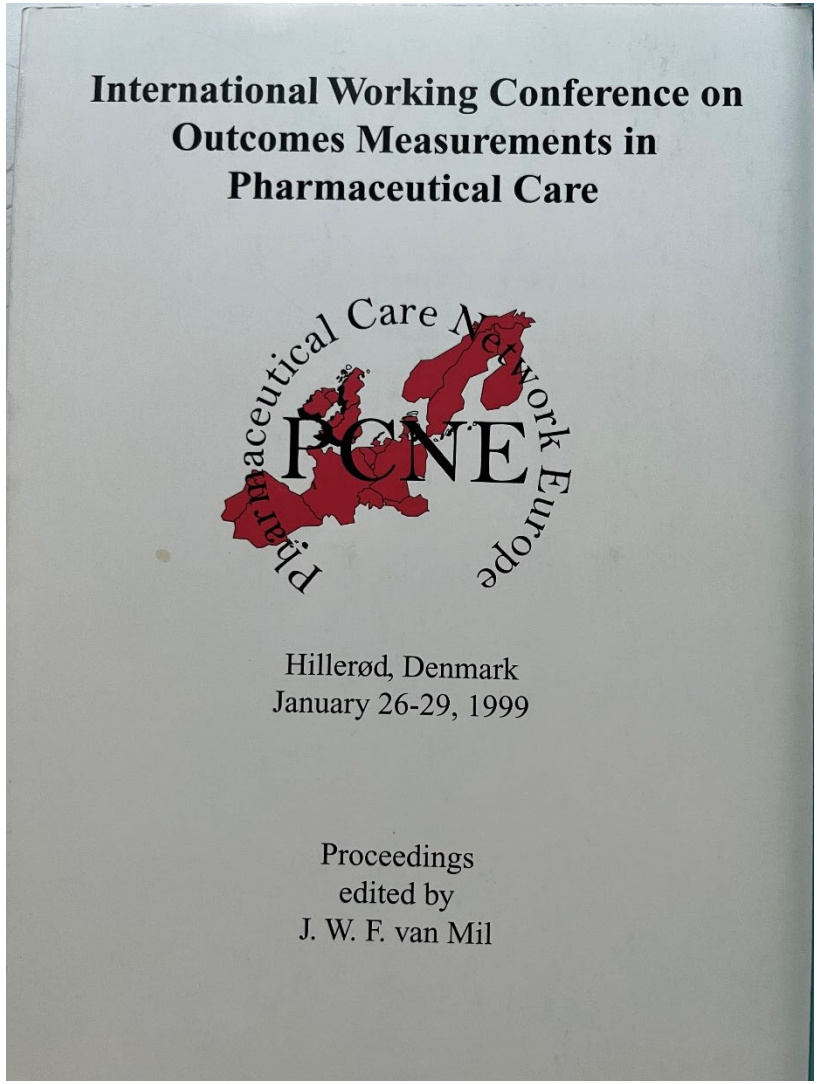
Joke Wuyts, Veerle Foulon, Samuel Sebastian Allemann & Fabienne Boeni

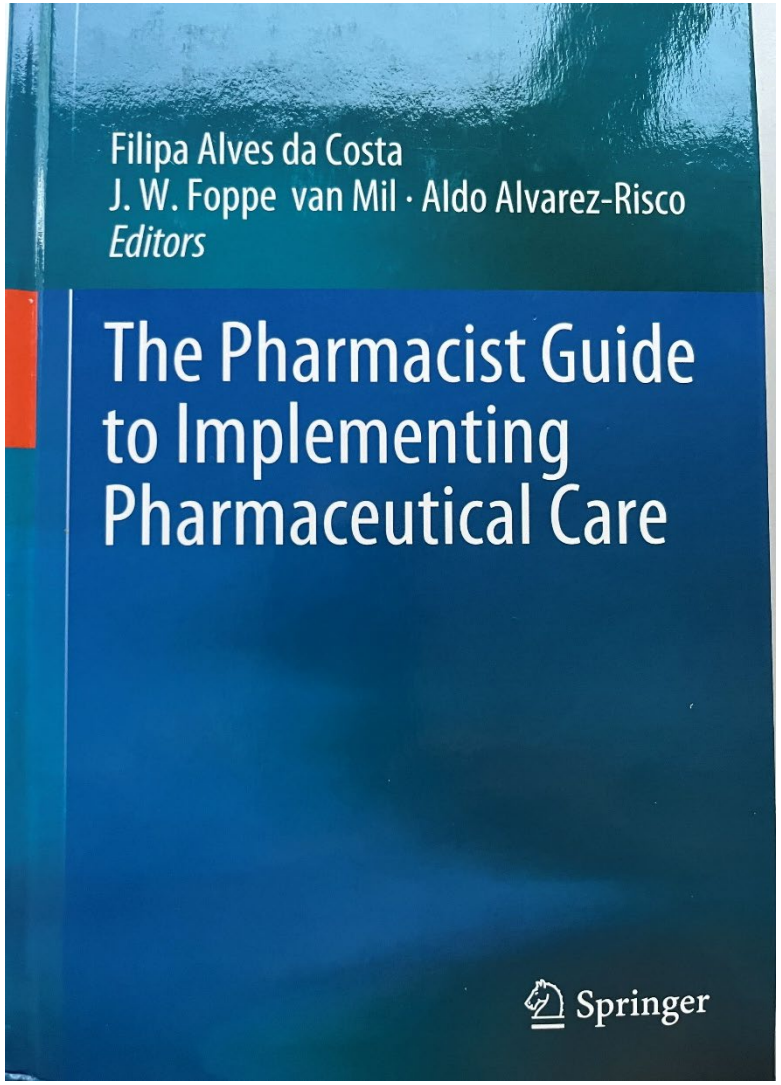
BMC Health Services Research **25**, Article number: 135 (2025) | Cite this article

The top 5 most frequently measured outcomes were readmissions, mortality, emergency department visits, outpatient physician visits and medication adherence.

In my library

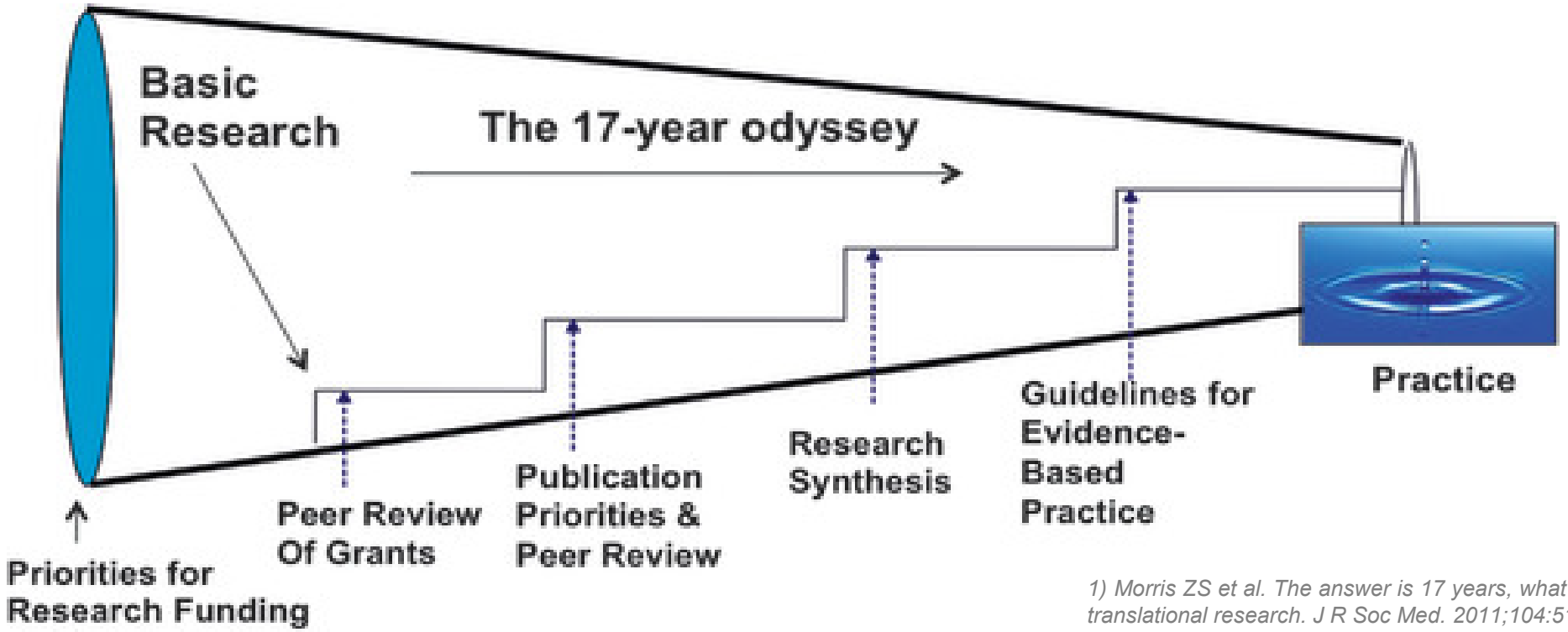






The Pharmacist Guide to Implementing Pharmaceutical Care

The 17 year odyssey» (1)



1) Morris ZS et al. The answer is 17 years, what is the question: understanding time lags in translational research. J R Soc Med. 2011;104:510-20. doi: 10.1258/jrsm.2011.110180.

Bridging the gap

«Science»

«Evidence»

«Performance»

«Practice»

«Performance»

«Evidence»

In PhC research it might be the opposite:?

We belief that we perform well and that our services have impact, but we are not able to prove that.

Medication Review

International Journal of Clinical Pharmacy (2018) 40:1199–1208
https://doi.org/10.1007/s11096-018-0696-7

RESEARCH ARTICLE

PCNE definition of medication review: reaching agreement

Nina Griese-Mammen[1] · Kurt E. Hersberger[2] · Markus Messerli[2] · Saija Leikola[3] · Nejc Horvat[4] · J. W. Foppe van Mil[5] · Mitja Kos[4]

"Medication review is a structured evaluation of a patient's medicines with the aim of optimising medicines use and improving health outcomes.

This entails detecting drug-related problems and recommending interventions"

Characterisation		*Information available:*		
Type	***Level***	Medication history	Patient interview	Clinical Data
Type 1	Simple	+		
Type 2a	Intermediate	+	+	
Type 2b		+		+
Type 3	Advanced	+	+	+

Table 1:

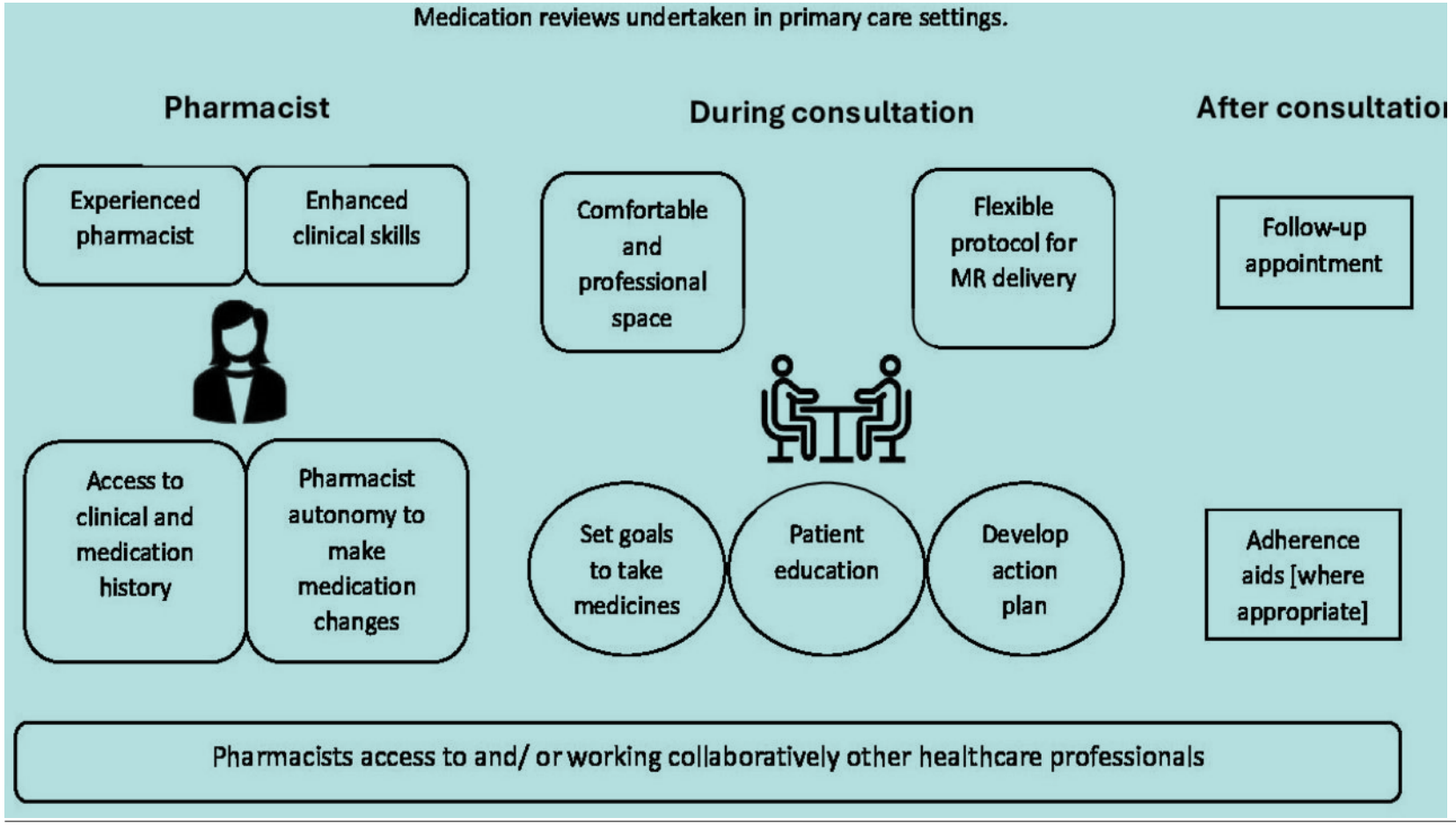
PCNE Typology of Medication Reviews[6]

PCNE Position Paper on Medication review, April 2016

BMJ Qual Saf. 2024 Nov 20;33(12):808-822. doi: 10.1136/bmjqs-2024-017283.

Components of pharmacist–led medication reviews and their relationship to outcomes: a systematic review and narrative synthesis

Miriam E Craske [1], Wendy Hardeman [2], Nicholas Steel [3], Michael J Twigg [4 5]



Discussion:

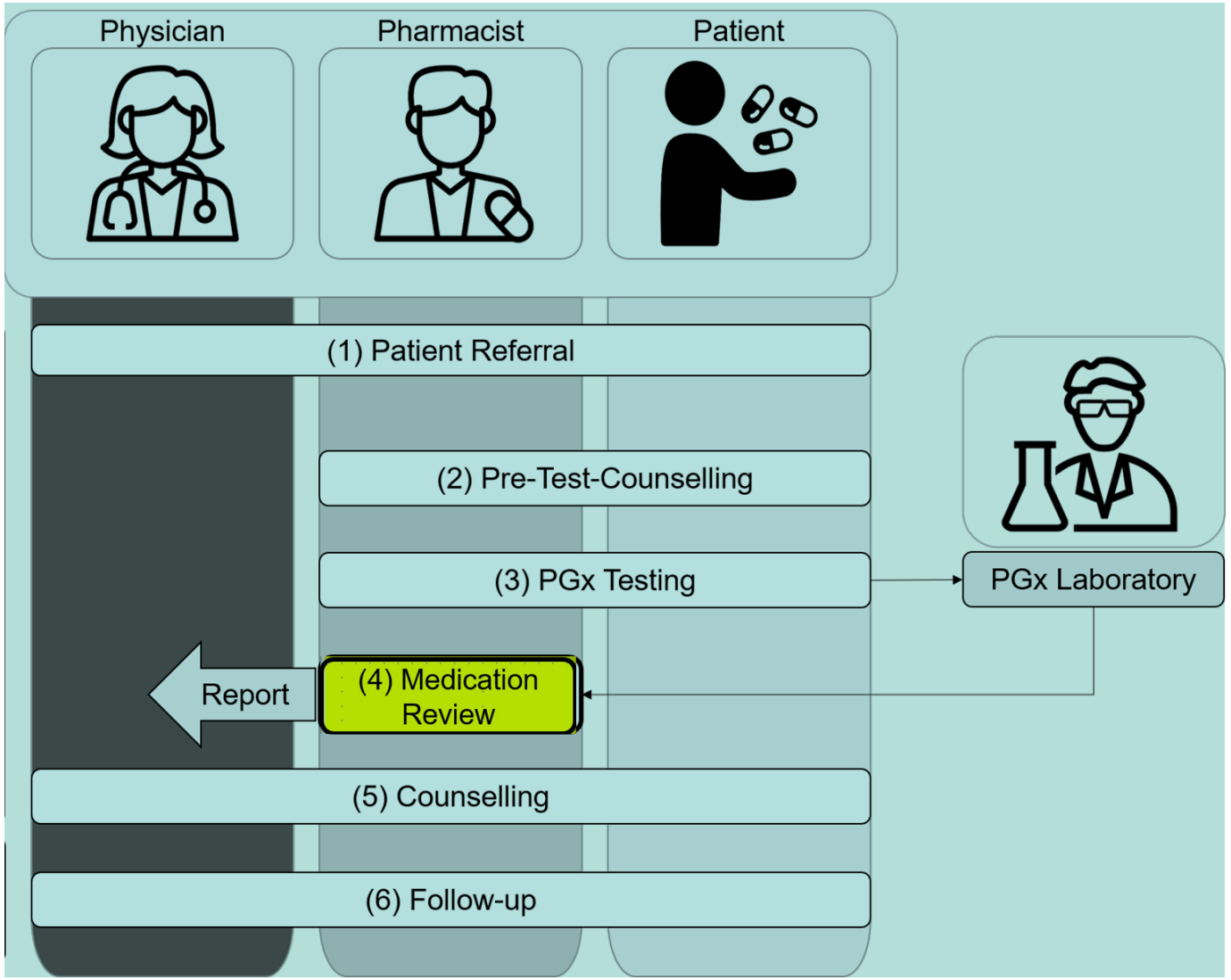
…"Most studies choose to report economic or clinical outcomes, with little focus on those reported by patients.
If future studies measure more patient-reported outcomes, medication reviews may be seen to have a greater impact on these."…

BUT
It is not enough to document patient satisfaction with a service – no, we must demonstrate relevant outcomes (ECHO).

Enriching medication reviews with pharmacogenetic (PGx) testing results

A Guide to a Pharmacist-Led Pharmacogenetic Testing and Counselling Service in an Interprofessional Healthcare Setting

by Céline K. Stäuble [1,2,3,*], Chiara Jeiziner [1], Anna Bollinger [1], Florine M. Wiss [1,2], Martin Hatzinger [4], Kurt E. Hersberger [1], Thomas Ihde [5], Markus L. Lampert [1,2], Thorsten Mikoteit [4], Henriette E. Meyer zu Schwabedissen [3] and Samuel S. Allemann [1]



Looking back to the legacy….

- Medication review is the core competence of pharmacists
- We have the tools 
- Implementation science is key
- Prospective studies on outcomes (ECHO) from pharmacist-led or collaboratively provided services

➡ **EVIDENCE**

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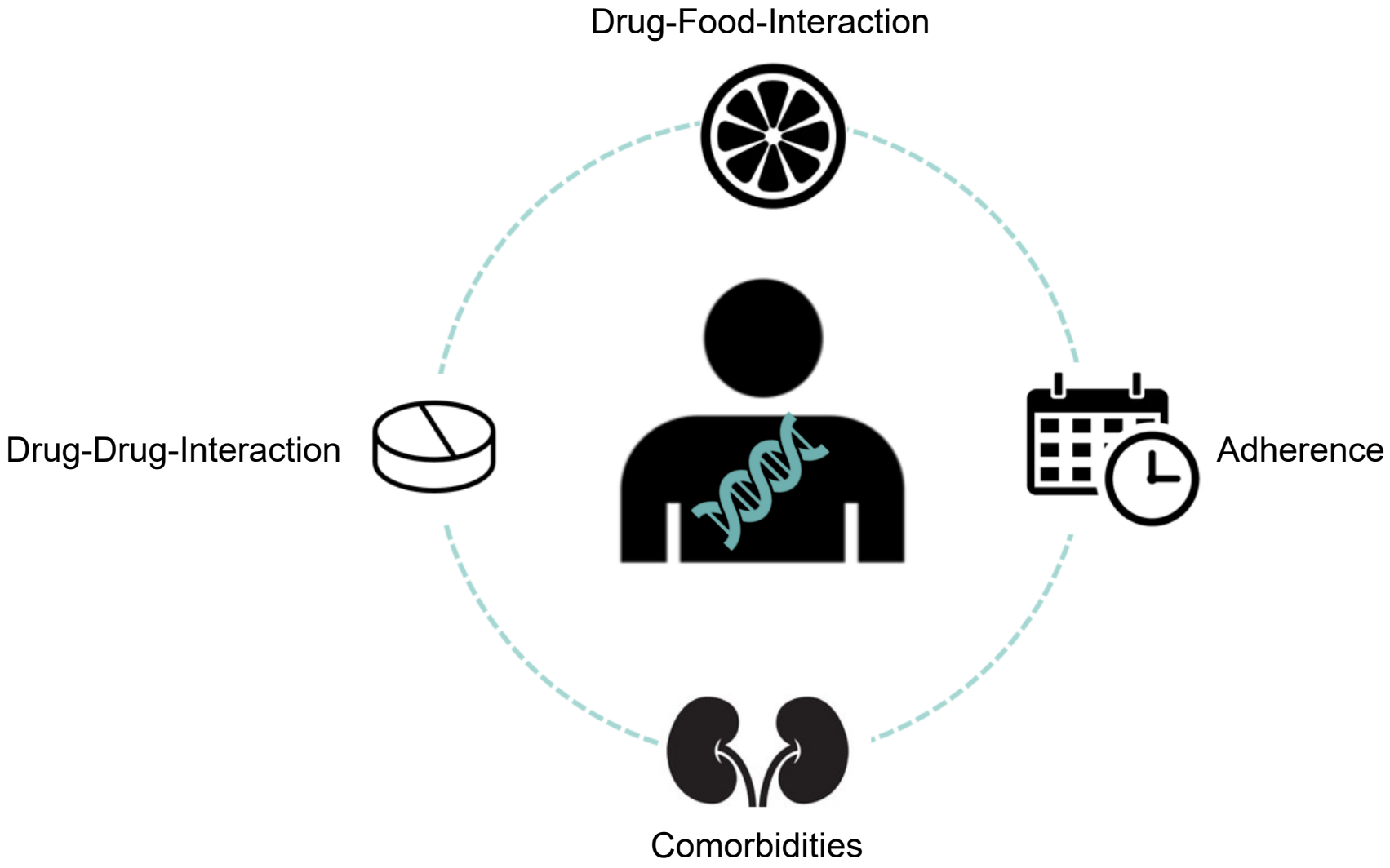
2	GENOTYPING PATIENTS WITH ADVERSE DRUG REACTION OR THERAPY FAILURE: **DATABASE ANALYSIS OF A PHARMACOGENETIC CASE SERIES**

Universität Basel

GENOTYPING PATIENTS WITH ADVERSE DRUG REACTION OR THERAPY FAILURE:
DATABASE ANALYSIS OF A PHARMACOGENETIC CASE SERIES

Anna Bollinger
Biopharmacy & Pharmaceutical Care Research Groups, University of Basel
14th PCNE Working Conference, Innsbruck, 05.02.2025

Background: Pharmacogenetics (PGx) in clinical practice



Background: Pharmacogenetics (PGx) in clinical practice

out-patient setting

in-patient setting

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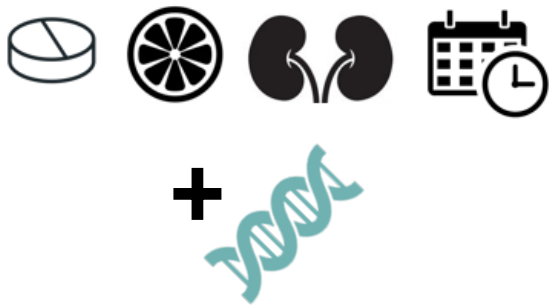
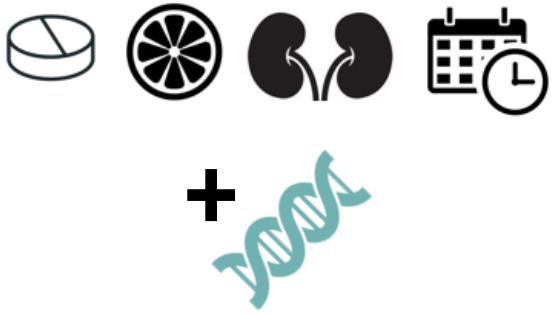
out-patient setting

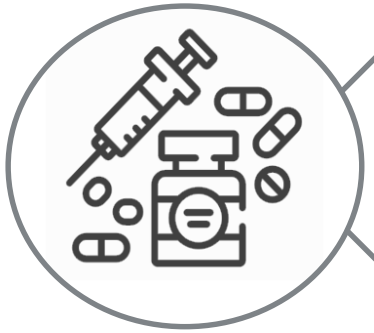


in-patient setting



Objectives

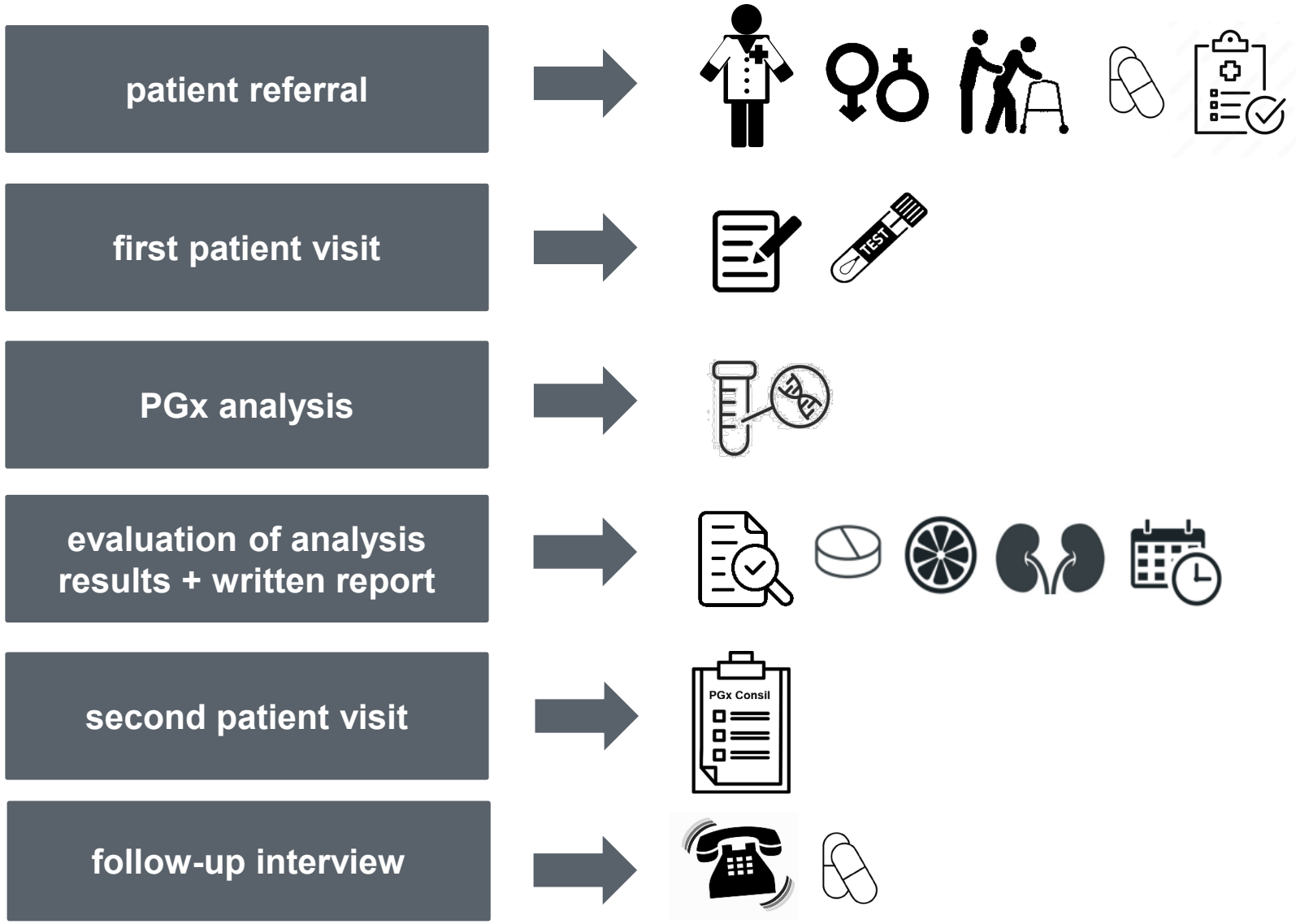
develop a **service** to use **PGx information** for medication optimization in **clinical practice**



identification of the **drugs** and **genes** that are most frequently associated as **Drug-Gene-Interactions (DGI)**

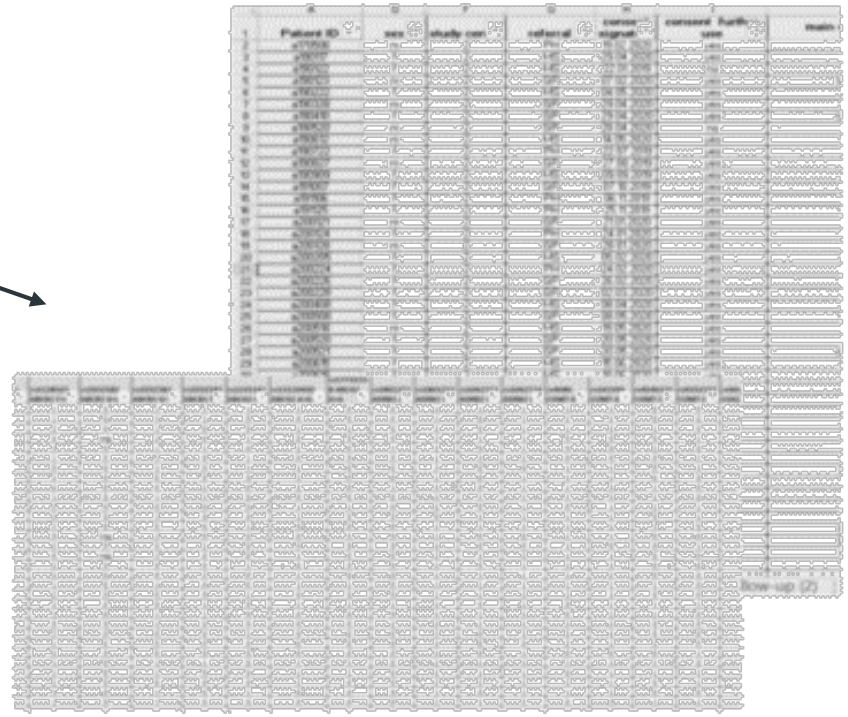
identification of the **target population** that may benefit the most from PGx testing

Setting: Case Series Study - PGx Testing of Patients with Adverse Drug Reactions (ADR) or Therapy Failure (TF)



Stäuble *et al.* [23]

Methods: Case Series Study Database



Database Analysis Results: Demographics

142 subjects
2019-2022

34%
male

66%
female

AGE

52 years
(IQR 40-63)

Database Analysis Results: Demographics

60%
primary care
recruitment

40%
hospital
recruitment

Database Analysis Results: Demographics

61% mental or behavioral disorder (ICD-10 = F)

21% musculoskeletal system and connective tissue disease (ICD-10 = M)

11% disease of the circulatory system (ICD-10 = I)

Database Analysis Results: Medication

65% patients with polypharmacy

median number of prescribed drugs: **7 (IQR 4-9)**

Database Analysis Results: Drug-Drug-Interaction (DDI)

47% patients with DDI

148 (n) DDI

median DDI (n) per patient:
2 (IQR 1-3)

73 (n) drugs
causing DDI

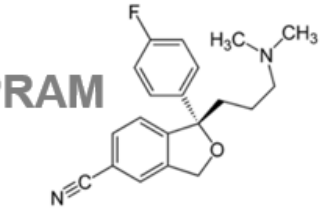
Database Analysis Results: Drug-Gene-Interactions (DGI)

142 (n) patients with suspected DGI	**141** (n) patients with confirmed DGI **(99%)**
559 (n) suspicions for DGI	**324** (n) confirmed DGI **(58%)**
median suspicions for DGI (n) per patient: **4 (IQR 3-5)**	median confirmed DGI (n) per patient: **2 (IQR 3-5)**
109 (n) suspected drugs for DGI	**64** (n) confirmed **drugs** for DGI (59%) based on **21** (n) different **genes**

Substance Example for Drug-Gene-Interaction (DGI)

Example:

ESCITALOPRAM



suspicion for DGI in 29 cases:
56% TF + 44% ADR

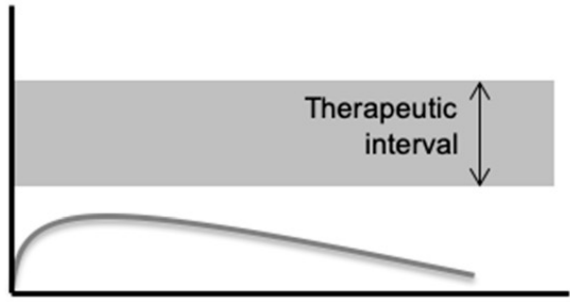
confirmed DGI in 23 cases (79%)

CYP2D6 variation: 12 / 23 cases
CYP2C19 variation: 7 / 23 cases
CYP2C19 & CYP2D6 variation: 4 / 23 cases

Case Example: Therapy Failure from Escitalopram

Presentation
- Mr. Smith, 42 years
- Diagnosis: Recurrent Depressive Disorder (F33)
- Medication: Escitalopram 10 mg, 2-0-0-0
- Suspicion: Therapy failure (after 3 months cont. intake)

Untersuchung	Resultat	Einheit	Referenzbereich
Klinische Chemie			
Escitalopram (20 mg/d)	29 *	nmol/l	46-247
Desmethylescitalopram	47	nmol/l	
Des./Escitalopram	1.6 *		0.3-1.0



Gene	Variant	Genotype	Activity	Phenotype
CYP2C19	rs12248560 (in *17) C>T	T/T	↑↑	Ultrarapid Metabolizer

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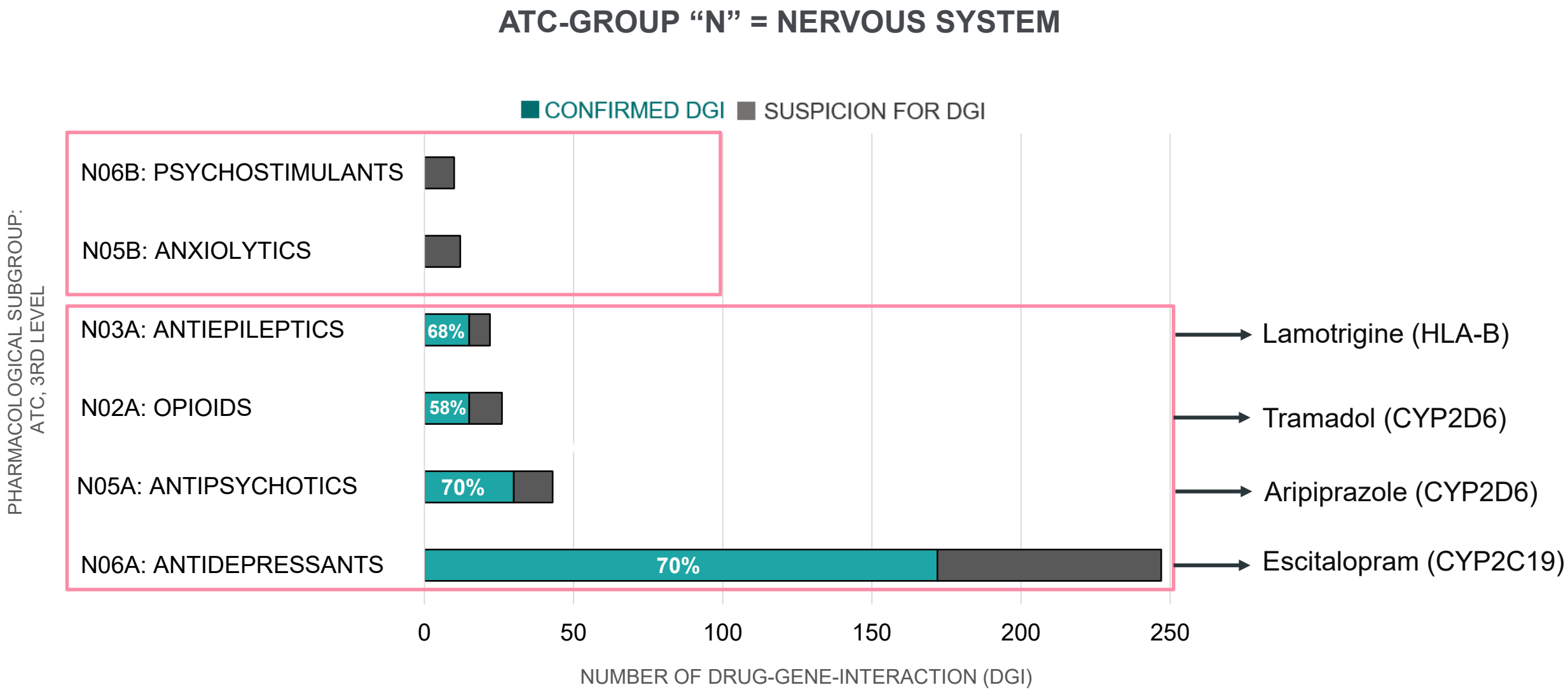
Table 3 Dosing recommendations for CYP2C19 and SSRIs

Table 3a Dosing recommendations for citalopram and escitalopram based on CYP2C19 phenotype

Phenotype	Implication	Therapeutic recommendation	Classification of recommendation[a]
CYP2C19 Ultrarapid metabolizer	Increased metabolism when compared to extensive metabolizers. Lower plasma concentrations will increase probability of pharmacotherapy failure.	Consider an alternative drug not predominantly metabolized by CYP2C19.[b]	Moderate
CYP2C19 Extensive metabolizer	Normal metabolism	Initiate therapy with recommended starting dose.	Strong
CYP2C19 Intermediate metabolizer	Reduced metabolism when compared to extensive metabolizers.	Initiate therapy with recommended starting dose.	Strong
CYP2C19 Poor metabolizer	Greatly reduced metabolism when compared to extensive metabolizers. Higher plasma concentrations may increase the probability of side effects.	Consider a 50% reduction[c,d] of recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by CYP2C19.[b]	Moderate

adapted from: www.cpicpgx.org

Database Analysis Results: ATC-Groups



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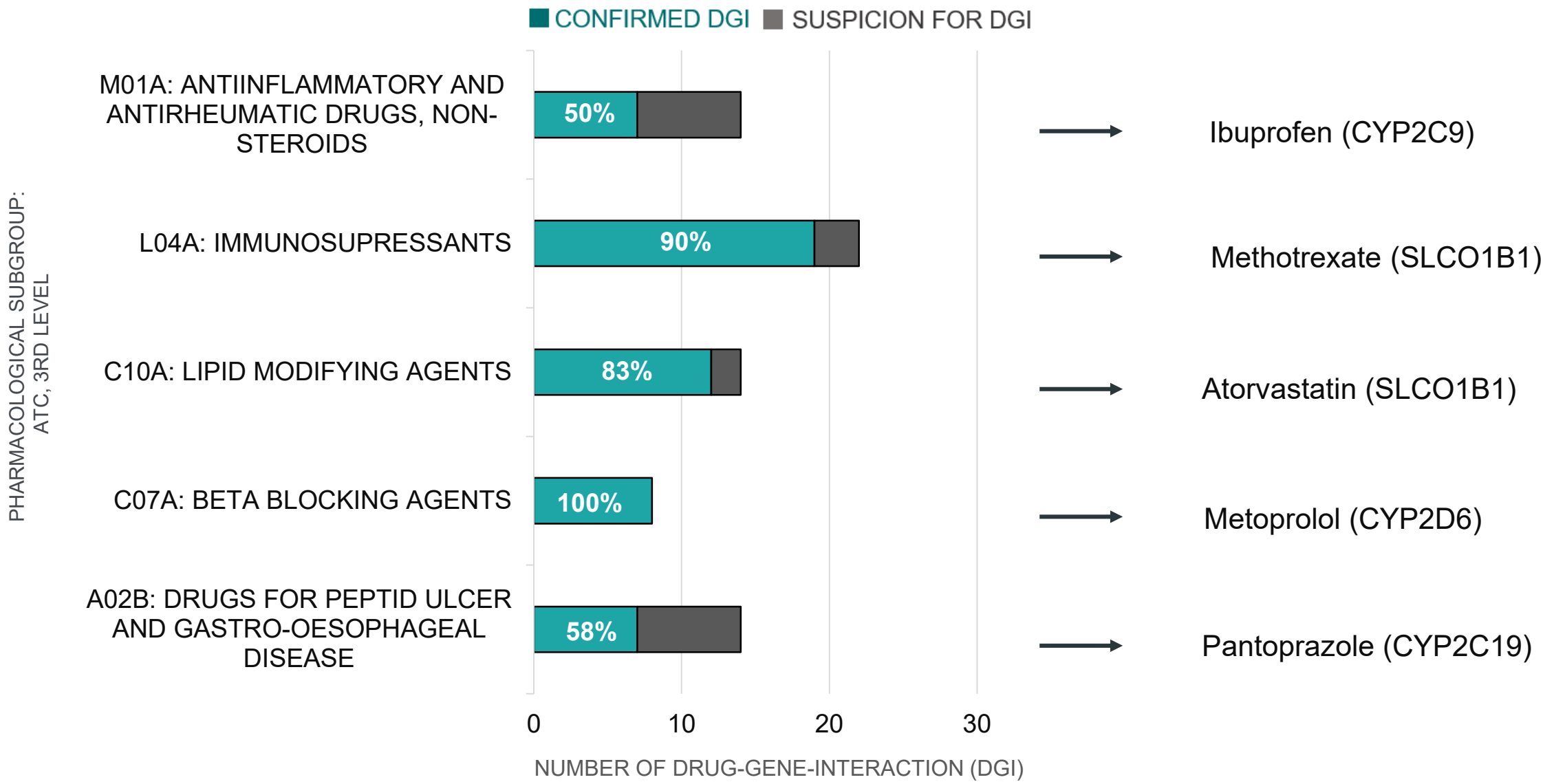


Database Analysis Results: Drug-Gene-Interactions (DGI)

INVOLVED GENES

TOP 4

CYP2D6: 129 Associations

CYP2C19: 67 Associations

CYP2C9: 35 Associations

SLCO1B1: 29 Associations

Drug-Drug-Gene-Interaction (DDGI)

CYP2D6: 12 Associations

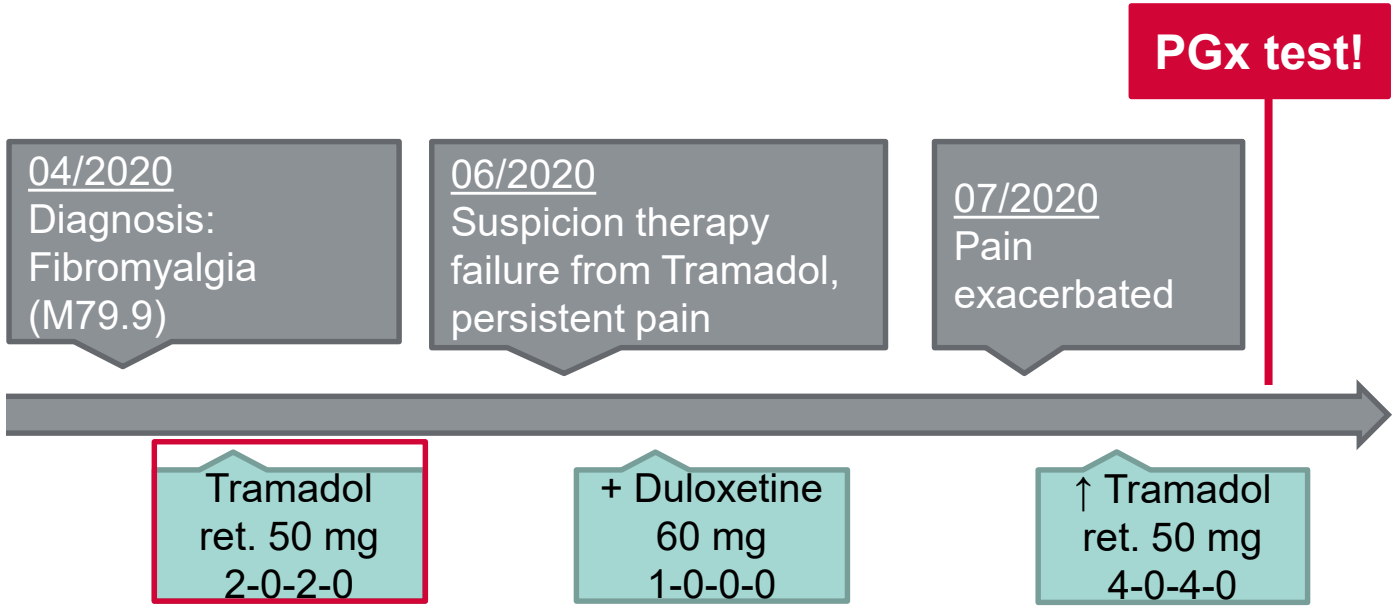
CYP2C19: 7 Associations

EXCURSUS: Case Example – Drug-Drug-Gene-Interaction (DDGI)

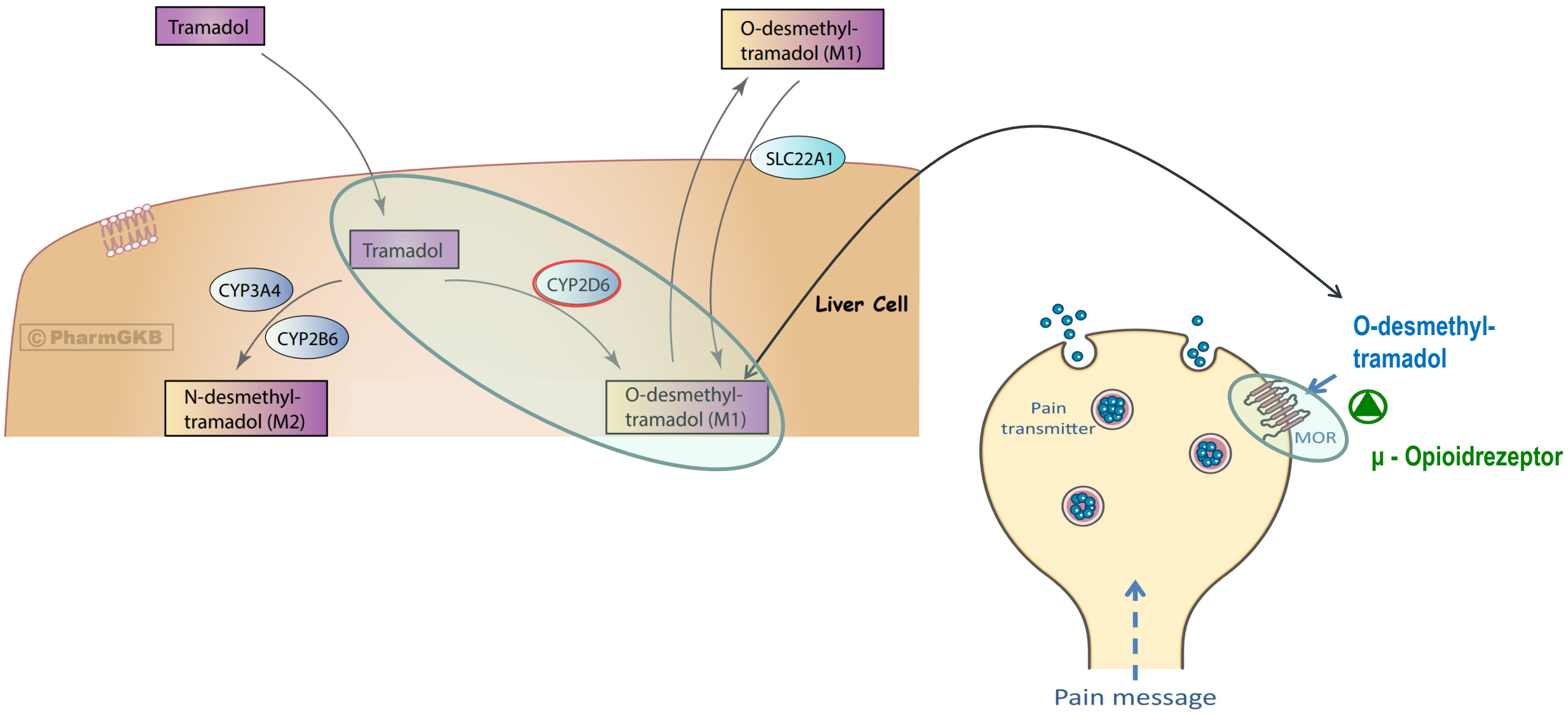
PRESENTATION
- Mrs. Doe, 55 years
- Chronic generalized musculoskeletal pain for 1 year
- Rheumatic inflammatory diseases ruled out

SUSPICION
- Therapy failure: Tramadol

RELEVANT PGX TESTING RESULT
- CYP2D6 *1/*4 (IM)



Pharmakokinetics: Tramadol – CYP2D6



Adapted from: www.pharmgkb.org & Faria J et al. *Eur J Pain*. 2018

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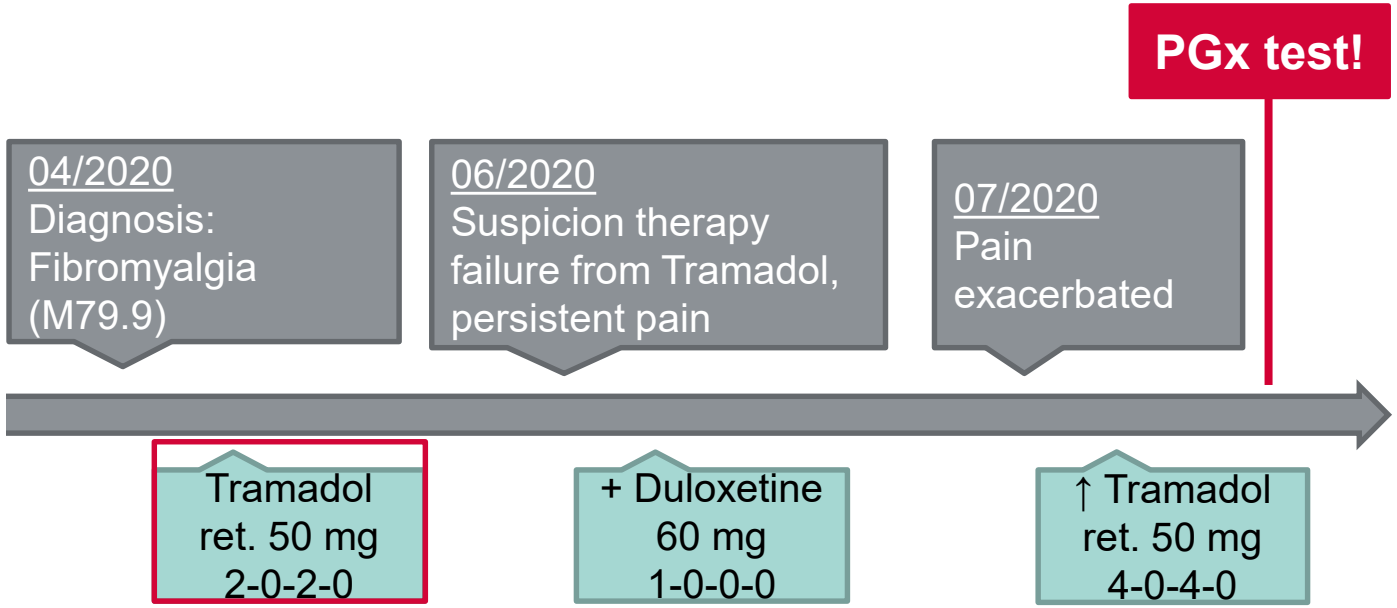

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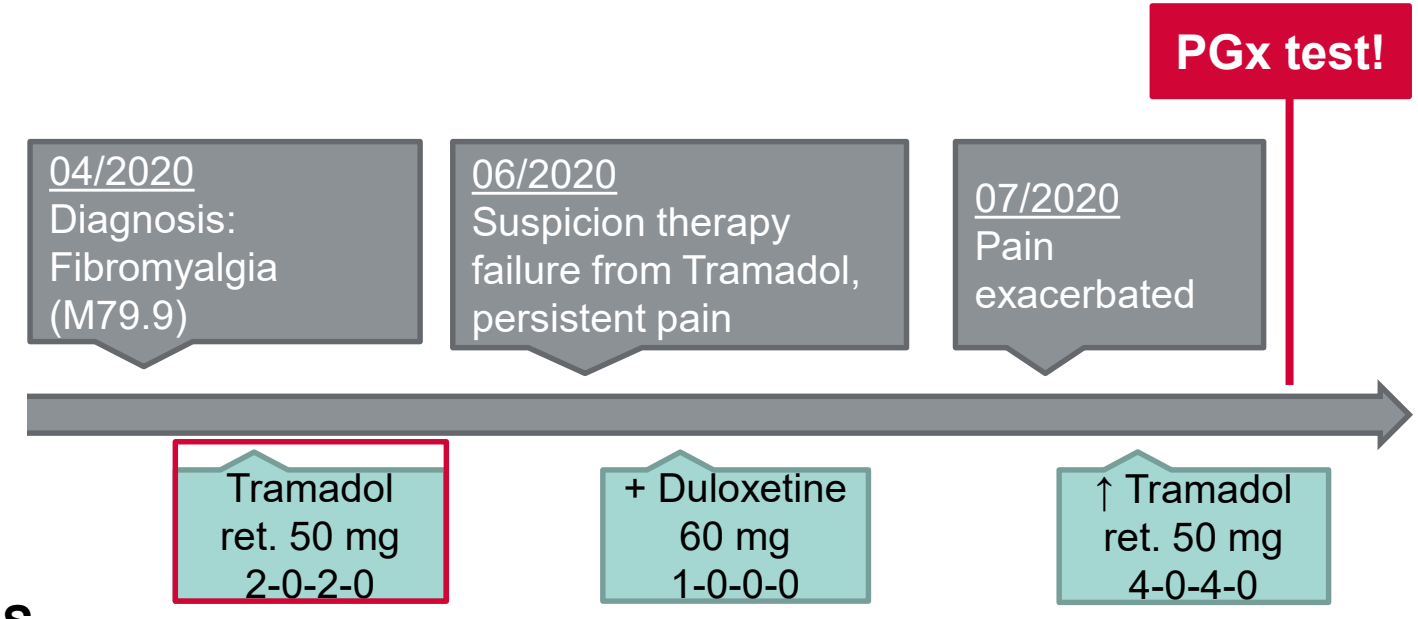
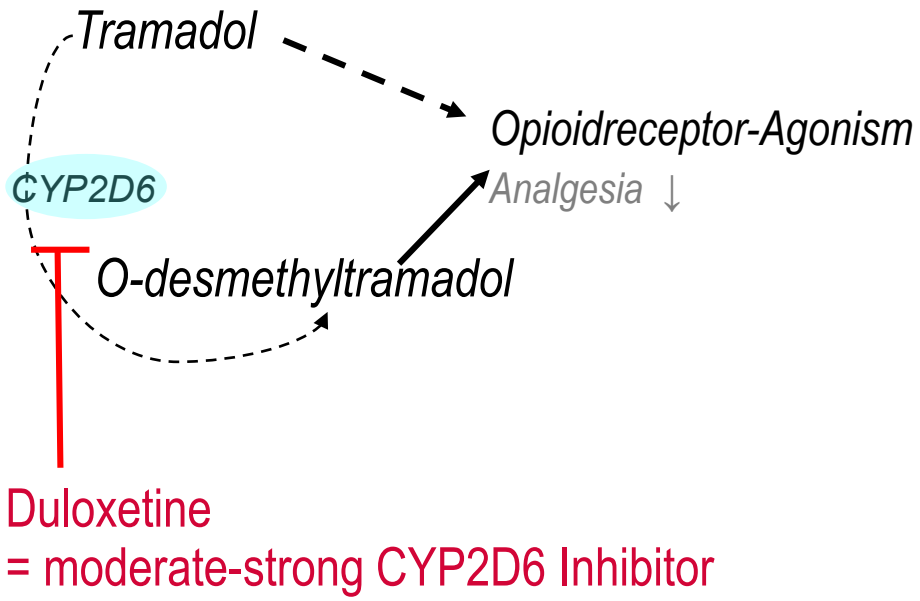
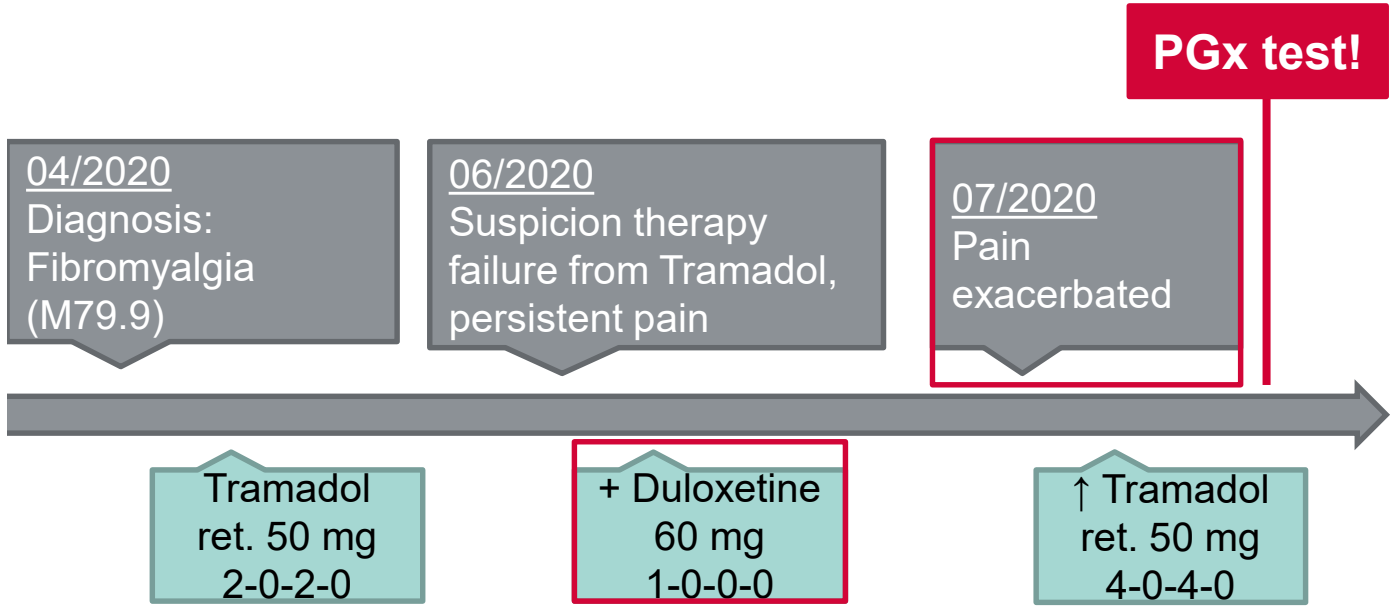


DPWG GUIDELINE FOR THE DRUG-GENE INTERACTION BETWEEN CYP2D6 AND OPIOIDS

Drug	CYP2D6 phenotype	Therapeutic recommendation
Tramadol	IM	1.**be alert** to a **reduced effectiveness** 2.**in the case of** inadequate effectiveness: 1.**try a dose increase** 2. **if this does not work: choose an alternative** Do not select codeine, as this is also metabolised by CYP2D6. Morphine is not metabolised by CYP2D6. Oxycodone is metabolised by CYP2D6 to a limited extent, but this does not result in differences in analgesia in patients. 3.**if no alternative is selected:** advise the **patient to report inadequate analgesia**

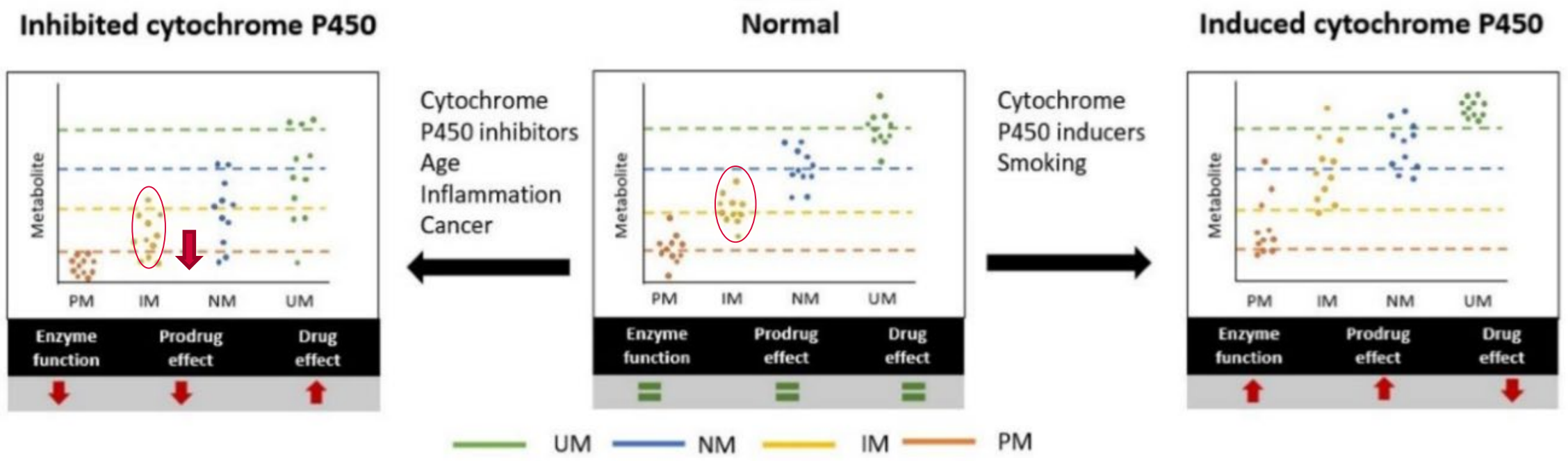
EXCURSUS: Case Example – Drug-Drug-Gene-Interaction (DDGI)





Phenoconversion:
CYP2D6 Intermediate Metabolizer → CYP2D6 Poor Metabolizer

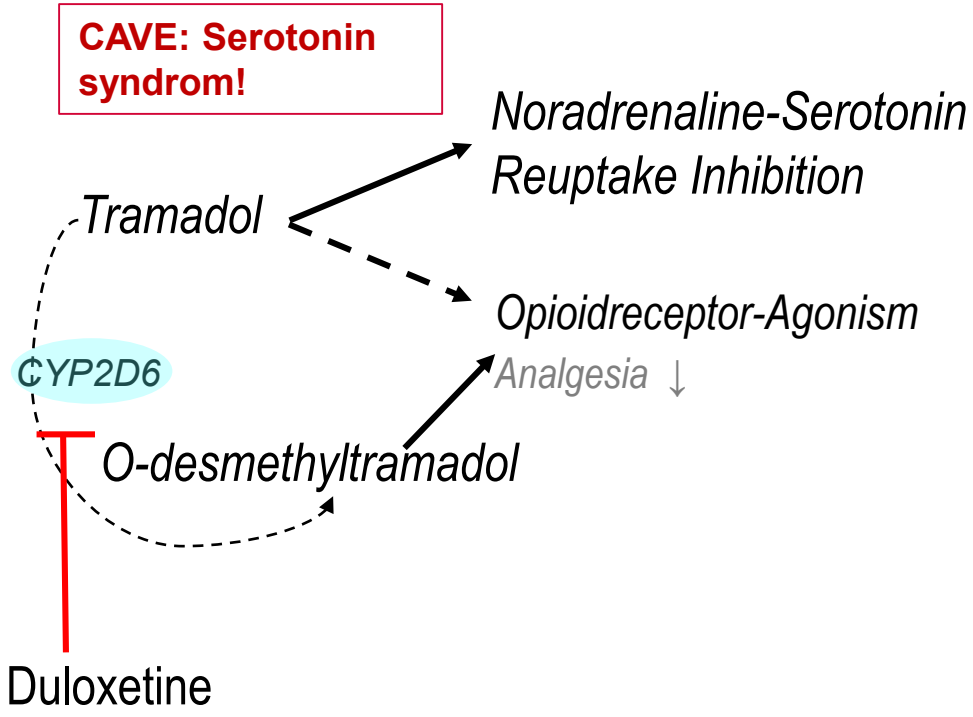
- Mrs. Doe genotype's predicted phenotype: CYP2D6 IM
- Duloxetine: moderate-strong CYP2D6 Inhibitor
- Tramadol: Active metabolite via CYP2D6

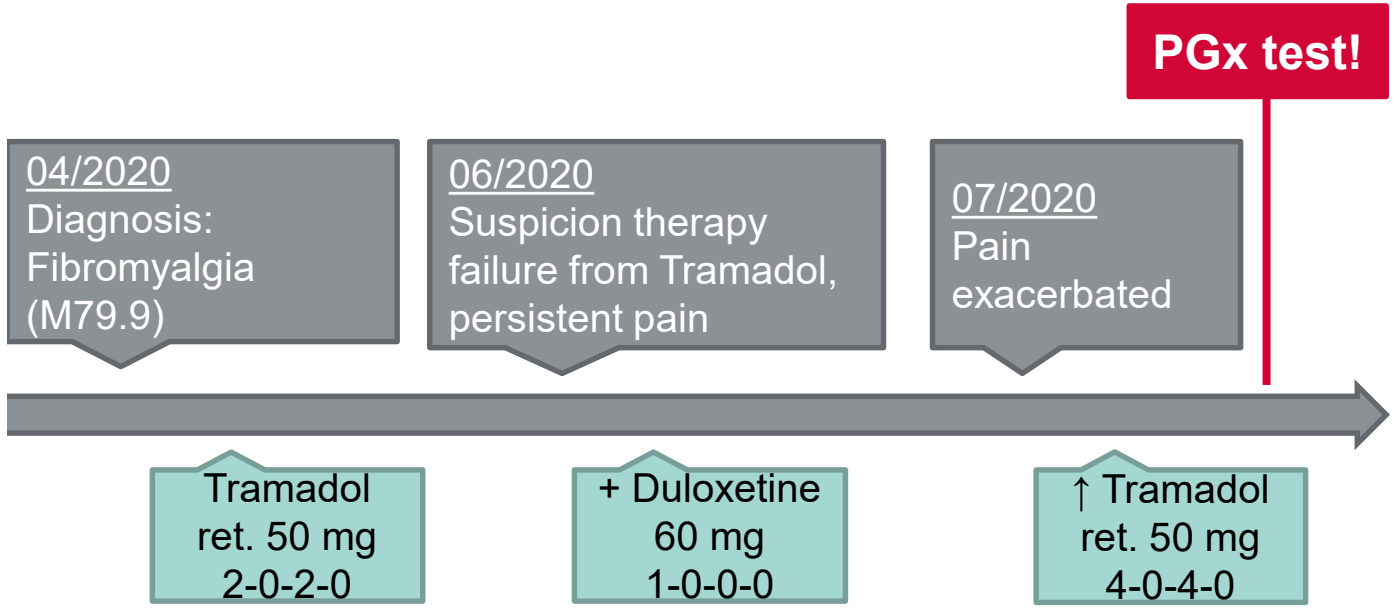


University of Florida, CYP2D6 Phenoconversion Calculator:
https://precisionmedicine.ufhealth.org/phenoconversion-calculator/

Klomp et al. *J. Clin. Med.*, 2020

EXCURSUS: Case Example – Drug-Drug-Gene-Interaction (DDGI)

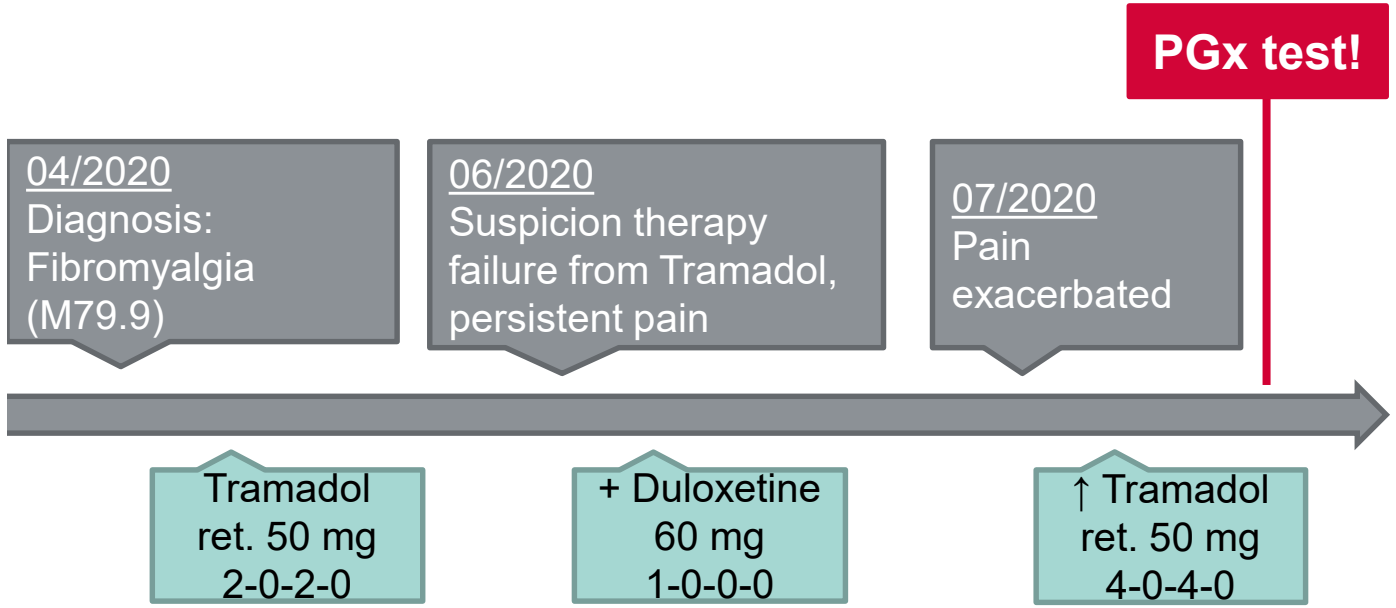




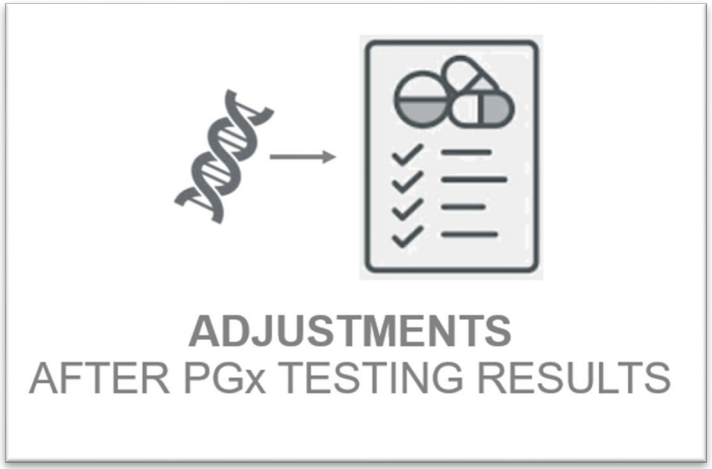
EXCURSUS: Case Example – Drug-Drug-Gene-Interaction (DDGI)

Pharmaceutical recommendation for Mrs. Doe:

- Tramadol, oxycodone, and codeine require activation via CYP2D6 for sufficient analgesic effect.
- Switch to an opioid, whose metabolism is not influenced by CYP2D6 (e.g. morphine, tapentadol)
- Duloxetine can be used as a co-analgesic (after switching to a non-CYP2D6 opioid).
  CAVE: Co-medication with CYP2D6 substrates.



Database Analysis Results: Medication Adjustments

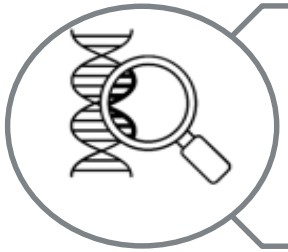


assessed after **6 months** of PGx testing

173 (n) medication adjustments
in **87** patients (62%)

examples for medication adjustments:
starting/ discontinuing of a drug,
dosage decrease/increase

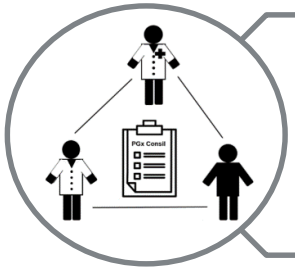
Conclusion & Outlook



PGx testing can be an effective method to detect the cause for ADR or TF

<u>suitable target groups:</u>

mental or behavioral disorders, circulatory diseases, musculoskeletal diseases, patients with polypharmacy



Implementation of PGx testing is **feasible**, but only as an **interdisciplinary approach**

PGx as **<u>one</u>** component of a complete medication review

Do not forget comorbidities, adherence, DDI and DDGI!

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Thank you
for your attention.

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Dr. Céline Stäuble
Dr. Fine Dietrich
Dr. Selina Barbati
Dr. Jennifer Alexa
Florine Wiss
Kirstin Messner
Julia Weber
Linnéa Wälti
Micheline Sarbach
Katharina Rekk
Ioana Maria Keller

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Prof. Henriette Meyer zu Schwabedissen
Isabell Seibert
Rebecca Meier
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Tanja Schüpbach
Julia Gianora

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