Leiden University Medical Center

# Preventing ADRs with Pharmacogenetics: *evidence from a prospective implementation study*

**MEB SCIENCE DAY 2023**

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## Disclosure belangen spreker

| (potentiële) belangenverstrengeling | Geen |
|---|---|
| Voor bijeenkomst mogelijk relevante relaties met bedrijven | Advisory boards Illumina, Agena |
| • Sponsoring of onderzoeksgeld<br>• Honorarium of andere (financiële) vergoeding<br>• Aandeelhouder<br>• Andere relatie, namelijk … | Horizon 2020 grant 668353 |

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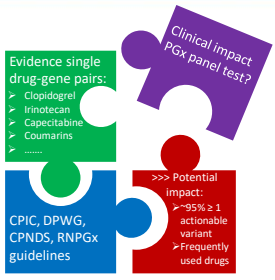
## Personalized medicine puzzle

*NEJM 2019;381:1621-1631*
*JAMA 2020;324(8):761-771*
*Eur J Cancer. 2022;162:148-157*
*Lancet Oncol 2018;19(11):1459-1467*
*NEJM 2013;369:2294-303*
*Lancet 2015 6;385(9984):2280-7*
*NEJM 2013;369:2304-12*




*Clin Pharmacol Ther 2008;83(5):781*
*Clin Pharmacol Ther 2011;89(5):662-73*

*Bank Eur J Hum Genet. 2019*
*Bank BMC Med 2019*

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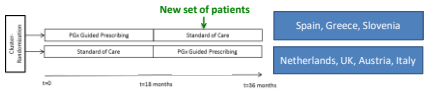
## *PRE*emptive *P*harmacogenomic testing for preventing *A*dverse drug *Re*actions (PREPARE)

- Design: Open-label, multicentre, controlled, cluster-randomised, crossover implementation study of a 12-gene PGx panel+ DPWG recommendations in 7 European countries
- Inclusion: 1st prescription for a drug with an actionable DPWG guideline
- Primary outcome: clinically relevant ADR by index drug in the 1st 12 weeks

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## Dutch Pharmacogenetics Working Group (n=107)

KNMP

**CYP2D6**
- Amitriptyline
- Aripiprazole
- Atomoxetine
- Carvedilol
- Citalopram
- Clomipramine
- Clozapine
- Codeine
- Doxepin
- Flecainide
- Flupentixol
- Haloperidol
- Imipramine
- Metoprolol
- Mirtazapine
- Nortriptyline
- Olanzapine
- Oxycodone
- Paroxetine
- Propafenon
- Risperidone
- Tamoxifen
- Tramadol
- Venlafaxine
- Zuclopenthixol

**DPYD**
- Capecitabine / 5-FU

**CYP2C9**
- Acenocoumarol
- Phenprocoumon
- Phenytoin
- Glibenclamide
- Glicazide
- Glimepride
- Tolbutamide

**UGT1A1**
- Irinotecan

**VKORC1**
- Acenocoumarol
- Fenprocoumon

**CYP3A5**
- Tacrolimus

**CYP2C19**
- Citalopram
- Clopidogrel
- Imipramine
- Lansoprazol
- Moclobemide
- (es)Omeprazol
- Pantoprazol
- Rabeprazol
- Sertraline
- Voriconazol

**TPMT**
- Azathioprine
- Mercaptopurine
- Thioguanine


DPYD + fluoropyrimidines[1]
CYP2D6 + Opioids[2]
CYP2D6, CYP2C19 + SSRIs[3]
UGT1A1 + irinotecan[4]
CYP2D6, COMT+ atomoxetine….[5]


Swen et al, CPT 2008;83(5):781
Swen et al, CPT 2011;89(5):662-73

[1]EJHG 28(4):508-517
[2]EJHG 2021 Sep 27
[3]EJHG 2021 Nov 16
[4]EJHG 2022 Nov 28
[5]EJHG 2022 Dec 12

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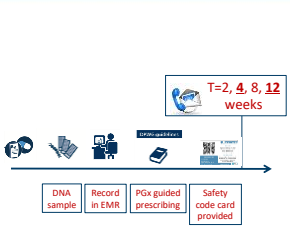
## Patient Journey Study Arm




**eCRF: ProMise**
Research Nurse Follow-up

Baseline*
4 weeks*
12 weeks*
End of Study

*For every newly prescribed drug of interest

**LIM**
Online Survey Follow-up

2 weeks*
8 weeks*

*For every newly prescribed drug of interest

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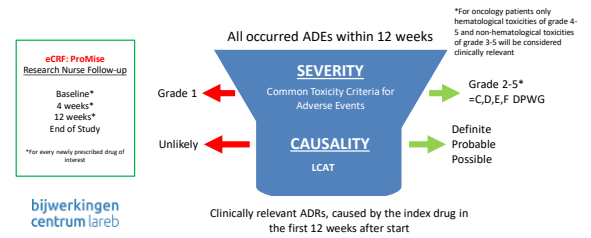
## Primary endpoint: clinically relevant ADR

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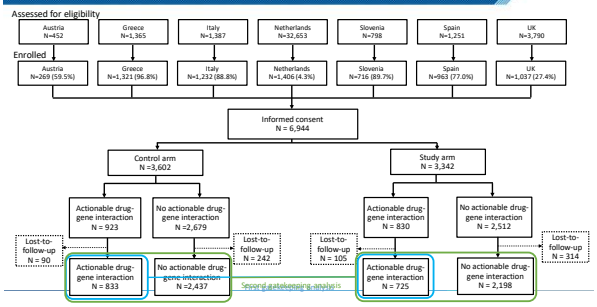
## Patient flow

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## Characteristics of the Patients at Baseline

| | All Patients n=6,944 | Study Arm n=3,342 | Control Arm n=3,602 |
|---|---|---|---|
| Age, median (IQR) | 57.3 (15.8) | 56.9 (15.7) | 59.0 (22.0) |
| Male | 48.6% | 47.5% | 49.6% |
| Global Health Score, mean (SD) | 0.69 (0.1) | 0.69 (0.1) | 0.70 (0.1) |
| Number of allergies, mean (SD) | 0.38 (1.0) | 0.36 (1.0) | 0.40 (0.9) |
| Number of comedications, mean (SD) | 7.88 (6.6) | 6.85 (5.8) | 8.83 (7.1) |
| Country, n (%) | | | |
| Austria | 269 (3.9) | 145 (4.3) | 124 (3.4) |
| Greece | 1,321 (19.0) | 684 (20.4) | 637 (17.7) |
| Italy | 1,232 (17.8) | 622 (18.6) | 610 (16.9) |
| Netherlands | 1,406 (20.2) | 643 (19.2) | 763 (21.2) |
| Slovenia | 716 (10.3) | 317 (9.5) | 399 (11.1) |
| Spain | 963 (13.9) | 489 (14.6) | 474 (13.1) |
| United Kingdom | 1037 (14.9) | 442 (13.2) | 595 (16.5) |

Lancet 2023 Feb 4;401(10374):347-356

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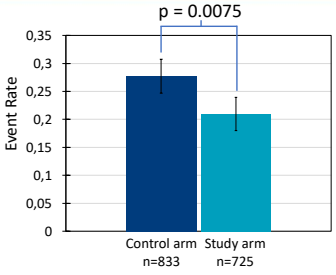
## Primary Endpoint: result in actionables (n=1,558)




- Intention-to-treat analysis
- 30% reduced ADR risk
- OR=0.70; 95% CI 0.54 – 0.91

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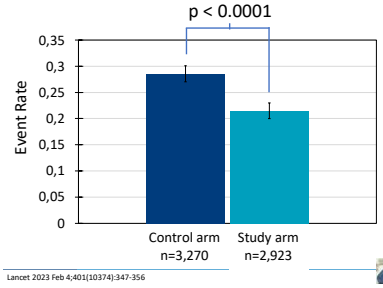
## Primary Endpoint: result in all patients




OR=0.70; 95% CI 0.61 – 0.79

Lancet 2023 Feb 4;401(10374):347-356

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## Conclusions

- 1st strategy study showing the benefits of a PGx panel approach across a diversity in EU health system organizations and settings
- **Substantially reduced risk for clinically relevant ADRs**
- U-PGx implemented important enabling tools:
  - DPWG guidelines in multiple languages and EJHG
  - Established PGx panel + proficiency testing (EMQN
  - Medication Safety Code Card + CDS system

22-03-23

- Provided PGx training, education, hands-on experience to healthcare professionals
- Evidence supporting implementation of PGx panel testing in all of EU

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## Thank you for your attention!

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www.upgx.eu


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