Leiden University Medical Center

Personalized Medicine with Pharmacogenetics: *from Promise to Practice*

GGG congres, Geneesmiddelen(technologie) op maat
11-04-2024

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Disclosure

(potentiële) belangenverstrengeling	Zie hieronder
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Advisory boards Illumina, Agena
• Sponsoring of onderzoeksgeld • Honorarium of andere (financiële) vergoeding • Aandeelhouder • Andere relatie, namelijk ...	

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Drug response can be improved

Effective (%).....

Asthma	60
Diabetes mellitus	57
Depression (SSRI)	62
Migraine (acute)	52
Migraine (proph)	50
Arrhythmia	60
Tumor	25
Schizophrenia	60
Rheumatoid arthritis	50

..... do cause ADRs

Spear, Trends Mol Med 2001;7(5):201

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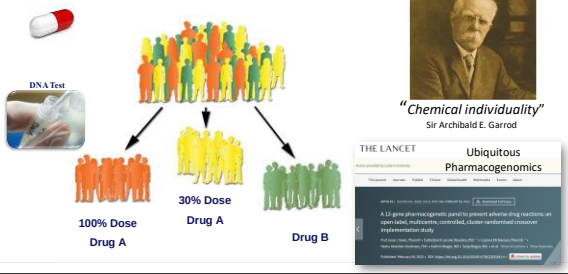
Pharmacogenetics



"*Chemical individuality*"
Sir Archibald E. Garrod

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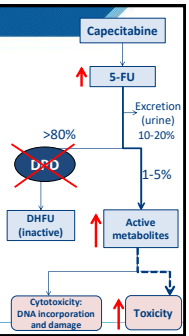
Poster child example: Fluoropyrimidines

- Widely used anticancer drugs
- 10-30% of patients develop severe (gr ≥3) tox
- ~1% of patients develops fatal toxicity
- DPD key role in fluoropyrimidine metabolism
- 3-5% of the population is deficient
- Deficiency is associated with substantially increased risk of severe / fatal toxicity
- Genetic variation



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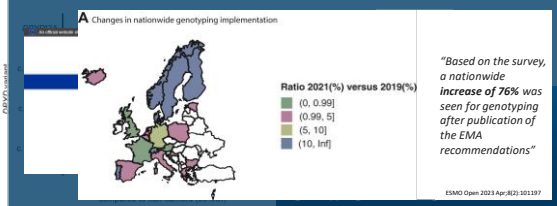
Results of the ALPE DPYD study (n=1,181)

THE LANCET Oncology



"Based on the survey, a nationwide ***increase of 76%*** *was seen for genotyping after publication of the EMA recommendations"*

ESMO Open 2023 Apr;8(2):101197

RR Fluoropyrimidine Related Tox

- *DPYD* genotyping strategy was cost-saving

Henricks LM et al Lancet Oncol 2018

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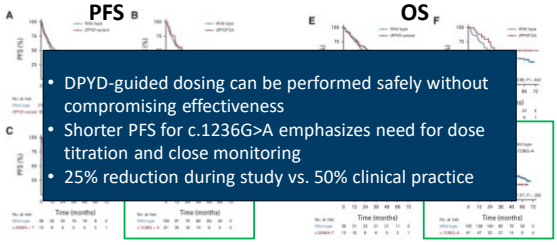
Survival of variant carriers with 25-50% dose reduction

156 *DPYD* variant carriers and 775 *DPYD* controls, Matched-Pair Analysis



- DPYD-guided dosing can be performed safely without compromising effectiveness
- Shorter PFS for c.1236G>A emphasizes need for dose titration and close monitoring
- 25% reduction during study vs. 50% clinical practice

J Clin Oncol. 2023 Dec 10;41(35):5411-5421

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Pre-therapeutic panel testing: a logical next step

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

Evidence single drug-gene pairs:
- Clopidogrel
- Irinotecan
- Capecitabine
- Coumarins
- .....

Clinical impact PGx panel test?

DPWG, CPIC, CPNDS, RNPGx guidelines

>>> Potential impact:
- ~95% ≥ 1 actionable variant
- Frequently used drugs

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
Bush Clin Pharmacol Ther 2016; 100(2):160-9

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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 test + DPWG recommendations** in 7 European countries
- Inclusion: 1st Rx for a drug with an actionable DPWG guideline (n=39)
- Primary outcome: clinically relevant ADR by index drug in the 1st 12 weeks

NCT03093818
Clin Pharmacol Ther 2017 101(3):341-358

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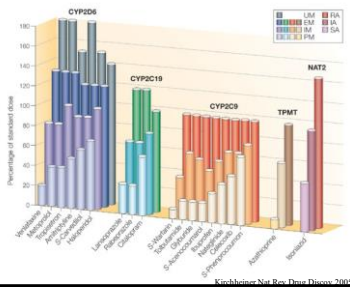
Tool 1: DPWG evidence-based PGx recommendations

- DPWG founded 2005
- Systematic literature review
- **Evidence-based** dose recommendations
- Available **point-of-care** + EJHG[1-5]

- Calculate dose adjustment to reach **similar exposure** as normal metabolizer

[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



Kirchheiner Nat Rev Drug Discov 2005

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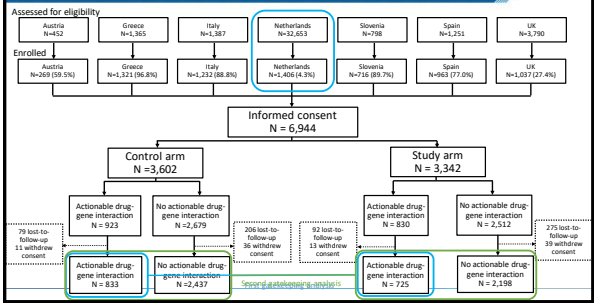
Patient flow



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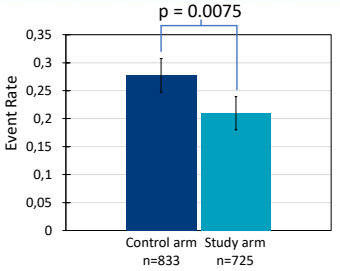
Primary Endpoint: result in actionables (n=1,558)



- 30% reduced ADR risk
- OR=0.70; 95% CI 0.54 – 0.91

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

U-PGx | Ubiquitous Pharmacogenomics

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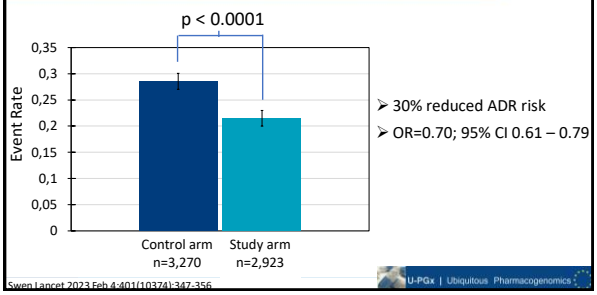
Primary Endpoint: result in all patients



- 30% reduced ADR risk
- OR=0.70; 95% CI 0.61 – 0.79

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

U-PGx | Ubiquitous Pharmacogenomics

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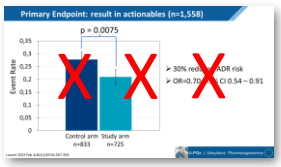
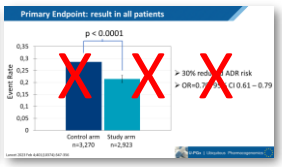
Changes in "case-mix" main contributor lack of dilution

Post-hoc analysis including index drug and an index drug-by-country interactions:





Actionables:
- Effect **increases**
- **OR 0.61** 95CI 0.51-0.74

All patients:
- Effect **decreases**
- **OR 0.87** 95CI 0.70-1.12

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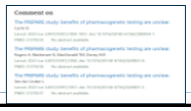
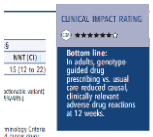
Outreach


The PREPARE study: benefits of pharmacogenetic testing are unclear – Authors' reply



- Blinding
- Causality
- Risk for undertreatment, efficacy not monitored
- Compromised effect, lack of dilution
- Patient reported outcomes
- Cost-effectiveness



Annals of Internal Medicine Vol. 176 No. 6 June 2023

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Cost-effectiveness analysis

- Overall analysis is ongoing
- 2 country specific analysis have been published and show positive results


Economic evaluation of pharmacogenomic-guided antiplatelet treatment in Spanish patients suffering from acute coronary syndrome participating in the U-PGx PREPARE study

The mean total cost of PGx-guided treatment was **50% less expensive** than conventional therapy with clopidogrel [€883 (95% UI, €316– €1582), compared to €1,755 (95% UI, €765–€2949)].

Hum Genomics. 2023 Jun 7;17(1):51


Pharmacological Research

Cost-utility analysis and cross-country comparison of pharmacogenomics-guided treatment in colorectal cancer patients participating in the U-PGx PREPARE study

Cost of the study arm was estimated at €380 (95%CI: 195–596) vs. €565 (95%CI: 340–724) of control arm while the mean survival in study arm was estimated at 1.58 (+0.25) LYs vs 1.50 (+0.26) (p=0.04). No statistically significant difference was found in QALYs. **ICER was estimated at €13.418 per QALY**

Pharmacol Res. 2023 Oct 5:197:106949

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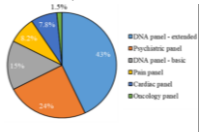
PGx application in Primary care in The Netherlands

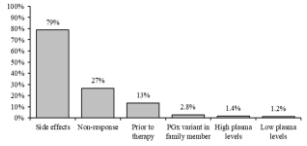
Implementation of Pharmacogenetics in First-Line Care: Evaluation of Its Use by General Practitioners

by Denise van der Drift [1], Mirjam Simoons [2], Birgit C. P. Koch [2], Gemma Brufau [1,3], Patrick Bindels [4], Maja Matic [1] and Ron H. N. van Schaik [1,*]

PGx panels were requested in 795/1206 patients (66%)



Main reasons for requesting PGx testing



Lack of knowledge is indicated as a major barrier, indicating the need for more education on PGx

Genes 2023, 14(10), 1841

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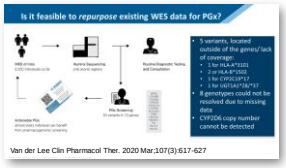
"*Complimentary*" pharmacogenetics

Increasing # patients receive a diagnostic genetic test:

- WES, WGS data in clinical genetics
- WGS data in oncology
- Biobanks

Common Medical Test/Scan/Med	Cost*
Head CT scan	$1,200
Abdominal CT scan	$1,420
MRI scan	$2,611
Echocardiogram	$1,300
10 "Most Important" Lab Tests*	$ 319
Crestor 1 year supply from Costco	$3,222
Xarelto 1 year supply from Costco	$4,444
3 Pharmacogenetic tests Quest*	$ 975
Whole Genome Sequence	**$ 999**



Van der Lee Clin Pharmacol Ther. 2020 Mar;107(3):617-627

mijndnamedicatiepas.nl

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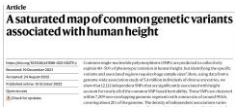
Next steps:

>> **Identify subgroups that benefit most**


Informatiepagina subsidieronde Personalised Medicine Farmacogenetica

Programma Goed Gebruik Geneesmiddelen
oktober 2023

>> **Improve ability to predict**


Article
A saturated map of common genetic variants associated with human height

- Height, is highly heritable (and easily measured)
- Common SNVs together explain 40-50% of variation in height
- Original GWASs (2007→) explained only a minor fraction
- Meta-analysis (**n=5.4 million**) identified **12,111 SNVs** that together account for the genetic variation

>> Need for larger datasets with well defined drug-response phenotypes
>> Initiatives such as **1+MG working group on pharmacogenetics**

Nature 2022 Oct;610(7933):704-712.

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Take home messages

- Evidence for **single drug gene-pairs** and **guidelines** to assist in PGx result interpretation available at point-of-care
- **~95% of the population** has ≥1 actionable genotype and **drugs** with PGx recommendation are **commonly used**
- PREPARE showed clinical implementation of **PGx panel** testing is **feasible, effective**, and **improves patient outcome**
- Clinical PGx is moving from:
  - Single gene → Panel ✓ → WGS?
  - Reactive → Pre-therapeutic ✓ → Pre-emptive?
- **Challenges for implementation**: cost-consequences, identifying "who benefits most", reimbursement, education, sharing data, changing medical practice
- **Opportunities**: rapid technological developments, increasing ability to predict drug response, building large cohorts with drug response phenotypes

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Thank you for your attention!

Horizon 2020 grant 668353

Hotel grant 435004018

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