One non-believer: response to "Obviously Nine Believers: Actionable Germline Genetic Variants for Pre-emptive Pharmacogenetic Testing"

Wouden, C.H. van der; Rhenen, M.H. van; Jama, W.O.M.; Ingelman-Sundberg, M.; Lauschke, V.M.; Konta, L.; ... ; Guchelaar, H.J.

Received: 25 September 2019 | Accepted: 25 September 2019

DOI: 10.1111/bcpt.13336

LETTER TO THE EDITOR

BCPT Basic & Clinical Pharmacology & Toxicology

One non-believer: Response to "Obviously Nine Believers: Actionable Germline Genetic Variants for Pre-emptive Pharmacogenetic Testing"

Dear Editor,

Dr Damkier presents an interesting, yet provocative, response to our recently published manuscript, claiming the narrative of the manuscript is "disproportional to the supporting evidence." The dichotomy between believers and non-believers is a concept that is commonly observed in the field of pharmacogenetics (PGx). As a non-believer, the presented concerns by Damkier include: the insufficiently substantive statement that a panel may be used to guide prescribing for 49 drugs, the lacking evidence for individual drug-gene interactions to be labelled as "actionable" and the undetermined evidence threshold required for clinical implementation. In contrast to considering ourselves believers, we consider ourselves rationally convinced of the clinical utility of pharmacogenetic testing based on the currently available data, regardless of the fact that these are not fully conclusive yet.

Firstly, we do not agree that stating that the presented panel can be used to guide prescribing for 49 drugs is insufficiently substantiated. In the original article, we stated that the published panel may be used in combination with the currently available DPWG recommendations. As such, we do not mandate either PGx panel testing or subsequent adherence to the DPWG recommendations. Interestingly, Damkier's argument, however, does highlight the demand for evidence supporting a PGx panel-based approach. While a number of small randomized and observational studies indicate promising clinical utility of PGx panel testing,[1-5] a sufficiently powered prospective study assessing the effectiveness of pre-emptive PGx panel testing is ongoing: the PREPARE study from the EU sponsored U-PGx consortium.[6] Currently, over 5,500 patients have been enrolled, and the trial is aiming to report by the end of 2020.

Secondly, Damkier uses the example of the promised outcomes of the Human Genome Project by the NHGRI to illustrate his concerns. However, the chosen example concerns the application of genetics in the development of novel designer drugs. In contrast, we simply presented a potential application of an individual's genetic profile to guide the dose and drug selection of approved drugs. Our example is one of the few examples of the successful applications of genetics in drug treatment. Although uptake into routine care has been gradual, currently approximately 15% of all drug labels include PGx information. Moreover, *HLA-B, TPMT* and *DPYD* testing to mitigate the risk of toxic adverse drug reactions before initiation of abacavir, thiopurines and fluoropyrimidines, respectively, is becoming routine practice across the globe. Additionally, the potential impact of PGx in patient care is also considerable with 95% of the population carrying an actionable variant and 5.4% of all new prescriptions in primary care potentially requiring an adjustment based on available guidelines.[7]

Thirdly, Damkier challenges the conceptual use of the term "actionable" stating that the designation of this term does not make an intervention meaningful. Although we agree with this perspective, we do not agree that the action may not be beneficial to the patient. The term "actionable" designates an intervention, such as dose adjustment, may be undertaken to optimize patient outcome, at the discretion of the treating clinician and should always be considered in the context of other available patient-specific data. Currently, over 150 guidelines are available from DPWG and CPIC.[8] Guidelines are based on systematic literature review and peer-reviewed. Initially, both consortia provided guidance for patients with a known genotype, and no recommendations on whom to test were provided. However, as underpinned by Damkier's argument, there is an increasing demand for clarity regarding when testing should be mandated. In an effort to overcome this lack of clarity and guide clinicians on requesting relevant PGx tests before initiating drug treatment, the DPWG has recently developed a Clinical Implication Score indicating if a PGx test is "Essential," "Beneficial" or "Potentially beneficial".[9] Only in the case of "Essential," pre-emptive testing is recommended. An example of a guideline with an "Essential" score is the *DPYD*-fluoropyrimidine guideline and with a "Potentially beneficial" score is the *CYP2D6*-amitriptyline guideline.

Lastly, Damkier initiates an interesting discussion on what the evidence threshold should be for clinical implementation of PGx testing. Indeed, multiple randomized, controlled trials (RCTs) supporting the effectiveness of testing for a single gene to guide dose and drug selection have been reported,[10-14] including a recent prospective study showing the

effectiveness of *CYP2C19* genotype-guided selection of oral P2Y12 inhibitors in primary percutaneous coronary intervention.[15] The discussion on what level of evidence is required remains ongoing. It is important to note that non-pharmacogenetic interventions, such as adjusting a dose based on renal function have been widely implemented into the clinic based on pharmacological reasoning, despite the availability of randomized, controlled trials for each individual drug. In fact, ignoring such knowledge in treating patients is considered malpractice. Genetic exceptionalism has been held responsible for this double standard.[16]

In conclusion, we share Damkier's aim to improve patient treatment and agree that scientific enthusiasm should not exempt us from generating sufficient evidence quantifying the effectiveness of PGx testing. We look forward to the results of the PREPARE study to provide initial proof of concept evidence providing and in the meantime rationally embrace the concept to use pharmacological knowledge to improve the care of our patients.

Cathelijne H. van der Wouden[1,2]
Mandy H. van Rhenen[3]
Wafa O. M. Jama[3]
Magnus Ingelman-Sundberg[4]
Volker M. Lauschke[4]
Lidija Konta[5]
Matthias Schwab[6,7]
Jesse J. Swen[1,2]
Henk-Jan Guchelaar[1,2]

[1]*Department of Clinical Pharmacy & Toxicology, Leiden University Medical Center, Leiden, The Netherlands*
[2]*Leiden Network for Personalised Therapeutics, Leiden, The Netherlands*
[3]*Royal Dutch Pharmacists Association (KNMP), The Hague, The Netherlands*
[4]*Department of Physiology and Pharmacology, Section of Pharmacogenetics, Biomedicum 5B Karolinska Institute, Stockholm, Sweden*
[5]*bio.logis Center for Human Genetics, Frankfurt am Main, Germany*
[6]*Dr. Margarete Fischer-Bosch Institute of Clinical Pharmacology, Stuttgart, Germany*
[7]*Department of Clinical Pharmacology and Departments of Biochemistry and Pharmacy, University Tuebingen, Tuebingen, Germany*

Correspondence
Henk-Jan Guchelaar, Department of Clinical Pharmacy & Toxicology, Leiden University Medical Center, P.O. Box 9600, NL 2300 RC Leiden, Leiden, The Netherlands.
Email: H.J.Guchelaar@lumc.nl

REFERENCES

1. Elliott LS, Henderson JC, Neradilek MB, Moyer NA, Ashcraft KC. Thirumaran RK. Clinical impact of pharmacogenetic profiling with a clinical decision support tool in polypharmacy home health patients: a prospective pilot randomized controlled trial. *PLoS ONE*. 2017;12(2):e0170905.
2. Brixner D, Biltaji E, Bress A, et al. The effect of pharmacogenetic profiling with a clinical decision support tool on healthcare resource utilization and estimated costs in the elderly exposed to polypharmacy. *J Med Econ*. 2016;19(3):213-228.
3. Pérez V, Salavert A, Espadaler J, et al. Efficacy of prospective pharmacogenetic testing in the treatment of major depressive disorder: results of a randomized, double-blind clinical trial. *BMC Psychiatry*. 2017;17(1):250.
4. Walden LM, Brandl EJ, Tiwari AK, et al. Genetic testing for CYP2D6 and CYP2C19 suggests improved outcome for antidepressant and antipsychotic medication. *Psychiatry Res*. 2019;279:111-115.
5. Espadaler J, Tuson M, Lopez-Ibor JM, Lopez-Ibor F, Lopez-Ibor MI. Pharmacogenetic testing for the guidance of psychiatric treatment: a multicenter retrospective analysis. *CNS Spectr*. 2017;22(4):315-324.
6. van der Wouden CH, Cambon-Thomsen A, Cecchin E, et al. Implementing pharmacogenomics in europe: design and implementation strategy of the ubiquitous pharmacogenomics consortium. *Clin Pharmacol Ther*. 2017;101(3):341-358.
7. Bank P, Swen JJ, Guchelaar HJ. Estimated nationwide impact of implementing a preemptive pharmacogenetic panel approach to guide drug prescribing in primary care in the Netherlands. *BMC Med*. 2019;17(1):110.
8. Bank P, Caudle KE, Swen JJ, et al. Comparison of the guidelines of the clinical pharmacogenetics implementation consortium and the dutch pharmacogenetics working group. *Clin Pharmacol Ther*. 2018;103(4):599-618.
9. Swen JJ, Nijenhuis M, van Rhenen M, et al. Pharmacogenetic information in clinical guidelines: the European perspective. *Clin Pharmacol Ther*. 2018;103:795-801.
10. Pirmohamed M, Burnside G, Eriksson N, et al. A randomized trial of genotype-guided dosing of warfarin. *N Engl J Med*. 2013;369(24):2294-2303.
11. Wu AH. Pharmacogenomic testing and response to warfarin. *Lancet*. 2015;385(9984):2231-2232.
12. Verhoef TI, Ragia G, de Boer A, et al. A randomized trial of genotype-guided dosing of acenocoumarol and phenprocoumon. *N Engl J Med.* 2013;369(24):2304-2312.
13. Coenen MJ, de Jong DJ, van Marrewijk CJ, et al. Identification of patients with variants in TPMT and dose reduction reduces hematologic events during thiopurine treatment of inflammatory bowel disease. *Gastroenterology*. 2015;149(4):907-17.e7.
14. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med*. 2008;358(6):568-579.
15. Claassens D, Vos G, Bergmeijer TO, et al. A genotype-guided strategy for oral P2Y12 inhibitors in primary PCI. *N Engl J Med*. 2019. [Epub ahead of print]. https://doi.org/10.1056/NEJMoa1907096
16. Relling MV, Altman RB, Goetz MP, Evans WE. Clinical implementation of pharmacogenomics: overcoming genetic exceptionalism. *Lancet Oncol*. 2010;11(6):507-509.