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The impact of non-genetic factors on drug metabolism: towards better phenotype predictions

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Citation
Jong, L. M. de. (2025, June 5). *The impact of non-genetic factors on drug metabolism: towards better phenotype predictions*. Retrieved from https://hdl.handle.net/1887/4249242

Version:	Publisher's Version
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Downloaded from:	https://hdl.handle.net/1887/4249242

Note: To cite this publication please use the final published version (if applicable).

Chapter 7

General discussion and perspectives

General discussion

Personalized medicine is anticipated to replace the conventional 'one-size-fits-all' approach to pharmacological treatments, enhancing both the efficacy and safety of therapy. The discovery of genetic variants that impact drug response, and subsequent implementation of guidelines on dose optimization for certain drug-gene pairs has greatly advanced our ability to tailor treatment to individual patients. However, not all variability in drug metabolism can be explained by current PGx. Besides heritable traits, metabolic activity of DMEs is also modulated by non-genetic factors, including concomitant medication and (inflammatory) comorbidities. In order to ultimately incorporate the impact of non-genetic factors into drug metabolizing phenotype predictions, it is imperative to acquire a quantitative understanding of the magnitude and duration of phenoconversion due to non-genetic factors. This thesis explores how non-genetic factors impact hepatic drug metabolism. In section I, we focus on the role of concomitant medication as a contributor to phenoconversion and its impact on drug metabolizer phenotype predictions. Section II delves into (pre)clinical evaluations of inflammation-induced alterations in drug metabolism and the potential of immunomodulating therapeutics to reverse these alterations. Section III moves to in vivo tools for studying alterations in enzyme activity and examines whether the CYP phenotyping cocktail approach accurately reflects alterations in enzyme activity under inflammatory and other (patho)physiological conditions. Together, these sections provide a comprehensive exploration of the non-genetic factors that influence drug metabolism, with the aim of improving drug metabolizing phenotype predictions and ultimately guiding more personalized treatment.

The prevalence of phenoconversion

It is important to get a grasp of the scale of phenoconversion in order to evaluate its clinical relevance. The scale of phenoconversion is likely dependent on several factors, including the characteristics of the patient population, their underlying comorbidities, and the type and dosage of concomitant medication (1). In the cohort of liver microsomes from 40 different patients included in chapter 2, we observed a 40% concordance between genetically-predicted CYP2C19 phenotypes and measured phenotypes, indicating substantial phenoconversion. This aligns with

findings from Kiss et al., who also reported a 40% concordance in a cohort of 114 CYP2C19 genotyped microsomes (2). In both cohorts, a significant increase in the amount of PMs was observed, that was not predicted based on genotype data. This can have significant clinical implications, as alterations in drug PK can be expected when the individual has a limited capacity in the primary metabolic pathway.

Discrepancies between genotype and phenotype are also observed in larger clinical PK studies. Lorenzini et al. found low concordances between genotype-predicted and measured phenotypes across several CYP enzymes including CYP2B6, 2C9, 2C19, 2D6 and 3A4/5, with genetically predicted NMs and UMs generally showing lower concordances compared to IMs and PMs (3). For example, the CYP2C19 PM phenotype was correctly predicted by PGx in 100% of patients, and the IM phenotype in 91% of patient. In contrast, PGx correctly predicted the phenotype in only 33% of NMs and 19% of UMs. These patterns of phenoconversion for key DMEs have been observed across different ethnic groups (4–6). Notably, discrepancies between genotype-predicted and observed CYP2C19 phenotype were also found in a healthy patient population without liver disease or drugs affecting CYP2C19 activity, were only approximately 20% of phenotypes were accurately predicted by PGx (7).

Importantly, the quantification of phenoconversion is highly dependent on the set thresholds between phenotype groups. Currently there is no standardized methodology for defining these thresholds – although efforts are made to address this challenge, at least for CYP2C19 phenotyping (7). As such, the extent of phenoconversion may vary according to the method applied, calling for a more uniform framework for phenotype thresholds to enhance consistency across studies. More real-world data is required to identify the prevalence of phenoconversion across different therapeutic contexts, and more importantly, to understand when a phenotype switch leads to clinically relevant change in efficacy or safety of a drug.

Section I: Impact of concomitant medication on drug metabolizer phenotype predictions

Phenoconversion due to the use of concomitant medication can reduce the accuracy of PGx-based drug dosing. For example, 32–47% of phenoconversion of CYP2C19 and CYP2D6 could be attributed to concomitant medication use (3). Integrating knowledge of drug-drug and drug-gene interactions remains a complex

challenge. There is however consensus that drug-gene guidelines should consider the influence of CYP inducers and inhibitors on PGx-phenotype predictions. For example, CPIC guidelines on CYP2C19 PGx and proton pump inhibitor dosing warn for a potential interaction when a PPI and a CYP inhibitor/inducer are co-administered chronically in CYP2C19 IMs or PMs, recommending interaction monitoring (8). Similarly, CYP2C19 PGx and clopidogrel guidelines emphasize that the impact of additional drugs in combination with CYP2C19 genotype warrants further investigations (9).

To provide concrete dosing recommendations for these potential DDGIs, it is crucial to gain an understanding of the phenoconversion that occurs following the administration of inhibiting or inducing concomitant medication, and whether this interaction is different for different genotypes. As such, in chapter 2, utilizing human liver microsomes, we quantified the phenoconversion in various CYP2C19 genotype groups following administration of either a strong (fluvoxamine), moderate (omeprazole or voriconazole) or weak (pantoprazole) inhibitor of CYP2C19. The relative CYP inhibition by the inhibitors was consistent across genotypes, but the outcome of phenoconversion varied per genotype, e.g. voriconazole caused IM/PM phenotypes in 50% of genetically-predicted NMs, but in only 14% of genetically-predicted RM patients. We subsequently concluded that the degree of phenoconversion is dependent on 1) the inhibitor strength, since phenoconversion towards a lower metabolic phenotype was more frequent with stronger CYP2C19 inhibitors, and 2) the basal CYP2C19 activity, which is only in part dictated by genotype. These findings were confirmed in a large clinical study in healthy volunteers with a similar objective, which showed that overall more than 80% of volunteers experienced phenoconversion to a lower phenotype upon fluvoxamine and/or voriconazole – with RMs experiencing the greatest shifts in metabolic ratios upon inhibition (7). Consequently, accounting for concomitant medications in phenotyping predictions appears essential for the optimization of PGx-based personalized therapy.

Section II: (Pre)clinical evaluation of inflammation-induced alterations in drug metabolism

Inflammation is shown to have major effects on the metabolism of drugs – primarily through downregulation of CYP enzymes – and hence contribute to

phenoconversion (1,10,11). The impact of inflammation on drug metabolism is well recognized but not yet well understood. A more profound understanding of the impact of inflammation on DMEs necessitates better insights into the mechanisms driving these changes. In chapter 3, we summarized how repression of important CYP enzymes during inflammation may proceed through 1) transcriptional downregulation of nuclear factors and other transcription factors which regulate the CYPs, 2) interference with dimerization or translocation of these (nuclear) transcription factors, 3) altered liver-enriched C/EBP signaling, 4) direct regulation of CYP expression by NF-κb, or 5) via post-transcriptional mechanisms. Here, the general consensus is that transcriptional alterations are the main regulatory mechanisms accountable for altered CYP activity during inflammation. This is supported by our analysis on the effects of IL-6 and IL-1β on DME expression and activity in chapter 4, where 90% of variability in DME activity was attributable to transcriptional changes (R2=0.9). These transcriptional changes might, in part, result from the inhibition of transcription factors that regulate DME expression (chapter 4). Consequently, it appears that transcriptional changes are significant drivers of altered enzyme activity in inflammation, at least in an in vitro setting.

Ultimately, we would like to identify for which inflammatory diseases and for which drugs the inflammation-induced changes in metabolism might result in clinically relevant alterations in drug efficacy or safety. Based on evidence assembled in this thesis, we conclude that the impact of inflammation on drug metabolism is multifaceted and contingent upon several critical factors:

1. **The type of inflammation or cytokine profile** is a key factor determining how DMEs are affected. The evidence assembled through in vitro liver models as summarized in chapter 3 highlights that the pro-inflammatory cytokines IL-6, IL-1β, TNF-α as well as lipopolysaccharides (LPS) exert the strongest suppressive effects on various CYPs, whereas cytokines like IL-22, IL-23 or IL-2 have minimal to no effect. Further supporting this, studies with immunomodulating biologics have shown cytokine-specific successes in reversing the inhibitory effects on CYP-mediated drug clearance. Chapter 5 systematically reviewed 12 clinical studies investigating the potential of immunomodulatory antibodies to counteract inflammation-induced CYP downregulation, with three trials highlighting risks associated with IL-6 targeting mAbs. No changes in PK

of probe drugs was observed following administration of mAbs targeting IL-2, IL-4R or IL-23. Incorporating evidence from in vitro and clinical trials, the EMA and FDA assesses the risk for these DDDIs and advices on this in the drug label. The analyzed labeling information designated the greatest risk for DDDIs to mAbs that neutralize the effects of IL-6, TNF-α and IL-1β, where for the latter two this is mainly based on in vitro work. Collectively, the data from chapter 3 and 5 indicate that patients suffering from inflammatory conditions that are marked by elevated levels of IL-6, IL-1β an TNF-α are likely to experience changes in CYP-mediated drug metabolism – whereas this is less likely in IL-17/IL-23-axis inflammatory diseases such as psoriasis.

2. **The degree of inflammation** is another determinant influencing the impact of inflammation on DMEs and subsequent clearance, as outlined in chapters 4 and 5. Whereas mAbs targeting IL-6 do result in restored CYP-mediated clearance of probe substrates in RA patients, this is not evident for mAbs targeting IL-6 in patient populations with lower levels of pro-inflammatory cytokines, such as kidney transplant patients. This is supported by the concentration-dependent effects of pro-inflammatory cytokine treatment on DME expression and activity in the HepaRG cell model presented in chapter 4. As such, when pro-inflammatory cytokines are only marginally elevated in the patient population, the risk for an alteration in drug metabolism is low. In line with this, the FDA advises investigating DDDIs in the population with the highest inflammatory burden (12).
3. The impact of inflammation and the magnitude of the alteration in drug PK might also be dependent on the **metabolic clearance route of the drug**. Data from in vitro models as summarized in chapter 3 have been instrumental to elucidate that CYP isoforms show distinct susceptibility to downregulation by inflammatory mediators wherein CYP3A4, CYP2C19 and CYP1A2 seems to be most affected by pro-inflammatory cytokine treatment, supporting clinical observations (13,14). Differences between DME families are also observed. In chapter 4, our concentration-response experiments defined differences in both the potency and efficacy of cytokines in inducing downregulation of

individual DME family members. The rank ordering revealed that CYP isoforms were the most responsive to IL-6 and IL-1β modulation, while enzymes from the FMO, CES, and UGT families consistently showed lower sensitivity. This differential sensitivity is confirmed by clinical observations. For example, posaconazole, metabolized by UGT1A4, showed no change in exposure related to CRP levels, whereas voriconazole, metabolized mainly by CYP2C19 and 3A4, exhibited increased trough levels during inflammatory conditions (15–17). This highlights the greater susceptibility of CYP-mediated clearance pathways towards inflammation. These findings suggest that inflammation may differentially affect drug PK depending on the relative contribution of DMEs involved in its clearance pathways. Subsequently, drugs relying on secondary or non-CYP pathways for clearance may be less affected by inflammatory processes than those predominantly metabolized by CYP enzymes.

4. Little is known about how **genetics** might predispose an individual towards the impact of inflammation on drug metabolism, but there are some hints for a genotype-dependent effect of inflammation on drug metabolism (chapter 3). These mainly stem from clinical studies that highlight a greater shift in CYP-specific metabolic ratios upon inflammation in RMs or NMs, as compared to IMs or PMs (18,19). Larger clinical trials that simultaneously investigate inflammatory status and pharmacogenetics are important to decipher whether genotype is a determinant in the impact of inflammation on drug metabolism.

Section III: In vivo tools to study alterations in drug metabolism during (inflammatory) disease

Ultimately, it is of interest to understand how the described changes in DME activity during inflammation translate to alterations in drug clearance in patients. Beyond enzyme activity, several factors – including protein binding, the blood-to-plasma ratio, and hepatic blood flow – also drive clearance and may be impacted by inflammation. As discussed in chapter 6, in vivo clearance data obtained using phenotyping cocktail approaches cannot always be directly attributed to changes in metabolism alone. Through PBPK modeling, we demonstrated that plasma

clearance of 13 commonly used phenotyping probes was not only sensitive to alterations in enzyme activity but also to changes in protein binding. Given that drug binding proteins may change under inflammatory conditions, such variations must be taken into account when using probe drugs clearance as a proxy for CYP enzyme activity in patient populations with inflammatory comorbidities. This can be achieved by using the R script provided in chapter 6. In light of phenotyping studies conducted in patient populations with inflammatory disease, the reported absolute percentual changes in CYP activity should be interpreted with care, as they may reflect not only changes in enzyme activity but also shifts in protein binding and/or blood-to-plasma ratio or hepatic blood flow during disease. This was recently confirmed in a cohort of liver cirrhosis patients which showed that the probe drugs used to quantify CYP enzyme activity are impacted by altered protein binding occurring in this disease, limiting the precision of probe drugs (20). As such, interpreting phenotyping results in the context of inflammatory or liver diseases requires a nuanced approach, considering not only enzyme activity but also the broader physiological changes that can influence drug clearance.

Perspectives

Following the great advances in PGx-based drug dosing, this thesis advocates that the CYP genotype should be evaluated within the broader context of the individual patient, considering it a starting point rather than an end point. Incorporating all relevant contributors to CYP metabolic function is critical to refining phenotype predictions that better reflect the real-time metabolizing status of the patient. This approach raises the central question: how can we effectively integrate the impact of non-genetic factors, such as concomitant medication and inflammatory status, into phenotype predictions to advance personalized medicine?

Evaluating the clinical relevance of inflammation-induced phenoconversion

A critical aspect to answering this question is identifying which drugs in which therapeutic context may be susceptible to clinically relevant alteration in efficacy or safety that requires dose adjustments. Whilst there is lots of evidence for altered drug PK during e.g. inflammatory episodes, there is little evidence for altered outcomes of treatment or more adverse events. Supratherapeutic exposure

of clozapine and theophylline during episodes of acute inflammation is linked with concurrent clinical manifestations of drug-related toxicity (21). However, for drugs like midazolam, voriconazole or tacrolimus, alterations in efficacy or increase side effects due to elevated concentrations during inflammation remain scarcely reported. This highlights that future studies should focus on systematically measuring clinical outcomes alongside PK changes during inflammation. This would help to clarify for which drug classes phenoconversion might be clinically relevant.

For inflammatory or metabolic diseases where changes in CYP-mediated clearance are a possible concern, the use of one or more inflammatory markers may inform on the likelihood and risk for clinically meaningful phenoconversion, considering the type and severity of inflammation are important determinants in this effect. Recommended inflammatory markers could include C-reactive protein (CRP), alpha-1-acid glycoprotein (AAG), albumin, IL-1β, IL-6 and TNF-α. For example, mild psoriasis patients have inadequate systemic inflammation to cause a meaningful alterations in CYP-mediated metabolic activity, with CRP levels usually below 10 mg/L (22). For diseases where e.g. CRP levels exceed 20 mg/L, for example in some cancers, the risk might be categorized as 'moderate' (23). Diseases might be put into the highest risk category if a combination of inflammatory markers is strongly altered, e.g. albumin levels dropping below 35 g/L and AAG > 1.2 g/L, such as seen in COVID-19 patients and severe rheumatoid arthritis patients (24–26). While using inflammatory markers to stratify disease-related phenoconversion risk provides a useful framework, it has limitations, including significant interpatient variability in cytokine levels. Nonetheless, it offers a practical starting point for categorizing diseases by their phenoconversion risk

Time dynamics of phenoconversion

A better understanding of the duration of phenoconversion is necessary in order to estimate how phenotypes of patients might change over time – and when dosing adjustments are necessary or close monitoring may suffice. This proves to be a challenge considering the duration of phenoconversion likely varies based on the underlying cause and the patient's unique physiological response. Duration of concomitant medication-induced phenoconversion is related to dose, duration of use and drug-specific properties like the drug's half-life and affinity towards its

target (1). Importantly, the inhibitory effect of some drugs, such as fluoxetine or paroxetine can persist days to weeks after discontinuation of the drug, complicating a general approach to predicting durations of concomitant medication-induced phenoconversion (27–29).

In contrast, inflammation-induced phenoconversion may have a more variable and potentially shorter duration, particularly in the case of acute inflammation. Here the key question is how long the inflammatory state – and its impact on drug metabolism – will persist. Only a few clinical studies have investigated the link between the resolution of inflammation or infection and the subsequent time dynamics of restoring hepatic metabolic capacity (13,14). Considering the half-life of DMEs likely plays an important role in this process, the field would benefit from a comprehensive analysis of both phase I and phase II DMEs half-lives, as conflicting reports have been published so far (30). Drug-induced resolution of inflammation showed us that the PK parameters of a CYP3A4 substrate given to tocilizumab-treated RA patients resembled that of healthy volunteers after 15 days of anti-inflammatory treatment, which indicates a time frame for the restoration of CYP3A4 activity post-treatment (31). Until the point of more data collection, creating awareness that clinical signs of inflammation, e.g. fever or elevated CRP levels can precede a rise in plasma concentrations of CYP substrates would already be a significant step forward.

Accurate measurement techniques to quantify phenoconversion

To effectively address the integration of non-genetic factors into phenotype predictions, it is essential to utilize accurate (measurement) techniques that can quantify phenoconversion. The large-scale implementation of the CYP phenotyping approach in clinical practice would be ideal to study phenoconversion, however this is not realistic considering it is expensive, labor-intensive and very invasive for the patient as it requires additional dosing of probe substrates. One way to circumvent this latter problem is by using endogenous phenotypic biomarkers to assess individual drug metabolism capacity. For example, the potato alkaloid solanidine serves as a sensitive and specific dietary biomarker for CYP2D6 activity (32). Endogenous biomarkers could serve as a valuable technique to quantify phenoconversion in future studies, if validation criteria are met (33).

In vitro hepatic models, such as liver microsomes or hepatocyte cultures allow for the controlled studying of modulation of DME activity under specific

conditions. By simulating conditions of phenoconversion, they can yield valuable data to support predictions of alterations in drug metabolism in vivo. However, translating findings from in vitro to in vivo have proven to be complex, as discrepancies often arise. In example, whereas we and others have consistently showed a downregulation of CYP2C9 and CYP2D6 activities upon stimulation with pro-inflammatory cytokines in vitro, in vivo results are conflicting. CYP2C9 activity is shown to increase during acute inflammation (13), diabetes (34) and non-alcoholic fatty liver disease (35), whereas clearance of CYP2D6 probe substrates is mainly unaffected during inflammation in vivo (13). Discrepancies in in vitro versus in vivo studies reporting on comedication-induced phenoconversion are also present, where the magnitude of phenoconversion for voriconazole and fluvoxamine was different (7,36).

PBPK models could aid in a better translation of in vitro to in vivo by integrating patient and system-specific characteristics to study how drug clearance is affected by non-genetic factors. Machavaram et al. pioneered in utilizing in vitro data in PHHs on IL-6-mediated CYP suppression to subsequently predict the impact of IL-6 on CYP3A4 substrates in vivo (37), and more studies followed (38–41). Similar successes have been achieved by utilizing PBPK approaches to predict DDGIs (42–45). These models do heavily rely on accurately determined in vitro kinetic parameters, which can vary significantly between labs, potentially compromising prediction accuracy (46). Additionally, most PBPK models simplify the inflammatory response by focusing on the effect of a single cytokine on CYP activity, overlooking the complex interplay between multiple cytokines and the influence of anti-inflammatory cytokines. They also often exclude the effects of cytokines on drug transporters and extrahepatic metabolism. Despite these limitations, PBPK modeling applications hold great potential to simulate these interactions and lay the groundwork for future research aimed at refining phenotype predictions by incorporating all feasible contributors to CYP metabolic function.

Integration of phenoconversion into clinical practice: the phenoconversion calculator

So how can we ultimately translate this acquired knowledge into usable clinical guidelines during routine pharmacotherapy? First of all, ensuring uniformity in the implementation of phenoconversion into phenotyping predictions is crucial.

In an attempt to enable consistent classification of CYP2D6 phenoconversion, various web-tools have been created to integrate genotype and drug interactions to ensure the correct clinical phenotype is utilized when making dosing decisions (47,48). This approach is founded on translating different diplotypes into activity scores, which are then adjusted according to the concomitant medication used, and subsequently, a clinical phenotype is inferred. This method has been shown to improve phenotype predictions, e.g. in breast cancer patients taking CYP2D6-related comedication (49), but in other patient cohorts there was little added benefit of corrected genotype-predicted activity scores in explaining the overall variability in drug PK (50). This highlights that more data is required to optimize such web-based tools. In example, one of the assumptions in the tools is that a PM phenotype is expected upon strong inhibitor use for all genotype-predicted phenotypes. Our data challenges this assumption and highlights that for some genotypes, an IM phenotype is more likely upon strong inhibition. Additionally, there are some reports that UMs might be less prone towards concomitant medication-induced phenoconversion, at least for CYP2D6 (51,52). More data is essential to capture the nuances in the specificity and strength of concomitant medication on specific CYP enzymes, which can then be use as input for the available tools.

Additionally, the phenotyping scoring system would benefit from an extension with other factors that impact phenotype, e.g. the presence of liver disease and other (inflammation-related) comorbidities. Integrating non-genetic factors into the activity scoring system and subsequent phenotype predications involves systematically evaluating when a phenotypic switch is evident during a certain comorbidity. Clinical trials on the impact of inflammation now mainly focus on how CYP activity is impacted, but future studies should simultaneously evaluate phenotypic switches during various comorbidities, or determine inflammatory marker cut-offs where this will likely happen. One difficulty is that patient medications and comorbidities are dynamic. Thus, the occurrence and extent of phenoconversion may fluctuate over time as interacting drugs are initiated or discontinued, or as underlying diseases emerge or are successfully treated. As such, it would be important for clinicians or pharmacists to evaluate the calculated phenotype prediction in the light of the current situation, and re-evaluate the calculator when necessary.

Until there is such a scoring tool available for clinicians, we should spread awareness of the potential impact of phenoconversion on PGx-based phenotype predictions, for example implement a warning into pharmacogenetic guidelines. CPIC guidelines for drug-gene pairs usually do contain a warning that concomitant medication or other patient specific-comorbidities might skew the assigned phenotype. But for example the EMA draft guideline on the implementation of pharmacogenetics could benefit from a warning concerning the impact of non-genetic factors on interpreting phenotypes. Creating awareness could help alert clinicians and other healthcare providers to consider phenoconverting factors when unexpected variations in plasma PK of DME substrates occur.

Conclusion

This thesis underscores the importance of broadening the scope of CYP phenotype predictions beyond genetic determinants by integrating non-genetic factors such as concomitant medication and inflammatory status. While significant strides have been made in personalized dosing through PGx, refining these predictions to reflect real-time metabolic status remains a critical challenge. This thesis contributes to a deeper quantitative understanding of how inflammation and concomitant medications impact drug metabolism, ultimately supporting the development of more accurate phenotype predictions and advancing personalized dosing strategies.

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