Evaluation of Endogenous Biomarkers in Context of Renal Transporter-Mediated Drug Interactions:

A Literature Review of Intrinsic, Extrinsic Factors, and Disease Impact on Biomarker Levels

HeeJae Choi[1], Shilpa Madari[1], Fenglei Huang[1]

1Translational Medicine and Clinical Pharmacology, Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT, United States

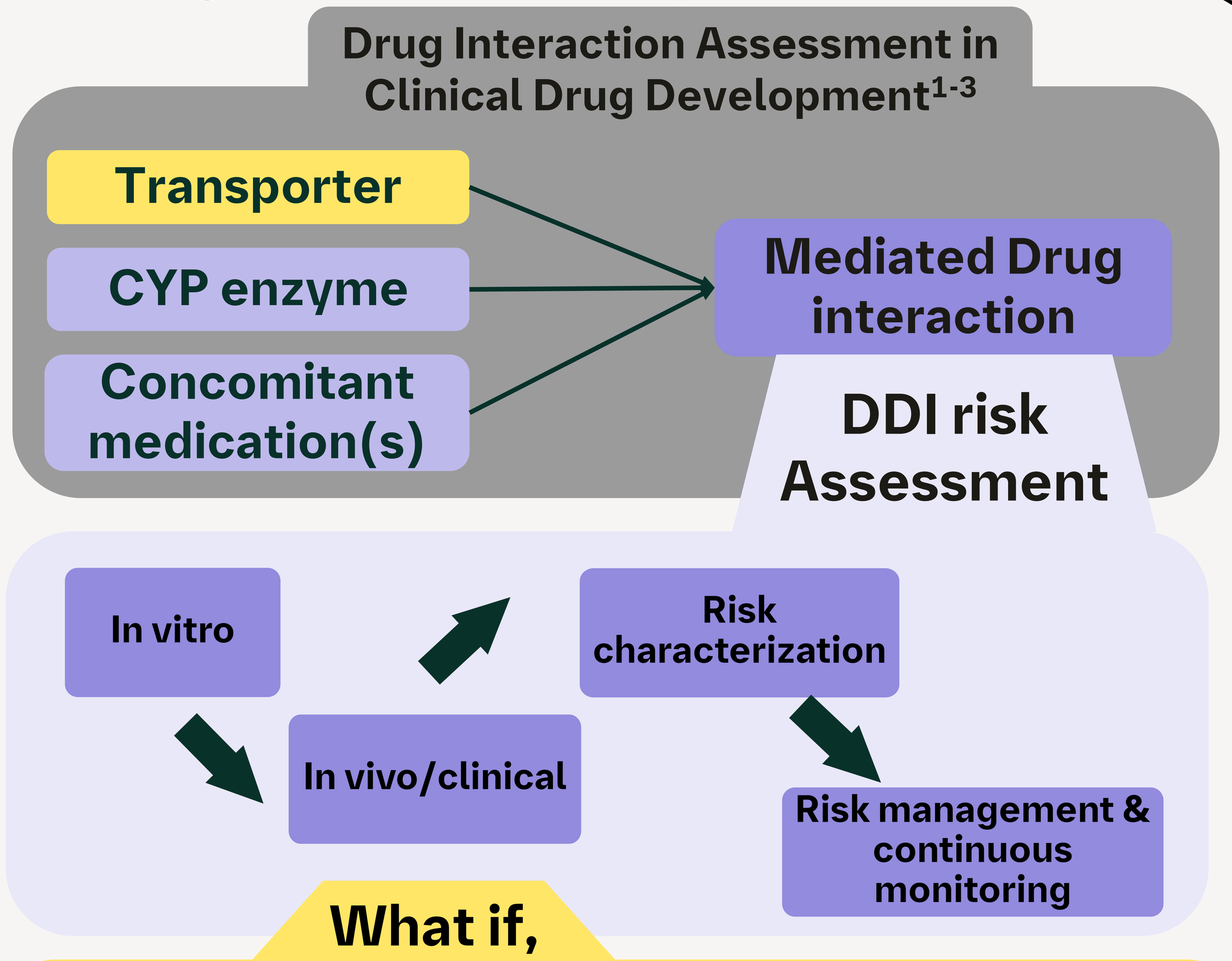
Research Objective

To evaluate potential renal transporter biomarkers, such as pyridoxic acid (PDA) and homovanillic acid (HVA), identified in prior in vitro and in vivo studies for their relevance to OAT1/3 transporters. This review focuses on the effects of intrinsic and extrinsic factors, including disease state impacts, on biomarker baseline level variations in humans

***: Note on Publication**

The core content of this poster was submitted for abstract consideration before it was accepted for manuscript publication on June 13, 2024. Since the abstract submission on April 09, 2024, a portion of this work has been published in Clinical Pharmacokinetics, Volume 63. This poster expands upon the published research by including additional data and insights not covered in the original publication, with no concerns regarding copyright.

Background story (aka. Introduction)


Drug Interaction Assessment in Clinical Drug Development[1-3]
Transporter
CYP enzyme
Concomitant medication(s)
Mediated Drug interaction
DDI risk Assessment
In vitro
In vivo/clinical
Risk characterization
Risk management & continuous monitoring

What if,

Utilizing endogenous biomarkers[3] to assess transporter mediated drug interaction in early phase I studies potentially circumventing the need for standalone clinical DDI studies?

If so, what are the potential benefits and challenges of integrating this approach[4*]?

Potential benefits	Potential challenges
• Safe • Saving time • Saving cost	• Baseline level measurements • The influence of intrinsic and extrinsic factors, and the impact of disease state on the baseline

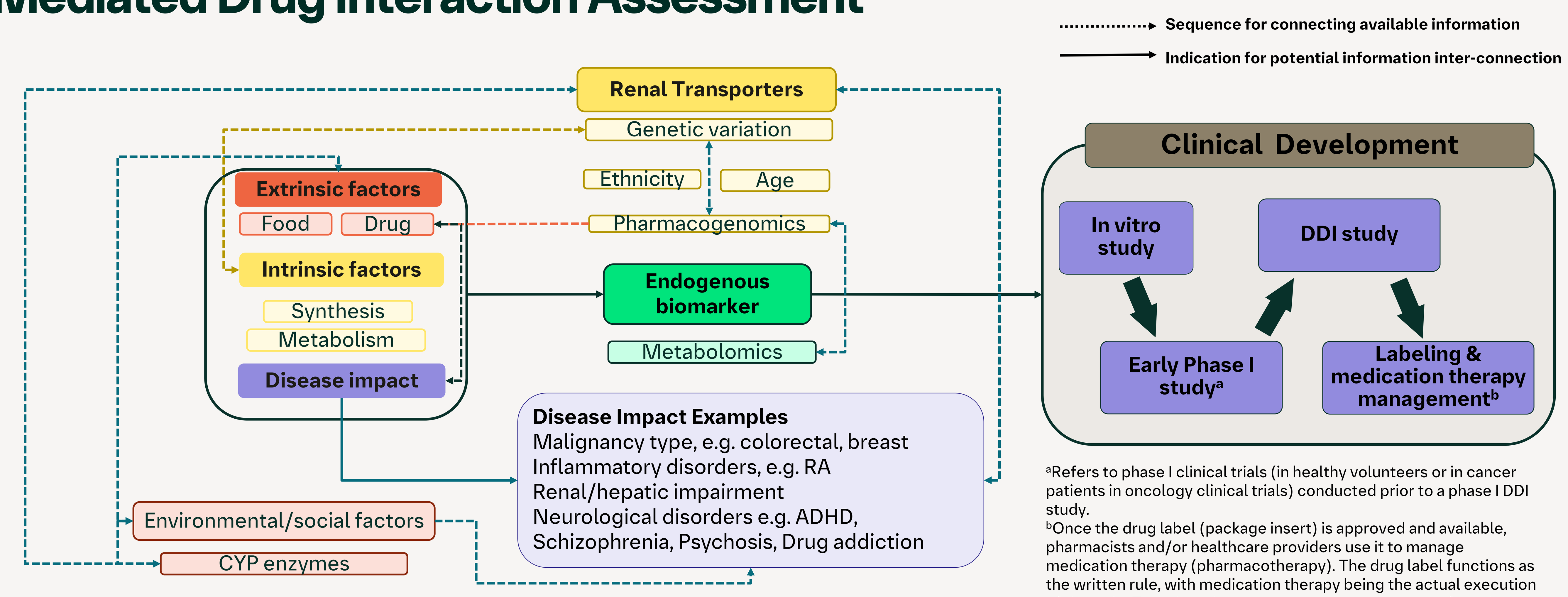
Then,

How to overcome challenges?

Literature search & review strategy (aka. Method)

- This review utilized the PubMed database. A keyword search was conducted using the following terms: ("selected biomarker-PDA/ HVA") AND ((food) OR (drug) OR (renal impairment OR hepatic impairment OR cancer OR pediatric OR special population OR transplant))
- Retrieved literature was categorized into intrinsic factors, extrinsic factors, and disease state impact after reviewing titles and abstracts, with the framework refined iteratively

Thought Process Schematic: How & What To Consider During Biomarker Level Measurement In The Context Of Renal Transporter Mediated Drug Interaction Assessment[4*]


Sequence for connecting available information
Indication for potential information inter-connection
Renal Transporters
Genetic variation
Ethnicity
Age
Pharmacogenomics
Extrinsic factors
Food
Drug
Intrinsic factors
Synthesis
Metabolism
Disease impact
Endogenous biomarker
Metabolomics
Clinical Development
In vitro study
DDI study
Early Phase I study[a]
Labeling & medication therapy management[b]
Disease Impact Examples
Malignancy type, e.g. colorectal, breast
Inflammatory disorders, e.g. RA
Renal/hepatic impairment
Neurological disorders e.g. ADHD, Schizophrenia, Psychosis, Drug addiction
Environmental/social factors
CYP enzymes

[a]Refers to phase I clinical trials (in healthy volunteers or in cancer patients in oncology clinical trials) conducted prior to a phase I DDI study.

[b]Once the drug label (package insert) is approved and available, pharmacists and/or healthcare providers use it to manage medication therapy (pharmacotherapy). The drug label functions as the written rule, with medication therapy being the actual execution of that rule. Together, these two components ensure safe and effective treatment.

Example 1: Pyridoxic acid[4*]

Figure 1: Conversion of Vitamin B6 to Pyridoxic acid[5]

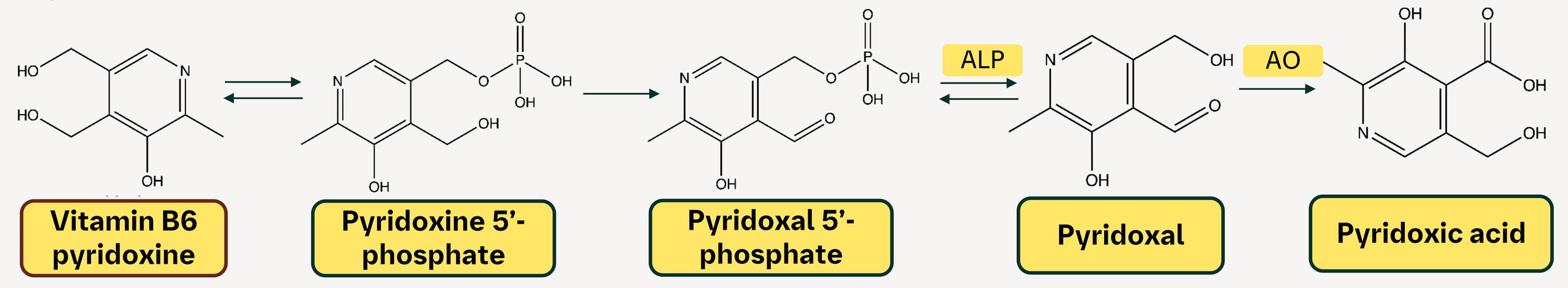


Table 1. Impact of Intrinsic & Extrinsic Factors and Disease States on PDA Baseline Levels[4*]

Multiple factors impacting biomarker levels		Results
Intrinsic factor	Synthesis[5]	Proportional ↑ of plasma biomarker level, to vitamin B6 catabolism
Extrinsic factor	Vitamin B supplement intake[5,6]	2.39-fold change of plasma baseline level
	Drug – oral contraceptive[5,7]	1.54-3.00-fold change of plasma baseline level
Diseases	Colorectal malignancy[8,9]	Up to 0.946-fold change of plasma baseline level
	Rheumatoid arthritis[10]	0.727-fold change in urine; no change in plasma
	ADHD[11]	• Untreated: 1.24-fold change in plasma • Treated with methylphenidate:1.02-fold change
	ESRD[12], chronic liver disease[13]	• ↑ in plasma baseline in ESRD patient (inclusive of hemodialysis and chronic renal impairment)[12,c]; • 0.697-fold change in plasma baseline in chronic liver disease[13]

c: As of September 2nd, 2024, only abstract was accessible; therefore, no numerical value is reported in the Table 1 &2.

Example 2: Homovanillic acid

Figure 2: Conversion of Tyrosine to Homovanillic acid[14]

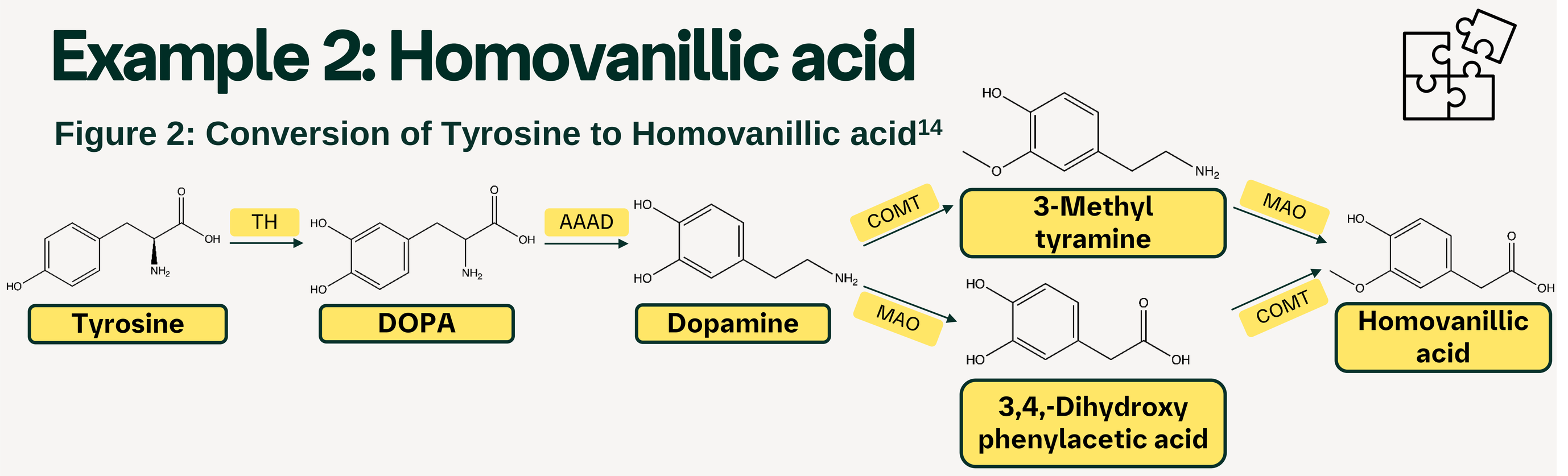


Table 2. Impact of Intrinsic & Extrinsic Factors and Disease States on HVA Baseline Levels

Multiple factors impacting biomarker levels		Results
Intrinsic factor	Synthesis[14]	Intronic *COMT* rs 165773 nominally associated with HVA concentrations
Extrinsic factor	Tobacco use[15]	No difference in plasma, 0.460-fold change in CSF concentrations in smokers compared to nonsmokers
Diseases	Schizophrenia[16-18]	• No difference in plasma baseline between schizophrenic vs. non-schizophrenic patients[16,c] • No difference nor variation range between chronic and acute patients[17] • ↑ of plasma baseline & 1 week post dose (of haloperidol) levels in first episode responders than non-responders[16,c] • ↑ plasma levels in female regardless of responsiveness[18,c]
	Psychosis[19-21]	• No difference in plasma baseline between relapsers vs non-relapsers[19] • No difference in plasma baseline between first-episode psychosis patients vs controls[20,c] • No difference in plasma baseline between responders vs. non-responders[21]
	Drug Addiction[22]	0.573-fold change of plasma baseline level in heroin or cocaine dependent compared to controls

Key messages

- **Complexities of Renal Transporter-Mediated Drug Interactions**: Our research identifies key intrinsic, extrinsic, and disease-state factors impacting baseline biomarker levels, crucial for accurate biomarker-based assessments.
- **Implications for Oncology**: Findings highlight the need to understand how conditions like cancer affect biomarker levels in oncology trials, which involve patients with pre-existing conditions, contrasting with non-oncology trials that mostly involve healthy volunteers.

References

1. Kanefendt F, Brase C, Jungmann N, Fricke R, Engelen A, Schmitz S. Pharmacokinetics of asundexian with combined CYP3A and P-gp inhibitors and an inducer: Target in vitro and in vivo studies. Br J Clin Pharmacol. 2024 Apr;90(4):1036-1049. doi: 10.1111/bcp.15981. Epub 2024 Jan 9. PMID: 38048692.
2. Chu X, Liao M, Shen H, Yoshida K, Zur AA, Arya V, Galetin A, Giacomini KM, Hanna I, Kusuhara H, Lai Y, Rodrigues D, Sugiyama Y, Zamek-Gliszczynski MJ, Zhang L; International Transporter Consortium. Clinical Probes and Endogenous Biomarkers as Substrates for Transporter Drug-Drug Interaction Evaluation: Perspectives From the International Transporter Consortium. Clin Pharmacol Ther. 2018 Nov;104(5):836-864.
3. Takita H, Scotcher D, Chu X, Yee KL, Ogungbenro K, Galetin A. Coproporphyrin I as an Endogenous Biomarker to Detect Reduced OATP1B Activity and Shift in Elimination Route in Chronic Kidney Disease. Clin Pharmacol Ther. 2022 Sep;112(3):615-626. doi: 10.1002/cpt.2672. Epub 2022 Jun 28. PMID: 35652251; PMCID: PMC9540787.
4. Choi HJ, Madari S, Huang F. Utilising Endogenous Biomarkers in Drug Development to Streamline the Assessment of Drug-Drug Interactions Mediated by Renal Transporters: A Pharmaceutical Industry Perspective. Clin Pharmacokinet. 2024 Jun;63(6):735-749. doi: 10.1007/s40262-024-01385-0. Epub 2024 Jun 13. PMID: 38867094; PMCID: PMC11222257.
5. UelandPM, UlvikA, Rios-Avila L, MidttunØ, Gregory JF. Direct and Functional Biomarkers of Vitamin B6 Status. Annu Rev Nutr. 2015;35:33-70. doi: 10.1146/annurev-nutr-071714-034330. Epub2015 May 13. PMID: 25974692; PMCID: PMC5988249.
6. Pfeiffer CM, Sternberg MR, Schleicher RL, Rybak ME. Dietary supplement use and smoking are important correlates of biomarkers of water-soluble vitamin status after adjusting for sociodemographic and lifestyle variables in a representative sample of U.S. adults. J Nutr. 2013 Jun;143(6):957S-65S. doi: 10.3945/jn.112.173021. Epub2013 Apr 10. PMID: 23576641; PMCID: PMC4822996.
7. Rios-Avila L, Coats B, Chi YY, MidttunØ, UelandPM, StacpoolePW, Gregory JF 3rd. Metabolite profile analysis reveals association of vitamin B-6 with metabolites related to one-carbon metabolism and tryptophan catabolism but not with biomarkers of inflammation in oral contraceptive users and reveals the effects of oral contraceptives on these processes. J Nutr. 2015 Jan;145(1):87-95. doi: 10.3945/jn.114.201095. Epub2014 Nov 19. PMID: 25527663; PMCID: PMC4264024.
8. Xu L, Fang YJ, Che MM, AbulimitiA, Huang CY, Zhang CX. Association of Serum Pyridoxal-5'-Phosphate, Pyridoxal, and PAwith Colorectal Cancer Risk: A Large-Scale Case-Control Study. Nutrients. 2022 Jun 9;14(12):2389. doi: 10.3390/nu14122389. PMID: 35745119; PMCID: PMC9230157.
9. GyllingB, MyteR, SchneedeJ, HallmansG, HäggströmJ, Johansson I, UlvikA, UelandPM, Van GuelpenB, PalmqvistR. Vitamin B-6 and colorectal cancer risk: a prospective population-based study using 3 distinct plasma markers of vitamin B-6 status. Am J Clin Nutr. 2017 Apr;105(4):897-904. doi: 10.3945/ajcn.116.139337. Epub2017 Mar 8. PMID: 28275126.
10. Chiang EP, Smith DE, SelhubJ, DallalG, Wang YC, RoubenoffR. Inflammation causes tissue-specific depletion of vitamin B6. Arthritis Res Ther. 2005;7(6):R1254-62. doi: 10.1186/ar1821. Epub2005 Sep 13. PMID: 16277678; PMCID: PMC1297572.
11. Dolina S, Margalit D, MalitskyS, RabinkovA. Attention-deficit hyperactivity disorder (ADHD) as a pyridoxine-dependent condition: urinary diagnostic biomarkers. Med Hypotheses. 2014 Jan;82(1):111-6. doi: 10.1016/j.mehy.2013.11.018. Epub2013 Nov 21. PMID: 24321736.
12. Lindner A, BanksonDD, Stehman-Breen C, MahurenJD, Coburn SP. Vitamin B6 metabolism and homocysteine in end-stage renal disease and chronic renal insufficiency. Am J Kidney Dis. 2002 Jan;39(1):134-45. doi: 10.1053/ajkd.2002.29904. PMID: 11774112.
13. LabadariosD, Rossouw JE, McConnell JB, Davis M, Williams R. Vitamin B6 deficiency in chronic liver disease--evidence for increased degradation of pyridoxal-5'-phosphate. Gut. 1977 Jan;18(1):23-7. doi: 10.1136/gut.18.1.23. PMID: 838399; PMCID: PMC1411256.
14. Andreou D, Söderman E, Axelsson T, Sedvall GC, Terenius L, Agartz I, Jönsson EG. Polymorphisms in genes implicated in dopamine, serotonin and noradrenalin metabolism suggest association with cerebrospinal fluid monoamine metabolite concentrations in psychosis. Behav Brain Funct. 2014 Jul 29;10:26. doi: 10.1186/1744-9081-10-26. PMID: 25073638; PMCID: PMC4123495.
15. Geracioti TD Jr, West SA, Baker DG, Hill KK, Ekhator NN, Wortman MD,Keck PE Jr, Norman AB: Low CSF concentration of a dopamine metabolitein tobacco smokers. Am J Psychiatry 1999, 156:130–132.
16. Javaid JI, Sharma RP, Janicak PG, Davis JM. Plasma HVA in psychiatric patients: longitudinal studies. Psychopharmacol Bull. 1990;26(3):361-5. PMID: 2274637.
17. Zumárraga M, Dávila R, González-Torres MA, Anguiano JB, Zabalo MJ, Basterreche N, Arrúe A, Zamalloa MI, Guimón J. Inter- and intra-individual variability in the levels of plasma homovanillic acid in schizophrenic patients. Prog Neuropsychopharmacol Biol Psychiatry. 2007 Apr 13;31(3):713-9. doi: 10.1016/j.pnpbp.2007.01.005. Epub 2007 Jan 16. PMID: 17291661.
18. Koreen AR, Lieberman J, Alvir J, et al. Plasma Homovanillic Acid Levels in First-Episode Schizophrenia: Psychopathology and Treatment Response. Arch Gen Psychiatry. 1994;51(2):132–138.
19. Kelley, M., Yao, J. & van Kammen, D. Plasma Catecholamine Metabolites as Markers for Psychosis and Antipsychotic Response in Schizophrenia. Neuropsychopharmacol 20, 603–611 (1999).
20. van de Kerkhof NW, Fekkes D, van der Heijden FM, Egger JI, Verhoeven WM. Relationship between plasma homovanillic acid and outcome in patients with psychosis spectrum disorders. Neuropsychobiology. 2015;71(4):212-7. doi: 10.1159/000431095. Epub 2015 Aug 7. PMID: 26279280.
21. Mazure CM, Nelson JC, Jatlow PI, Bowers MB. Plasma free homovanillic acid (HVA) as a predictor of clinical response in acute psychosis. Biol Psychiatry. 1991 Sep 1;30(5):475-82. doi: 10.1016/0006-3223(91)90309-a. PMID: 1932395.
22. Gerra, G., Leonardi, C., Cortese, E. et al. Homovanillic acid (HVA) plasma levels inversely correlate with attention deficit-hyperactivity and childhood neglect measures in addicted patients. J Neural Transm 114, 1637–1647 (2007).

Abbreviations

AAAD Aromatic amino acid decarboxylase ADHD attention deficit hyperactivity disorder ALP alkaline phosphatase AO aldehyde oxidase COMT catechol-O-methyltransferase CYP cytochrome P450 enzymes DDI drug drug interaction ESRD end stage renal disease HVA homovanillic acid MAO monoamine oxidase PDA pyridoxic acid RA rheumatoid arthritis TH tyrosine hydroxylase

Boehringer Ingelheim