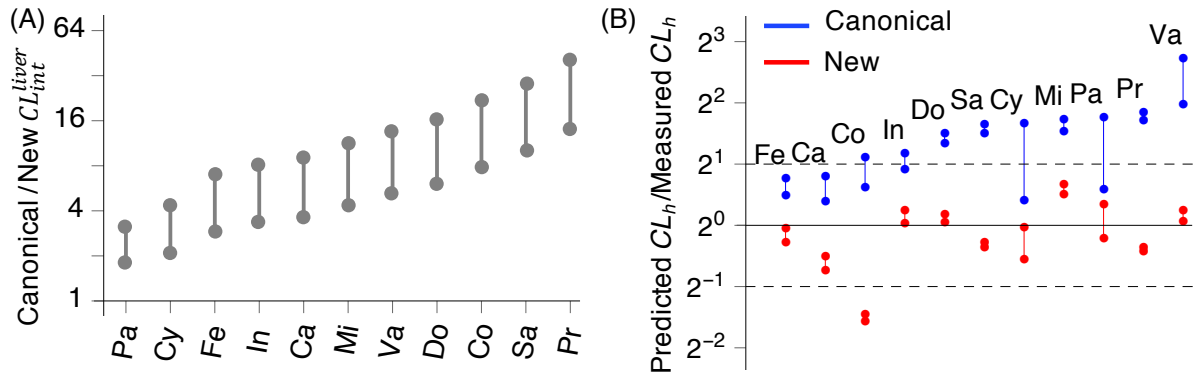

Figure S1. Prediction of *in vivo CL* based on hepatic CYP concentration considering its subcellular localization. (A) While the CL_{int}^{liver} obtained with the canonical approach depends on the amount of CYPs in liver (i.e. $\tilde{E}_T$ in Eq. 5), the CL_{int}^{liver} obtained with the new approach depends on both the amount of CYPs and their concentration in the liver (i.e. $\tilde{E}_T$ and E_T in Eq. 7). Thus, the prediction of the new approach changes depending on the volume of CYP distribution (V) in the liver, which is a critical factor determining E_T. In Table 1 and Fig. 2B, we assumed that CYPs are evenly distributed in hepatocytes to estimate the concentration of CYPs in the liver, although CYPs are primarily localized in the membrane of the endoplasmic reticulum[1]. In hepatocytes, the endoplasmic reticulum can comprise less than 20% of the total cell volume[2,3]. Thus, when such subcellular localization of CYP is considered, the estimated concentration of CYP isoforms increases by ~5-fold (100/20) compared to the previously estimated one, which increases the $K_M + E_T$ in the denominator of Eq. 7 (Table S1). This decreases the estimated CL_{int}^{liver} with the new approach further and thus increases the difference in CL_{int}^{liver} predicted with the canonical and new approaches (Table S1). (B) When the higher concentration of CYPs, which was estimated considering their localization in the membrane of the endoplasmic reticulum (Table S1), is used, our new approach improves the accuracy and precision of the prediction for CL_h by two-fold and four–fold, respectively compared to the canonical approach (Table S2). In particular, 10 out of 11 drugs, except for coumarin, fell within two-fold error. Note that as the experimentally measured $f_{\text{u-mic}}$ of coumarin is not known, it is estimated from the partition coefficient of coumarin (Log$P$ =1.39) (see Table 2 for details). However, such an approach is known to overestimate $f_{\text{u-mic}}$ when drugs are hydrophilic (i.e. Log$P$<2)[4]. This indicates that the overestimation of $f_{\text{u-mic}}$ might be the cause of the considerable underestimation for CL_h of coumarin with the new approach.

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