Predictive Value of Nonclinical ADME Findings for Clinical Excretion Routes

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INTRODUCTION

- A mass balance study uses a radiolabeled drug to obtain quantitative and comprehensive information on the absorption, distribution, metabolism and excretion (ADME) of an investigational drug.
- Nonclinical mass balance studies help inform the clinical ADME study design. Specifically, the absorbed radioactivity dose, estimated duration of confinement and anticipated main excretion route are needed to support human ADME studies. However, there are several metabolic and technical inter-species factors that may impact the translation of nonclinical to clinical ADME results.

OBJECTIVES

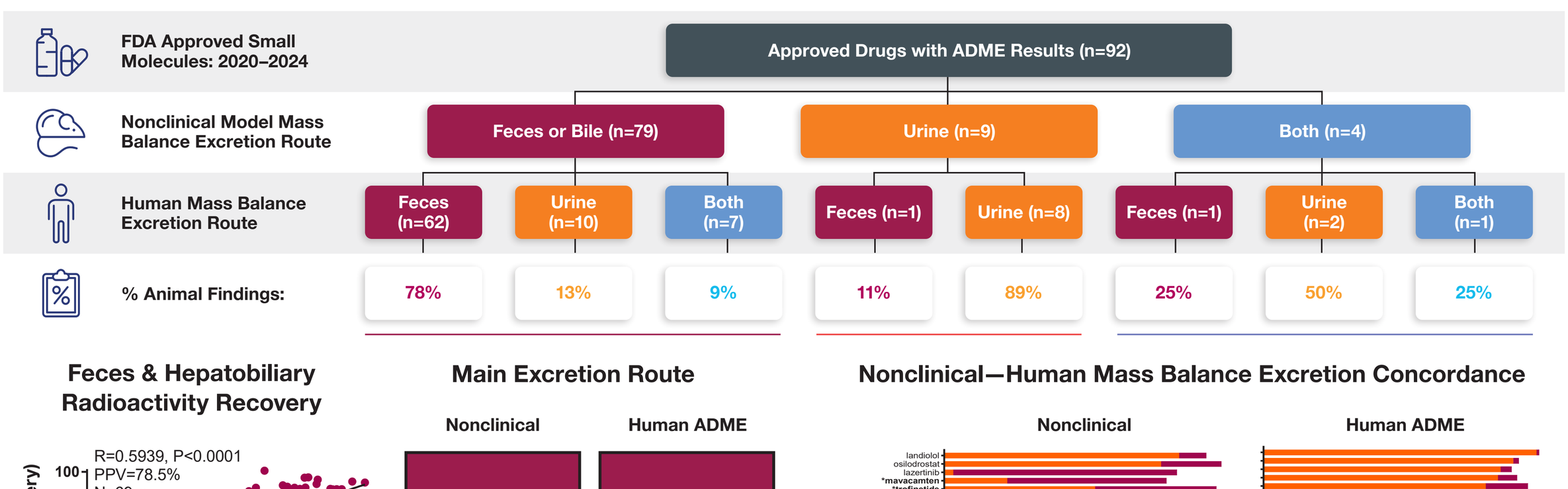
- The aim of this study was to examine the performance of nonclinical models to predict the predominant excretion route of a drug in humans.

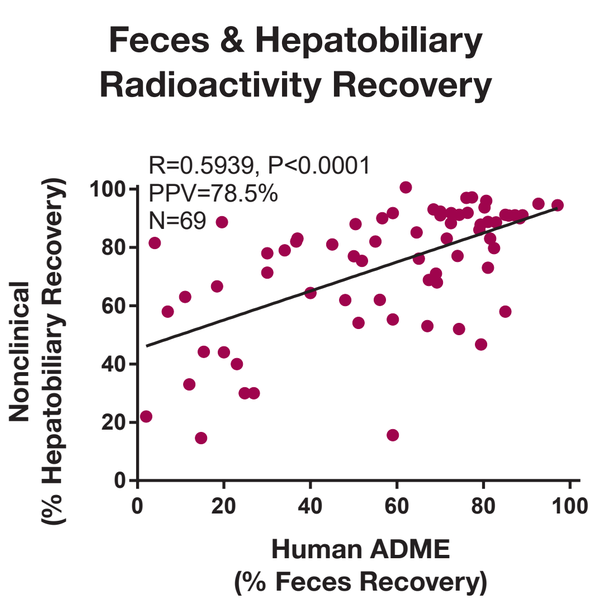
METHODS

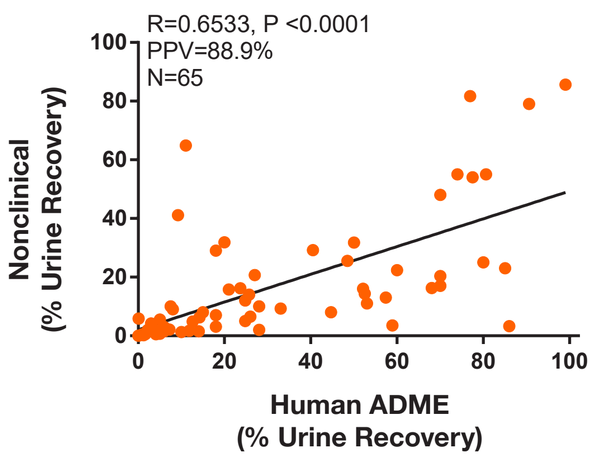
- Radioactivity recovery excretion data were extracted from the FDA clinical pharmacology reviews from Drugs@FDA.
- Results were compiled from clinical and nonclinical pharmacology dossiers for FDA approved small molecules from 2020–2024.
- Nonclinical-clinical performance was assessed by positive predictive value (PPV) (%, [95% CI]) and Pearson correlation (R, p-value).

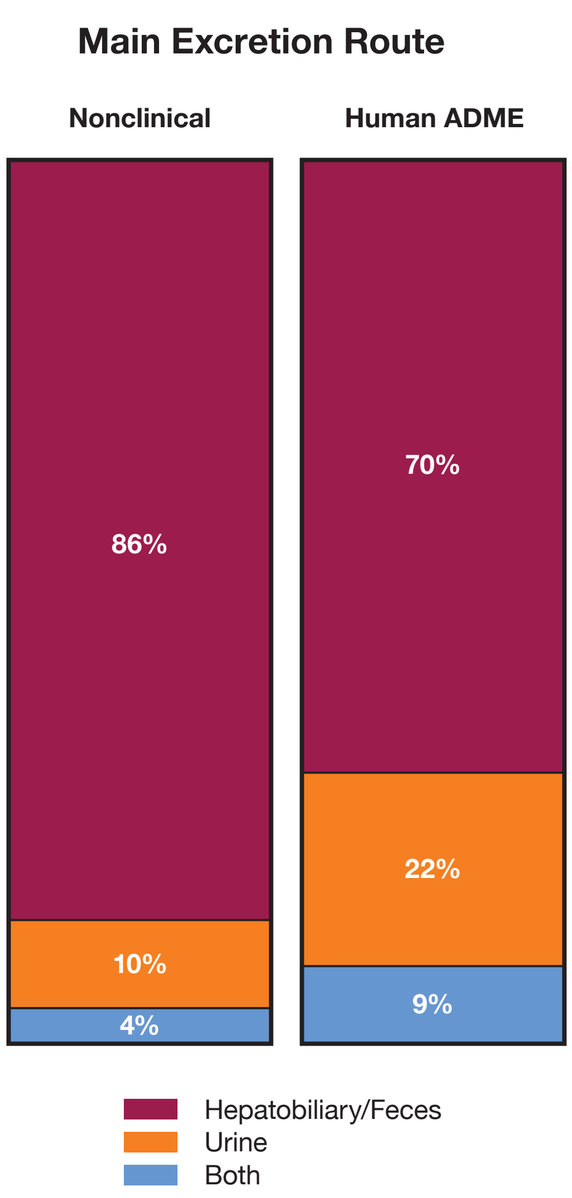
RESULTS

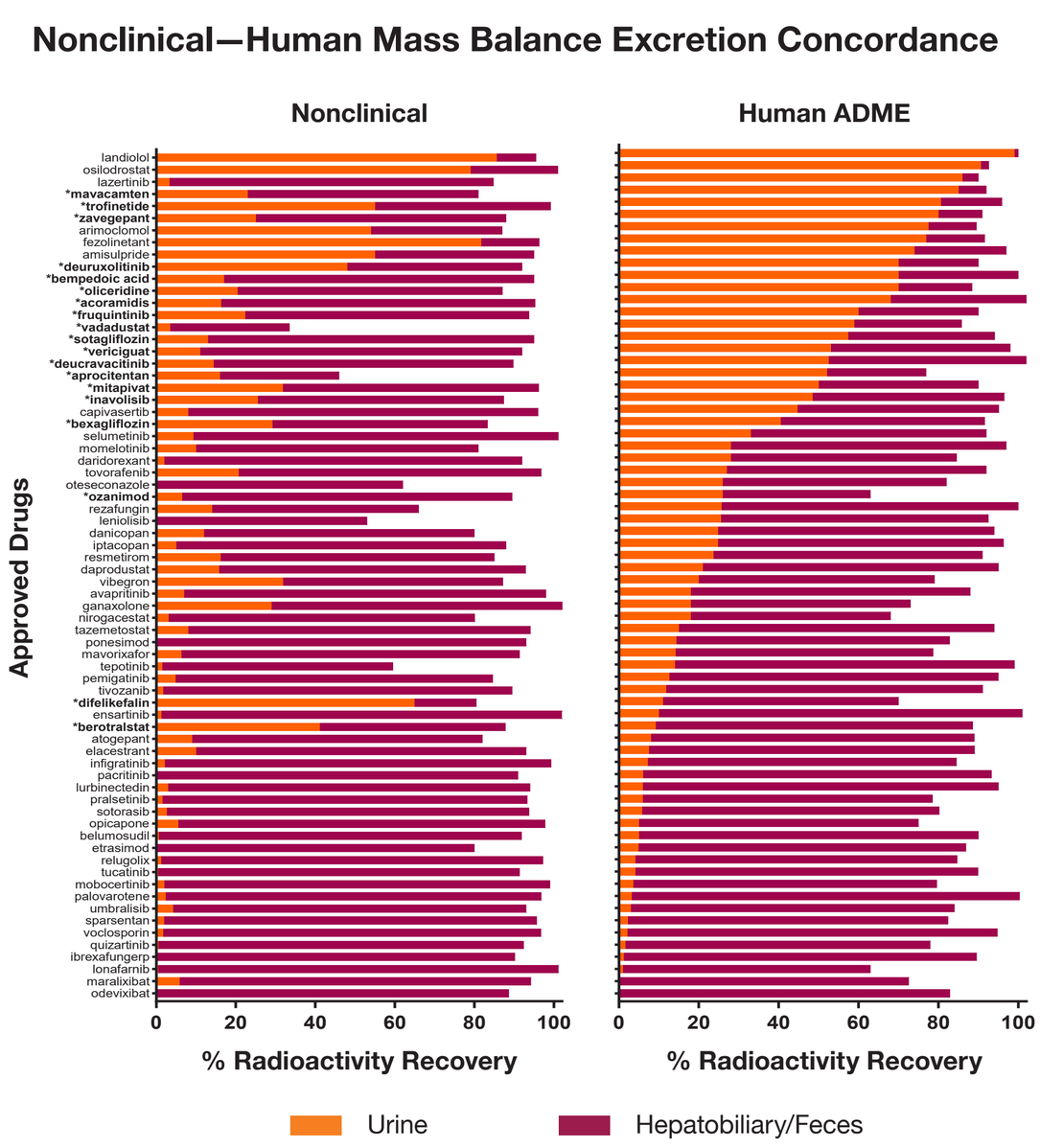
Animal ADME Data Strongly Predict and Correlate with Human Findings











- Of 109 small molecules that were approved by the FDA over the past 5 years, 92 drugs had publicly available mass balance study results.
- Drugs indicated for oncology (37%) and classified as kinase inhibitors (34%) represented the largest therapeutic area and class, respectively.
- Excreta profiles reveal similar nonclinical and clinical recovery rates with feces as main route of elimination.
- Only 23% of drugs demonstrate profile discordance between nonclinical-clinical recovery and drugs excreted mainly in urine or through both pathways were most likely to display discordant results.
- Potential factors contributing to discrepancies in main excretion routes include the animal model sensitivity, species differences in CYP activity, and role of glucuronide metabolites.

CONCLUSION

- In spite of technical and innate differences between nonclinical and human ADME studies, animal data tend to predict and correlate with human findings.
- Only a few cases had large discrepancies, which were associated with human-animal differences in CYP activity and drug glucuronidation.
- Adding metabolic profiling to human mass balance studies enables a more complete understanding of the metabolite profile in humans, which in some cases could be quite different from the animal models.

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