

Development of a curated hepatic steatosis database (HSDB) to enable Quantitative Structure-Activity Relationship (QSAR) modeling

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Introduction

- Hepatic steatosis, also known as non-alcoholic **fatty liver disease**, is characterized by abnormal fat accumulation in the liver.

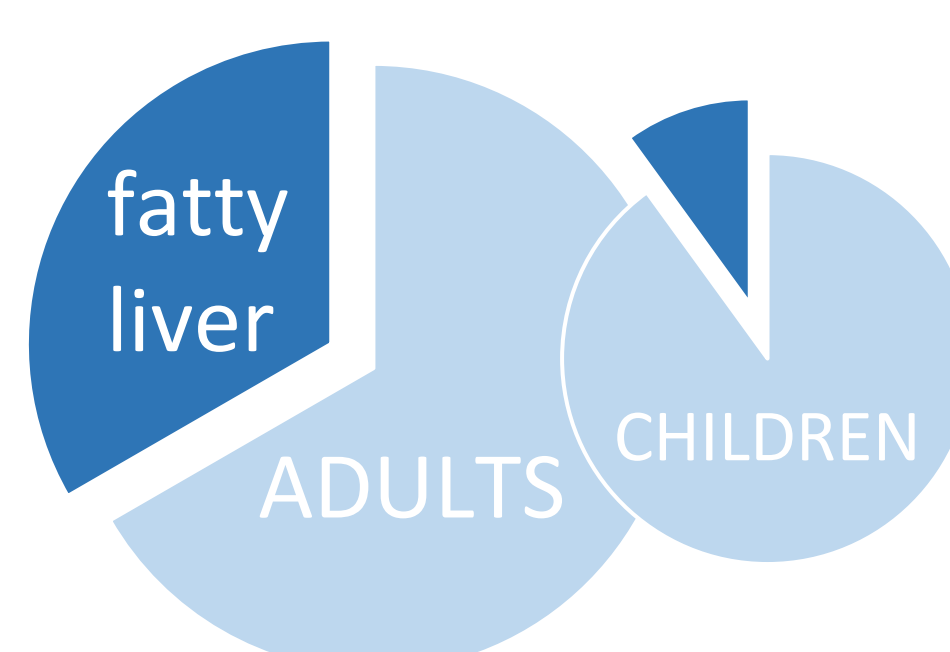


Four apical key events serve as the fulcrum potentiating additional disease outcomes of HS.

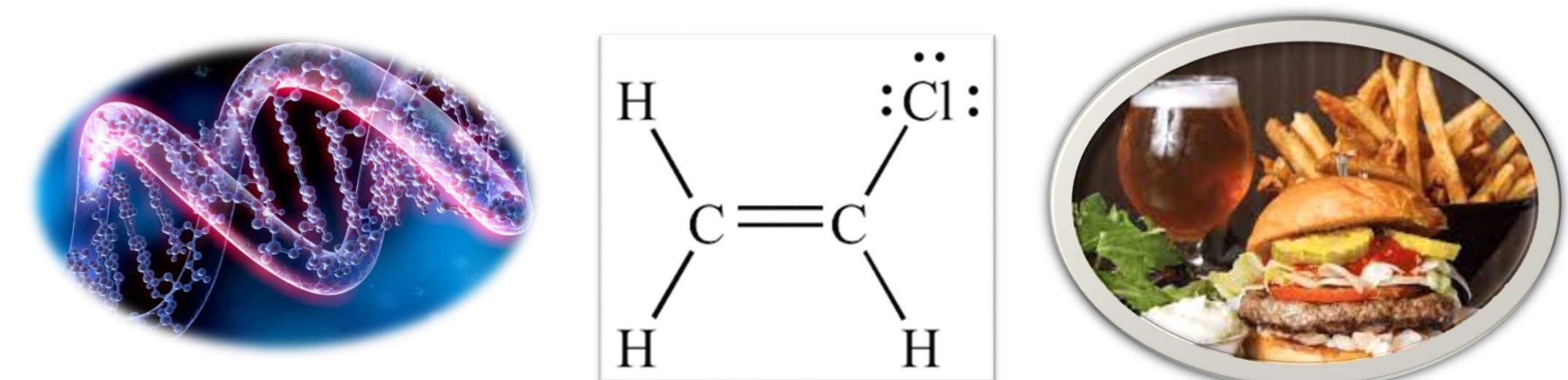
Angrish et al. 2016

- Disease impacts

one in three adults
one in ten children
in the US.



- Multifactorial causes / susceptibility sources:
Genetics, chemical exposure, psychosocial factors



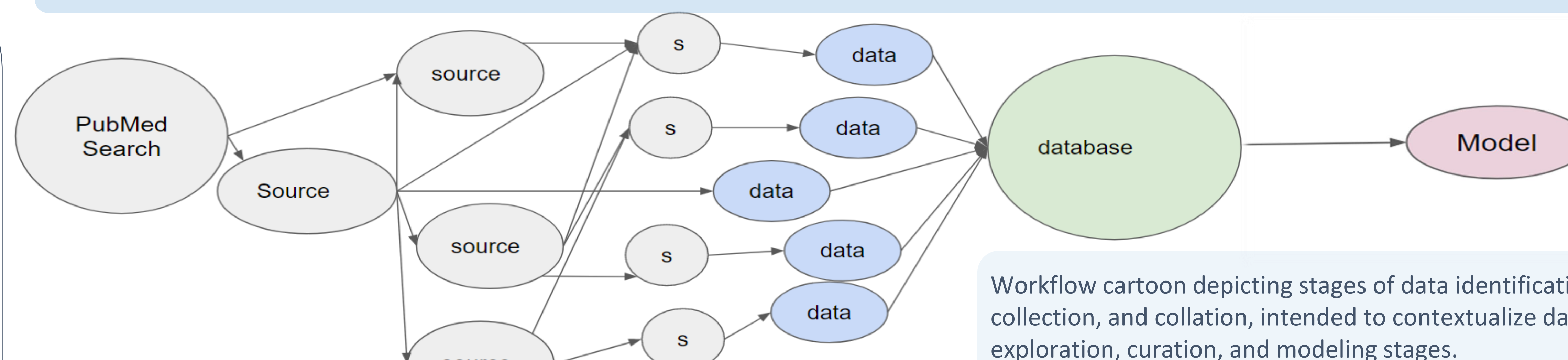
- Hepatic steatosis can progress into an additional adverse outcome including fibrosis, cirrhosis, cancer, and death.

Key References

- Angrish et al. 2016 [10.1093/toxsci/kfw018](https://doi.org/10.1093/toxsci/kfw018)
- Fourches et al. 2016 [10.1021/acs.jcim.6b00129](https://doi.org/10.1021/acs.jcim.6b00129)

"The views expressed in this presentation are mine and not official policy stances by NIH."
"AT and ENM are co-founders of Predictive, LLC, which develops computational methodologies and software for toxicity prediction."

Materials and Method



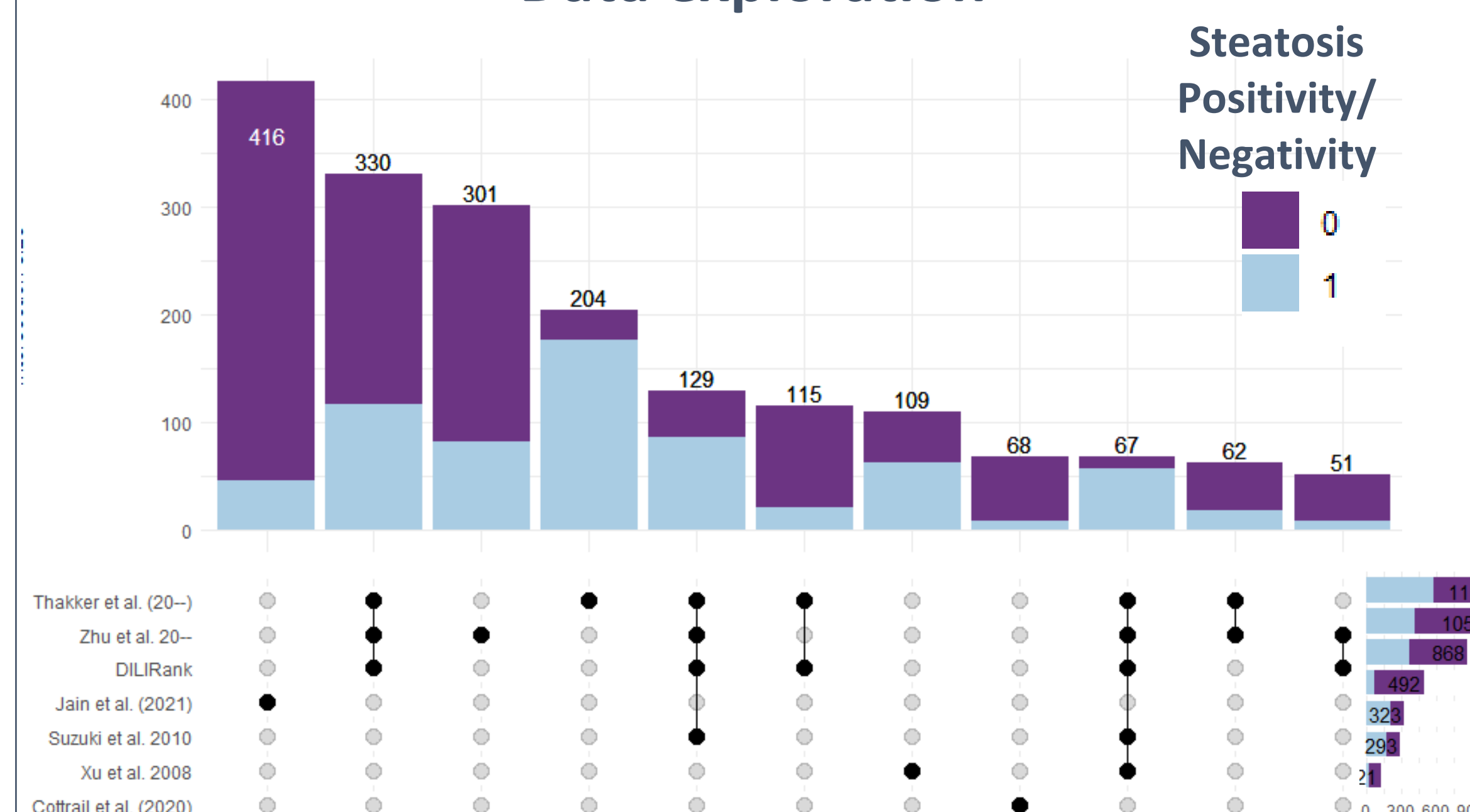
a. Data compiled via literature and web search using PubMed, supplementary materials, publicly accessible electronic databases, & private contributions.

b. Data integration, curation, analysis, and visualization executed in R and KNIME.

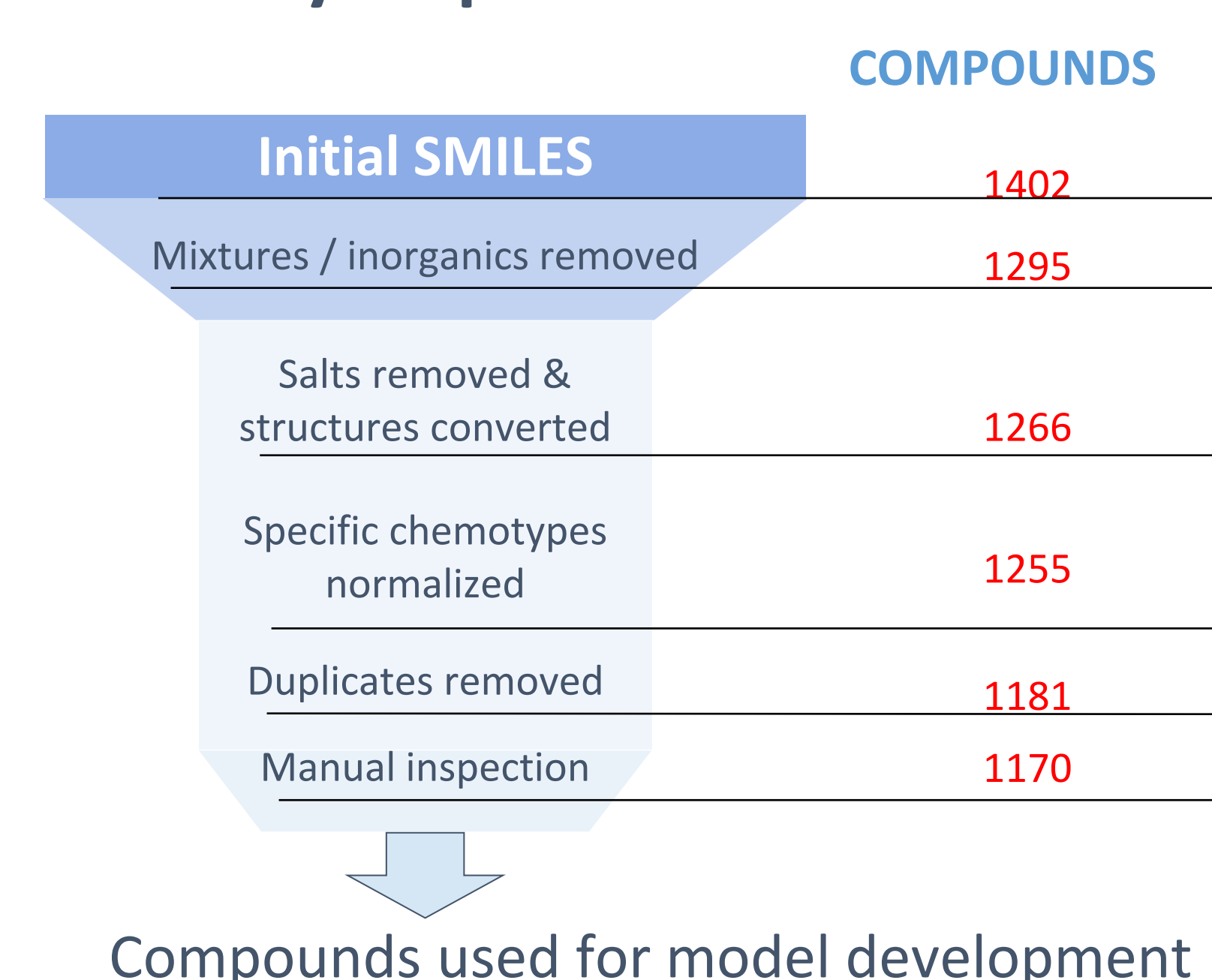
Results

Data overview and curation

Data exploration



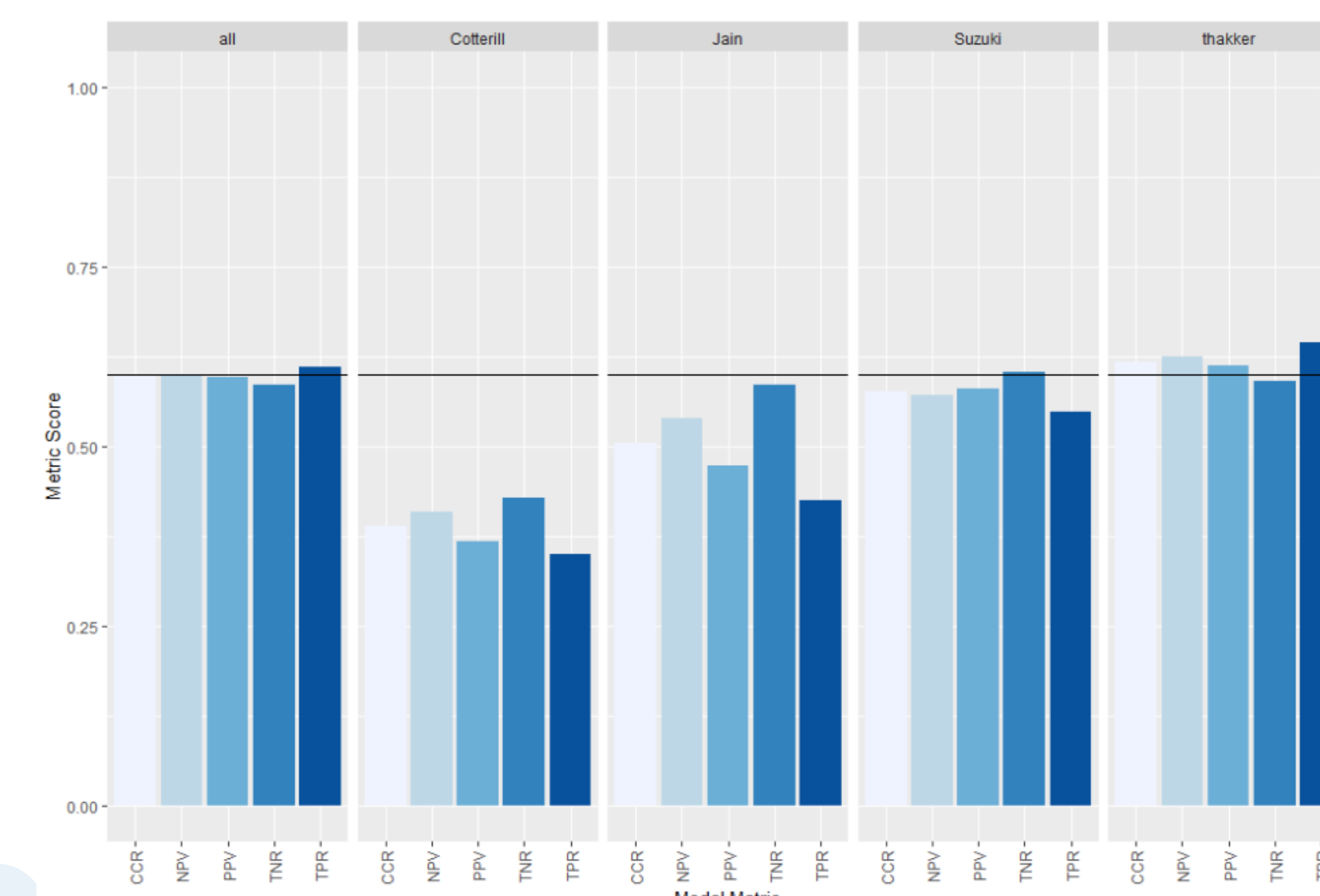
Key steps of curation



Chemical data overlap between top source datasets, visualized by count overlapping and entire set size, color coded by consensus steatosis positivity/negativity.

Summary of the chemical curation workflow, modified from [Fourches 2016]. Initial curation executed using subset of identified sources.

Data modeling



Models developed using similarity balancing, Random Forest with RDKit/Morgan fingerprints, and 5-fold external validation.

Future Directions

Data collection

- Augment with known steatosis treatments
- Annotate sources with assay variables, i.e. organism, endpoint, modality

QSAR Modeling

- Silo models per data source hierarchy
- Build individual event models
- Model interpretation to identify statistically validated chemical moieties associated with HS.

Conclusions

Here represents an attempt to collect, curate, and integrate the largest annotated liver steatosis dataset and use it to develop QSAR models to enable the accurate identification of novel potential steatosis causing agents.

Using public sources, developed the largest curated hepatic steatosis database incorporating 1170 unique compounds.