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Systems Toxicology Computational Challenge explores toxicant prediction

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Singapore: The Systems Toxicology Computational Challenge run under the sbv IMPROVER umbrella, a crowdsourcing initiative led and funded by Philip Morris International which is designed to test and verify scientific methods and results, demonstrated that how transcriptomics information present in the blood can be used to predict whether people have been exposed or not exposed to specific toxicants.

The findings have important implications across a range of disciplines including diagnostics, toxicological risk assessment and personalized medicine. Challenge participants used their own computational techniques to make their predictions, with best-performers achieving accuracy of up to 95%. A total of 135 scientists from around the world registered for the challenge.

"The real-world application of models based on blood gene expression markers for predictive classification in toxicology is uniquely challenging," said Dr Carine Poussin, Computational Biology, Philip Morris International. "The difficulty resides in the identification of relevant markers in blood after chemical exposure and the low success of correct classification when predictive models are applied on new individual blood samples. Furthermore, most pre-clinical toxicological in vivo studies are conducted in rodents, adding a degree of complexity when applying the results to humans. The Systems Toxicology Computational Challenge has explored these questions and helped to increase our understanding of what is necessary to reach higher levels of predictability and robustness in both humans and across species."

The Systems Toxicology Computational Challenge aimed to verify that robust markers could be extracted from blood gene expression data that would distinguish current tobacco smokers from non-smokers, and then discriminate non-smokers as former smokers and never smokers. This question was addressed in two sub-challenges, the first one looking at human data only, the second one investigating human and mouse data together. Anonymized participants' submissions were scored against a gold-standard dataset. Final results and team rankings were reviewed and approved by an independent expert scoring review panel.
Participants were successful in developing models with a high level of predictive performance in distinguishing current

tobacco smokers from non-smokers. Predicting whether non-smokers were former smokers or never smokers was more challenging, suggesting that these two groups are likely to have similar gene expression profiles.

"While the Systems Toxicology Computational Challenge asked participants to make predictions on smoking status, the techniques that participants put forward could in theory be applied to make predictions on exposure to any toxicant or external stimuli," said Dr Julia Hoeng, Director of Systems Toxicology, Biological Systems Research, Philip Morris International. "Importantly, the challenge rules stipulated that models had to be applicable to new individual blood samples without the need for adjustments, making them potentially suitable for ready-to-use diagnostic tools."

Dr Vincenzo Belcastro, Systems Biology, Philip Morris International, commented, "The best-performers in the Systems Toxicology Computational Challenge have achieved near perfect prediction to discriminate smokers from non-smokers. Different methods were used and it is worth considering how these methods could be combined to improve predictability even further, and to add to the confidence we can have in using them. Many of the techniques that have been tested in this challenge should be highly interesting for scientists working in a number of different fields, as well as for industries such as pharmaceuticals and bio-tech."

The challenge provided the opportunity for participants to vigorously and objectively test their methodologies whilst collaborating with global leaders in the field. "We were driven by the desire to create a model that can both lead to valuable biological insight, and be implemented in practice at the lowest possible cost," said Adi Tarca, Associate Professor, Wayne State University, School of Medicine, and a member of one the best-performing teams. "The Systems Toxicology Computational Challenge has allowed us to test the quality of our research and I'm delighted that our approach has proved to be robust."

The three previous challenges were the Diagnostic Signature Challenge, which asked participants to identify robust diagnostic signatures across four disease areas, the Species Translation Challenge, which sought to refine understanding of the limits of rodent models as predictors of human biology, and the Network Verification Challenge, designed to review biological network models for use in toxicological risk assessment.