Smoking behaviours, including cessation, are different for men and women. Women tend to have a harder time quitting cigarettes, and research demonstrates that popular treatments like nicotine replacement patches are much more effective for men. In addition to having greater difficulty quitting, women also experience a heavier health burden from smoking. Understanding how sex and gender interact with genetics to influence smoking behaviours and cessation may help determine why quitting is more difficult for women. Could integrating sex and gender into pharmacogenomics research on smoking be the key to helping women kick the habit?

WHERE THERE’S SMOKE THERE’S SEX DIFFERENCE
Genetics affect how nicotine and smoking-related carcinogens interact with the body, influencing levels of dependence, response to cessation treatment, and even risk for smoking-related cancers.

Two types of genes are primarily responsible for variation in how nicotine acts in the body. The first, which codes for the metabolic function of the CYP2A6 enzyme, influences how quickly nicotine is metabolized, affecting how soon a person might crave their next cigarette. The second type, which includes the protein-coding genes CHRNA5 and CHRNA3, plays a role in the downstream release of serotonin and dopamine—two chemicals that influence the reward response to smoking. Variation in the expression of these genes affects how people metabolize and respond to nicotine, which influences how they become addicted to cigarettes and their ability to quit.

Dr. Rachel Tyndale, Senior Scientist and Head of the Pharmacogenetics Lab at the Centre for Addiction and Mental Health, and Professor in the Departments of Pharmacology and Toxicology and Psychiatry at the University of Toronto, says that “while we have substantial data to support a role for nicotine metabolism in optimizing smoking cessation treatments, less work has been done examining the effects of sex hormones.” The sex hormone estrogen, which is more prevalent in females, increases the amount of nicotine-metabolizing enzymes. Therefore, we know that women often metabolize nicotine more quickly than men, which means they may require different cessation therapies. In general, smokers with genetically slow nicotine metabolism find it easier to quit than those who metabolize nicotine more quickly. In addition, nicotine replacement therapies, like the nicotine patch, are better at helping slow metabolizers quit than...
In addition to more research on sex and genetic influences on smoking, therapies should aim to account for the unique gendered experiences of individuals. Gender-specific therapeutic approaches could offer support for stress management and weight loss, as well as strength-based interventions through online networks. These approaches could lead to more success for men, women and people of all genders who are trying to kick the habit.

CONCLUSION
As we continue to develop approaches for smoking cessation that tailor treatments to genetic variation and environmental influences, assessing how to account for sex will be key to ensuring these therapies benefit women as much as men. Bringing together the distinct but interlocking puzzle pieces of sex, gender and genetics offers a path towards improving smoking cessation treatments that accounts for the uniqueness of each person. In our increasingly personalized medical environment, this promising direction for future research and treatment optimization could help more people of all genders quit smoking and have better health outcomes for life.

ABOUT THE RESEARCH
Dr. Rachel Tyndale is a CIHR-funded researcher and the Canada Research Chair in Pharmacogenomics. She studies variation in drug response in the field of addictions and mental health at the University of Toronto and Centre for Addiction and Mental Health. Her focus is on how genetic variation in drug metabolism alters both the risk for addiction and the response to drug treatments.