SRTP - Project Description Form #210

PART I:

Name of Schulich faculty member who will supervise the project	Aze Wilson
Supervisor's Schulich, Western, Hospital or Lawson Email	azesuzanne.wilson@lhsc.on.ca
Schulich Department	Medicine

PART II - Project Description

Title of Project	NOD2 variation as a genetic prediction tool in IBD drug therapy selection for patients with Crohn's disease

Background

Crohn's disease (CD) is a type of inflammatory bowel disease (IBD). CD, along with the other form of IBD, ulcerative colitis (UC) are important Canadian diseases affecting nearly 1% of Canadians with direct costs of $1.28B annually1. CD is an immune-mediated disease of intestinal inflammation that is punctuated by periods of activity and quiescence. It is associated with significant and debilitating symptomatology that is hugely impactful on an individual's quality of life, ability to participate in the workplace, and to perform activities of daily living

NOD2 encodes a protein responsible for the detection of a bacterial cell wall peptidoglycan. Variation in NOD2 has been the most replicated genomic predictor of ileal Crohn's disease (CD) in European-Caucasian populations, conferring a 20-40-fold increased risk of CD in individuals who carry homozygous variant genotypes.

The 3 most common genetic variations in the coding region of NOD2 are c.2104C>T (rs 2066844, p.R702W, MAF=0.026), c.2722G>C (rs2066845, p.G908R, MAF=0.011) and c.3019_3020insC (rs2066847, pL1007fs, MAF=0.015).

Variation in NOD2 is associated with ileal disease with a stricturing phenotype. The strong genotype-phenotype connection reinforces the potential for NOD2 to exist as a genomic prediction tool.

There are data supporting NOD2 variation as being associated with increasing odds of complicated Crohn's disease needing surgical intervention.

Hypothesis

In addition, to identifying patients with high-risk Crohn's disease, we speculate that NOD2 variation may be helpful for identifying individuals who would benefit from early intervention with specific advanced therapies (biologics) as well as the timing and sequencing of advanced therapies.

Proposed Methodology

A retrospective cohort study will be carried out in adult participants with Crohn's disease who have provided a DNA sample. Included participants will have a CD diagnosis date after December 31, 2015. This will ensure the availability of 3 common advanced therapy classes (TNF antagonists, IL12/23 antagonists, anti-integrins). Participant charts will be reviewed for their CD phenotype, disease location (Montreal classification), drug exposures, drug timing and response to therapy (at 8-weeks, 24-weeks, 52 weeks), date of diagnosis, number and time to any CD-related surgical interventions, age, sex, weight, smoking history. Participants will be evaluated from the date of diagnosis to their last CD-follow-up. Participant DNA will be genotyped for two (three?) common NOD2 variants associated with a deleterious impact on NOD2 function. The effect of the genotype and various haplotype combinations on CD outcomes such as small bowel stricture, time to "significant" stenosis (imaging, with or without features of inflammation), hospitalization

for obstruction (functional stricture), need for surgery, time to surgery, number of surgeries, corticosteroid use per year of disease, response to advanced therapies, will be assessed.

Cohort will be divided into NOD2 wildtype vs NOD2 variant carriers (any variant)
The “any” NOD2 variant group will be additionally analyzed based on the presence of one, two or variants (dependent on power).

Expected Outcomes
1) we anticipate that up to 30-40% (150-200) of our CD population will carry a variant in NOD2 based on prior studies
2) we anticipate that NOD2 variation will be associated with a stricturing phenotype
3) we anticipate that NOD2 variation will be associated with increased occurrence of poor outcomes such as hospitalization, surgical resection due to complications related to stricturing disease
4) We anticipate that patients with NOD2 variation who receive biologic therapies early (3 mos vs 6mos vs 12mos from diagnosis) in their disease course will have less hospitalization, surgery. We will compare them to patients who are wildtype for NOD2.
5) We anticipate that biologics targeting inflammatory cytokines will be more effective in patients with NOD2 variation than biologics that target lymphocyte trafficking.

Research Environment – Description of the number of research personnel, primary location of research, size of lab, etc
WORK ENVIRONMENT: All research will be conducted in the Personalized Medicine Laboratory (C9-100, University Hospital). This is a large laboratory occupying most of the C9 wing. It is equipped with state-of-the-art molecular biology, genotyping, and drug level analysis technologies, including two triple quadrupole tandem mass-spectrometers. In addition, there are -80◦C freezers (3); two tissue culture rooms (BL-2 level), dark room, and two large equipment rooms with centrifuges (mid speed to ultracentrifuge (1 million G capable), an ABI quantitative real-time-PCR machine, scintillation counters, microscopes (including immunoflurescence), 96-well fluorescence plate reader, and an Kodak Imagestation, Agilent Bioanalyzer. All the major equipments are fully networked and data captured through a central lab/computer-server. Furthermore, there will be access to technicians, and MSc students with strong backgrounds in molecular biology and genomics.

Names and titles of other individuals who will be involved with the research project?
Research Technician (pending - in process of hiring)

Can this project be done remotely?	No
Duration of Project	Two Summers

Expected Objectives/Accomplishments for Student for Year 1?
Assist with genotyping of patient cohorts
Characterize CD patient target population from the Personalized Medicine Research Database (N=500) with respect to important outcomes
Prepare a poster for presentation at a local or national conference, presenting interim data

Expected Objectives/Accomplishments for Student for Year 2?
Completion of genotyping of patient cohorts
Completion of chart review for patient outcomes
Assist with final analyses for clinical outcomes
Manuscript preparation
Preparation for presentation of results at a local or national GI conference

PART III - Certifications

If the project will require any certification approvals from one or more of the following offices, please check the

appropriate box below.	- Human Ethics - Biohazard
Human Ethics: If you have the protocol information, please enter it below (or enter the status of the approval).	Pending - REB will be submitted and approved before summer 2024
Biohazard: If you have the protocol information, please enter it below (or enter the status of the approval).	approved

Note: certification approval should be obtained prior to the start of the summer. Projects without this approval will not be a priority for funding.