

A.1: Mentor information

Name Laurent Briollais Scientist in biostatistics/statistical genetics	Institution Lunenfeld-Tanenbaum Research Institute/Mount Sinai Hospital	Department Prosserman Centre for Health Research
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A.2: Co-mentor information (if applicable)

Name Yun-hee Choi Associate Professor	Institution Western University	Department Epidemiology and Biostatistics
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A.3: Research proposal (maximum two pages)

Title
Multistate models for cancer risk prediction of hereditary breast ovarian cancer patients

Background
Women with pathogenic variants in *BRCA1* and *BRCA2* genes are at high risk of developing breast and ovarian cancers. They usually undergo intensive cancer surveillance and may also consider surgical interventions such as risk-reducing mastectomy (RRM) or risk-reducing salpingo-oophorectomy (RRSO). RRSO has been shown to reduce ovarian cancer risk, but its association with breast cancer risk is less clear. The difficulty in evaluating interventions such as RRSO or hormone-replacement therapy (HRT) is that their association with breast cancer can vary with time in a complex manner. Therefore, recent results on the benefits of such interventions have been controversial.

Aims
To assess the impact of RRSO and HRT on the risk of breast cancer in women with pathogenic variants in *BRCA1* and *BRCA2* genes using families recruited through the breast cancer family registry (BCFR).

Research methodology
We are planning to use a multistate modeling approach to assess the risk of breast cancer following RRSO, HRT or the combination of HRT after RRSO. In this framework, RRM, RRSO and HRT will be considered as intermediate time-to-event outcomes before breast cancer onset. Ovarian cancer and death from other causes than breast and ovarian cancers will be considered as competing risks events. We will also include contralateral breast cancer and death after a first breast cancer as successive events.

Training objectives + Mentorship plan
The goal of the internship will be to train the selected student in application of complex survival models, multi-state models and analysis of genetic/familial data. In terms of biomedical application, the student will be able to foster knowledge on the evaluation of treatment/intervention in the context of cancer studies. The mentorship will consist of weekly meetings with the two supervisors (likely through zoom). The student will also be able to attend seminars related the topics of interest, including the statistical genetic seminar offered bi-weekly at the Lunenfeld research institute as well as bio-statistical seminars at UofT. The student will be requested to write progress reports on a bi-weekly basis and will be part of a publication in a biomedical journal if the results warrant such publication.

Necessary intern background/strengths
Background in survival analyses and regression models is necessary. Knowledge of multistate models and analysis of familial data would be an asset but not mandatory.



**Form I: BTI Internship Program
Mentor Application**

Fit OICR strategic plans

The project falls directly into OICR strategic plans, in particular, related to translational cancer research and personalized medicine. The results of this research could better guide decision-making of women carrying pathogenic variants in BRCA1/2 genes including the choice between intensive surveillance and prophylactic surgery and the timing of such intervention. It could lead towards a more personalized intervention tailored at the specific genetic risk (for example based on the mutation-specific cancer risk).