Canadian Cancers of the Lung in Light and Never Smokers (CLANS) Network Website

September 30, 2024

Dear Member of the GOMRG Selection Committee,

RE: COVER LETTER

Please accept this application, entitled "The CLANS Network Website".

When thinking about this modest $25,000 grant opportunity, we thought about the goals of the Geoffrey Ogram Memorial Research Grant and what can be done to leverage this amount of funding for the greatest impact. The study of the etiology and early detection of lung cancer already aligns well with much of the research in my lab:

1. We are part of a US NCI U01 funded grant on implementing radiomics and biomarkers into screening of lung cancer, focused on heavy smokers meeting current lung cancer screening eligibility (INTEGRAL-AT study), and I am a lead site participant and enroller.

2. My trainees have led the analysis and publication of the following screening-related studies recently:
    a. Fares AF et al. Association between duration of smoking abstinence before non-small-cell lung cancer diagnosis and survival: a retrospective, pooled analysis of cohort studies. Lancet Public Health. 2023 Sep;8(9):e691-e700.
    b. Zhang Y et al. Using Recurrent Neural Networks to Extract High-Quality Information From Lung Cancer Screening Computerized Tomography Reports for Inter-Radiologist Audit and Feedback Quality Improvement. JCO Clin Cancer Inform. 2023 Mar;7:e2200153.
    c. Aggarwal R et al. Outcomes of Long-term Interval Rescreening With Low-Dose Computed Tomography for Lung Cancer in Different Risk Cohorts. J Thorac Oncol. 2019;14:1003-1011.
    d. Lam ACL et al. Point-of-Care Spirometry Identifies High-Risk Individuals Excluded from Lung Cancer Screening. Am J Respir Crit Care Med. 2020 Nov 15;202:1473-1477.
    e. Aggarwal R, et al. Stratification and management of patients ineligible for lung cancer screening. Respir Med. 2021;188:106610.
    f. Lam ACL et al. Predictors of participant nonadherence in lung cancer screening programs: a systematic review and meta-analysis. Lung Cancer. 2020;146:134-144.

3. We are a main recruiting site and investigators of a CCSRI Breakthrough Grant in lung cancer screening of incidental pulmonary nodules (IDEAL study)

4. We have acquired two industry funding sources and a CCSRI Innovation Grant for breathomics studies for early detection, where we have focused partly on light/never smokers.

5. We have acquired funding for a pilot screening program of East Asian never-smoking females for low dose CT guided screening (SHINES study), where participants are identified through a website.

6. I lead a national 20+ site real world evidence network focused on rare molecular alterations in lung cancer, where many of these alterations occur in lifetime never or light smokers (CARMA BROS).

In addition, there are clear pockets of clinical, epidemiological, and translational research across Canada that are focused on lung cancer in never or light smokers, including nodes in Vancouver, Alberta, Ontario, Quebec, and the Maritimes. CCSRI has funded breakthrough grants in risk factors/preventive strategies in never-smoking related lung cancer, and cancer risk in incidental pulmonary nodules, the latter of which we are investigators in (IDEAL study).

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However, what is lacking in Canada is a coordinated effort to bring together all of these researchers working in light/never smoking related lung cancer, with engagement of other stakeholders such as advocacy partners, patients, and their supporters. There are unmet needs, including better understanding of preventive strategies, improved early detection strategies regardless of smoking status, and better management and treatment of never/light smoking related lung cancers. This was the genesis of the concept of the Canadian Cancers of the Lung in Light and Never Smokers (CLANS) Network Website

When developing our Screening in HIgh risk NEver Smokers (SHINES) study focused on CT screening of never-smokers with other high risk features, such as East Asian background, we realized that an efficient way to identify light and never smokers (both cases and controls) was to use a multitude of information dissemination techniques, where all of the potential participants accessed a single website. An efficient method would also be to collect the risk factor information through this website. In our discussions with Prof. Martin Tammemägi, we worked to minimize missing and imprecise data in our self-administered surveys, and modeled them on coordinator-administered surveys that Martin had developed for the never smokers at the Lahey clinic in the US. We then also incorporated survey items from other groups, such as Renelle Myers and Stephen Lam from BC, and Rayjean Hung from Sinai Health Systems in Toronto. We are just about to launch this SHINES study (REB revisions submitted).

When the GORMG call for applications came, we realized that we could expand this website to be Canada-wide, and use it to bring researchers in this area together. We see an opportunity to use this website to identify and recruit potential participants not just for our own studies, but for other studies across Canada. As this application call came from LCC, we saw additional opportunities to use such a website for educational and advocacy work, given how little the public is aware that lung cancer can occur in light/never smokers.

Thus, this specific GORMG application submission, the CLANS network website, connects existing research in early detection lung cancer methodologies by streaming potential eligible participants to matched studies across Canada, including studies investigating blood- and breath-based biomarkers for early detection. CLANS focuses on early detection for the entire population of adults not meeting current screening criteria. CLANS links patients and the public to studies on the etiology of lung cancer, specifically in ex-smokers (who tend to be light smokers) and non-smokers. In this way, this proposal has direct practical relevance to Canadians with lung cancer, while leveraging a modest budget into a bigger entity.

In supporting CLANS, we see future leveraging opportunities to sustain our efforts long term in myriad ways: by applying for funding of the analysis of the risk factor data and its modeling, applying for industry and donor support to maintain this website (it is an attractive concept for both groups), and by utilizing the development of this website to bring together researchers in this field and generate new research partnerships and collaborations capable of obtaining large collaborative grants.

We hope that the committee can also see the potential for this project that directly engages in research into the risk factors associated with lung cancer in never/light smokers, as well as builds infrastructure to support other research, with secondary benefits of promoting advocacy and educational efforts.

Sincerely

Geoffrey Liu, MD FRCPC FISPE
Princess Margaret Cancer, University of Toronto and Dalla Lana School of Public Health

Canadian Cancers of the Lung in Light and Never Smokers (CLANS) Network Website

Summary of Proposed Research SEPT 30, 2024

Background: Lung cancer screening using low dose computed tomography has been established as a cost-effective method of reducing lung cancer mortality in heavy smokers[1]. Canadian screening programs specifically target individuals with a significant smoking history. With falling rates of smoking and growing incidence of lung cancer in never and light smokers, a substantial proportion of lung cancer patients would not have qualified for screening based on current screening eligibility criteria[2]. There are clearly risk factors aside from smoking that are driving lung cancer cases in never and light smokers, but more research is needed to identify these factors and convert them into meaningful screening action.

Globally, there is increased lung cancer risk in women of East Asian descent[3]: the incidence rate of lung cancer in Taiwanese female never smokers is 2.6%[4], and in Japan 32% of all lung cancer cases occur in never-smoking women[5]. The Female Asian Nonsmoker Screening Study in the US has also found a lung cancer initial screening incidence rate of 1.5%[6]. Aside from genetic ancestry and family history of lung cancer, increased risk can be conferred from environment factors such as microparticle pollutants[7] and radon exposure[8].

In Canada, research in risks and outcomes of lung cancer in never/light smokers is growing but fragmented. There are two CCSRI Breakthrough Team Grants – one focused on the influence of arsenic, radon, and pollution on lung cancer risk for never smokers; and one focused on the risk of lung cancer in individuals with incidental pulmonary nodules (we are co-investigators and a recruiting site for the latter). Further, our lab is launching a pilot Toronto study to screen never smoking women of East Asian descent for lung cancer (SHINES study), with ancillary studies of blood-based biomarkers, radiomics, and breathomics; the goal is to identify innovative early detection methods applicable to all high risk individuals, regardless of smoking history. A similar study is being independently conducted in Vancouver. Encouragingly, work on a risk calculator for never smokers has been started in recent years by Prof. Martin Tammemägi[9], creator of the $PLCO_{m2012}$ risk calculator used to guide screening in heavy smokers in Canada, in partnership with the Lahey Medical Center in the US. We have partnered with Prof. Tammemägi to develop a lung cancer risk stratification tool for never/light smokers that is applicable to the Canadian population. We originally intended to create a local website to survey risk factors in never/light smoking lung cancer cases and controls in the Toronto region to obtain the data to develop this tool, and then to stream individuals eligible for any of our other research studies (such as the East Asian screening study) through this website.

With the announcement of 2024 GOMRG, we saw an opportunity to expand such a website to become Canada-wide, allowing us, where geographically feasible, to stream patients to other studies of never/light smokers with lung cancer to our colleagues from BC to the Maritimes, where the two CCSRI Breakthrough grants are anchored. Building such a website would encourage networking across all investigators performing research on light/never smoking lung cancers, as investigators would be invited to help develop the content of the website. The website could also tie in with CARMA-BROS, the Canadian network for real world evidence in lung cancer, as many of the rare molecular alterations associated with lung cancer occur in light/never smokers. We also see an opportunity to tie such a website with advocacy and education efforts, including acting as a resource for Lung Cancer Canada and the Lung Health Foundation, both organizations that our lab has been working with.

Our overarching goals are to coordinate research efforts and educate the public and health professionals on lung cancer in never/light smokers, and eventually identify improved methods to prevent, detect early and manage such patients.

Primary Aims:

1. To build a centralized website connecting researchers working on understanding risk factors for lung cancer in light and never smokers, which can help catalyze discussions for potential alignment and collaboration;
2. To develop a Canada-wide database of risk factor and clinical information on lung cancer in patients with little to no smoking history, in a comprehensive, standardized database platform (REDCap) for research.

Secondary Aim:

To provide a platform for public/professional education & advocacy on lung cancer in never or light smokers

Methods:

We have already developed a local Princess Margaret-hosted centralized website that invites individuals with or without lung cancer who are light or never smokers to share risk factor data. This online survey is connected to

a REDCap database, and was co-developed with tools from our own lab, and that from our colleagues, Profs. Rayjean Hung, Renelle Myers, Stephen Lam, and Martin Tammemägi, as part of our local *S*creening in *HI*-risk *NE*ver *S*mokers study (SHINES study, funded by AstraZeneca; see Figure 1, left panel). We will use this experience as a template for developing a website to suit national needs in CLANS (Figure 1, right panel). The SHINES study is currently under REB review, and should be operational by December 2024. The information collected in the REDCap database has been based on the modified Tammemägi risk calculator for light or non-smokers, and augmented to include any additional features that were deemed potentially relevant during our initial expert consultations. We anticipate that this database will not be changed much, if at all, for the Canada-wide CLANS network website.

The development of the CLANS website will be guided by a committee of experts, including epidemiologists, clinicians, research and clinical experts, and patient advocates. To identify research and clinical experts to join the committee, we will first perform a scoping review with the help of a research student. We will search a variety of online resources for current research (e.g. clinicaltrials.gov, PROSPERO registry, CIHR funding decision database) to thoroughly understand the current state of the field, and ensure proper representation on committee. We will contact any Canadian principal investigators identified in this review, which will also serve as an opportunity to introduce them to the consolidation efforts we are undertaking. We will also utilize our extensive network of research, advocacy and clinical contacts to ensure that additional appropriate stakeholders are invited. We will survey the committee for their opinion of the Canadian landscape of lung cancer in never/light smokers, including what unmet needs exist, and what role the CLANS website can play to address the identified needs. This data will be collated for two purposes: to develop the content of the national website, and as a starting point for a possible future white paper on this subject (to be separately funded, but white papers are a method that we have used before to effectively bring stakeholders together to collaborate). In our local SHINES study, we have developed a plan to drive recruitment to our website; this includes planned media interviews around the Toronto area, dissemination of flyers in oncology and primary care practices, and organic recruitment through the website via search engine optimization. For CLANS, we will include consultations with our expert committee to expand the website reach to other Canadian cities and provinces. Individuals who access the site are divided into lung cancer cases and non-lung cancer controls. A set of questions on the website will determine eligibility of the individual to complete the appropriate risk factor/clinical survey. Based on postal code information collected in the online survey, any participant within a 50km radius of a study site in Canada known to be recruiting patients for research involving light or never smoking lung cancer cases or controls will be contacted and alerted to the potential to enroll in that secondary study. Thus, our central database will serve not only as a large source of clinicodemographic data, but also as a net to catch and direct patients toward other high-impact research. The CLANS website will also host educational materials from our partner advocacy groups.

Measures of project success: We will track and report how many individual principal investigators we identify as having a project relevant to this area of research, how many we are able to successfully contact, and how many are willing to participate on the committee, and/or give permission to have us summarize their research or link to their websites. We will measure traffic (unique webpage visitors) to the CLANS website over time, defining success as consistent growth in traffic month over month. We will measure the number of participant questionnaire responses, and consider this form of wide-sweeping recruitment feasible if, by the end of the funding period, we are recruiting at least 30 participants to fill out the questionnaire per month; lower numbers will signal the need to discuss new strategies of outreach. We will also track the number of participants who are eligible for another study at the time they enroll in our study, and the number who consent to being contacted for these other studies.

Sustainability: Once the website is developed, tested, and implemented, we anticipate that costs to maintain website will be low. We will leverage efforts to sustain funding by applying for grants to support the risk stratification tool development, in addition to industry/donor support.

Timeline: Scoping and Committee Consultation: 5 months; Website development, 4 months; Website implementation, 3 months. Since this will replace the SHINES website, we will only need a brief REB amendment to switch over the risk factor questionnaire from one website to another, incurring no delays.

Canadian Cancers of the Lung in Light and Never Smokers (CLANS) Network Website

References

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2. (Unpublished) Review of lung cancer patients diagnosed at Princess Margaret Cancer identified 68% of patients in 2022-2023 would not have qualified for lung cancer screening under $PLCO_{M2012}$ criteria at 2.0% lung cancer rate over 6 years.

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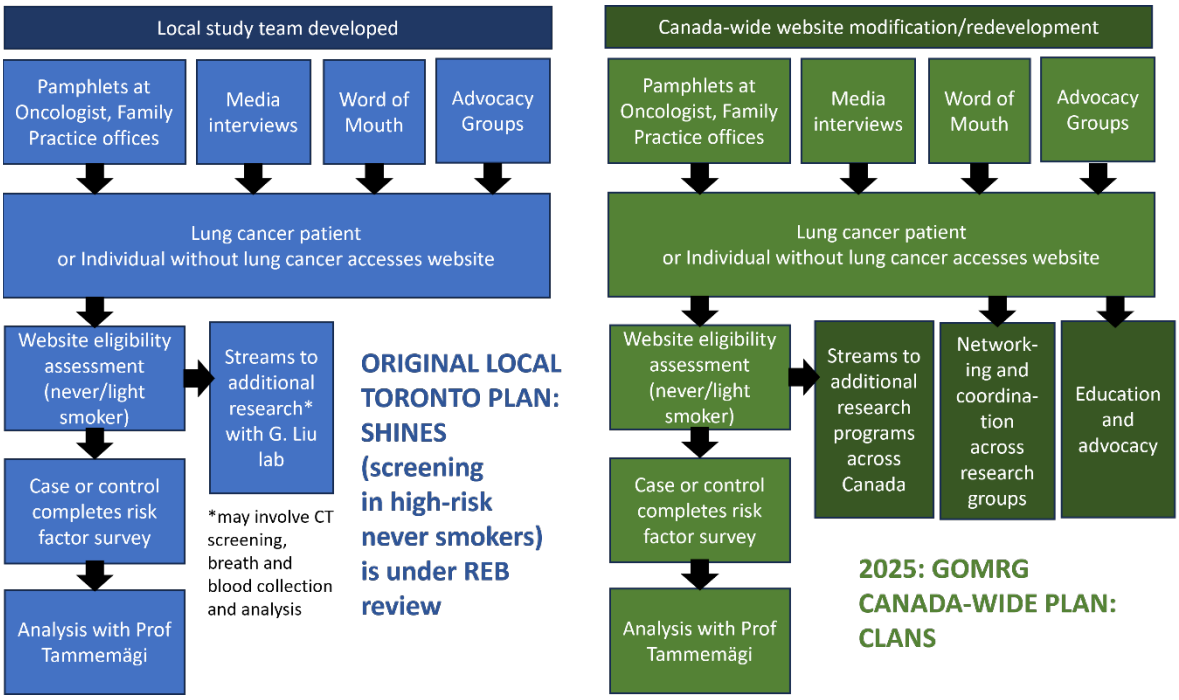

Figure 1: Comparison of the Screening in High Risk Never Smokers (SHINES) study already developed in the local context (left panel, blue) with the proposed CLANS redevelopment (right panel, green). Minimal programmatic changes are needed to create a much wider-reaching project.

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Impact Statement

The main purpose of the CLANS network website is to collect data to facilitate the development of a Canadian-based risk stratification model for lung cancer risk in individuals who are never or light smokers. Prof Martin Tammemägi had developed the original PLCOm2012 risk stratification model that is currently used for heavy smokers, and originally had adapted that model to include never smokers. However, it is well known that light and never smokers have very different types of lung cancer, each with distinct biological, etiological, epidemiological, and molecular characteristics. Thus, Prof Tammemägi has been developing a separate risk stratification model, and we have partnered with him to adapt and co-develop this model for Canadians. Developing an early detection strategy for light and never smokers is critical to improve lung cancer outcomes, as currently in Canada, a substantial proportion – perhaps even the majority of lung cancer patients in some major cities – would not have qualified for lung cancer screening based on current criteria. Early detection has been demonstrated to lead to stage migration, leading to improved cure rates, long term quality of life, and reduced mortality; we would like to achieve this goal for lung cancers in light and never smokers.

Secondly, this project will connect potential study participants to other studies of lung cancer in never or light smokers, including two CCSRI Breakthrough grants (one on risk factors/prevention and the other on incidental pulmonary nodules), and innovative research in alternative biomarkers for early detection such as breathomics, radiomics, and blood-based biomarkers. In this way, the CLANS website will directly promote the advancement of lung cancer research in never and light smokers.

Thirdly, the development of this website will bring together Canada-wide efforts to study lung cancer in never or light smokers, which will accelerate this research, and transform into a network. The Liu laboratory has a longstanding tradition of building such networks, as Prof Liu runs the Clinical Outcomes Studies of the International Lung Cancer Consortium (COS-ILCCO; 30+ international sites), and the Canadian Rare Molecular Alterations Basket-umbrella Real-world Observational Study (CARMA BROS; 20 Canadian sites and growing); he will utilize his expertise to bring together the diverse groups of stakeholders through the formal process for identifying and including stakeholders, with the help of LCC executives and other lung cancer knowledge leaders. Stakeholders will not only be focused on early detection, but such a network can bring together clinicians and translational researchers with expertise in improving the treatment and management of such tumours, which are often molecularly targetable. The inclusion of other key stakeholders such as patients and advocacy groups will help to translate these findings into optimization of patient care, improved treatment options, and reduced burden.

In the short term, this project will collect clinico-risk data on light/never smokers to help adapt/develop a lung cancer risk stratification tool appropriate for Canadians who are not heavy smokers, and to bring together researchers across Canada to brainstorm, align, and collaborate on research. The primary medium-term goal (to be funded separately) is to generate consensus, in the form of a white paper, on the unmet needs and directions of research for lung cancer in never/light smokers through these stakeholder meetings. Another medium-term goal is to improve the education of the public and health care professionals on the distinct presence lung cancer in light and never smokers, as well as non-smoking risk factors. A final medium-term goal is to utilize this new network to develop large scale Canada-wide competitive grant applications. By enabling continued collaboration and knowledge synthesis, CLANS will ultimately be a platform for long-term innovation to reduce the disease burden of lung cancer in light and never smokers.

Canadian Cancers of the Lung in Light and Never Smokers (CLANS) Network Website

SEPT 30, 2024

Public, Non-Scientific Summary

CLANS (Canadian Cancers of the Lung in Light and Never Smokers) is an innovative research program aimed at addressing the burden of lung cancer that is growing at an alarming rate in Canadians who have never smoked or have smoked very little. The main goals of this project are (i) to collect information across Canada in order to identify risk factors associated with the development of these lung cancers, and (ii) to unite researchers who are already working in this area. All together, the project's long term goals are make it easier to prevent, diagnose early, and treat lung cancers that occur in never or light smokers. To make this happen, CLANS will bring together a group of experts, including physicians, researchers, patients and their supporters, to form a network through the creation of the CLANS website. The website will allow people from anywhere in Canada to safely share specific information about their environment, their medical histories, and demographic information, so that researchers can learn what factors make them more likely to develop lung cancer. The CLANS website will also help match people with other ongoing studies about lung cancer in people who do not smoke or only smoke a little. If someone visits the website and fits the requirements for a study, they will be invited to learn more about such a study. This could help speed up research into these types of lung cancers across Canada. CLANS also wants to team up with groups that support lung cancer patients, such as Lung Cancer Canada and the Lung Health Foundation. Working with these groups will help teach more people about the risks of lung cancer in non- or light smokers. In conclusion, the CLANS network is taking a big step to address the growing problem of lung cancer in people who never smoked or smoked very little. By bringing together research, collecting data, and teaching people, this project could really improve how we understand and help this growing group of lung cancer patients.

Canadian Cancers of the Lung in Light and Never Smokers (CLANS) Network Website

SEPT 30, 2024

Proposed Budget

Amount (CAD)	Description
$10,000 from OGRAMS, matched 1:1 ($10,000) with Chair funds	0.3 FTE research manager for 1 yr
$5,000 from OGRAMS, matched 1:1 ($5,000) with Chair funds	Two research students: for Scoping review and for working with subcommittees (research, advocacy/education) on website development
$5,000 from OGRAMS, matched 1:1 ($5,000) with Chair funds	0.2 FTE data analyst for 6 mos
$2,900	Basic website design services
$1,000	Certified website translation (Eng -> French)
$1,000	Patient education material development
$100	Website domain registration and 1 yr maintenance
$25,000 OGRAMS matched with $20,000 of Chair funds	TOTAL + matched funding for personnel

Two personnel will be primarily responsible for the project, a research manager (C. Deutschman, M.Sc., involved for the duration of the project) and a data analyst (L. Zhan, MPH, involved in REDCap development and evaluation of the project). Both personnel are full time employees of my lab and will have dedicated and protected time to move this project forward. The research manager will be responsible for setting up the website, engaging design, education, and translation services, and managing content. This includes reaching out to identified subject experts and other investigators across Canada to invite them to participate in the committee. He will also be involved in the management of research ethics for the screening arm of the project. The data analyst will be responsible for the development and integration of the screening REDCap, as well as developing success metrics for each aim and evaluating them at the 1-year mark.

In addition to these two individuals, the scoping review and management of stakeholder committee meetings will be undertaken by two research students; both students will be co-supervised by C. Deutschman and Prof G. Liu.

Funding for all personnel will be derived half from the Geoffrey Ogram Memorial Research Grant, and half from matched funding through the M. Qasim Choksi Chair in Translational Lung Cancer Research, held by Prof G. Liu. Dr. Liu's Chair dictates that all funds used must be matched with external non-Chair funding, and the CLANS network website would be an excellent use of this required matching.

As all aims involve communication via a website, we will need to pay to register and maintain a specific website domain for the duration of the project. We will enlist basic design services in the creation of our site pages so that the website is more readily readable, taking into account wherever possible standards of accessibility such as colour-blind friendly colours, alt text for screen readers, larger font for those with low vision, etc. We will work with our hospital's Patient Education and Engagement department to create a dedicated site page written for the general public, containing basic education on lung cancer in light and never smokers. A translation of the primary body of the website into French is a critical component of the project, as we aim to reach a pan-Canadian audience of researchers and patient advocates.

Aaron Schimmer, MD, PhD, FRCPC
Director, Research
Princess Margaret Cancer Centre
7-504, 610 University Avenue
Toronto, Ontario M5G 2M9
Phone: (416) 946-2068
Email: aaron.schimmer@uhn.ca

September 27, 2024

Lung Cancer Canada
133 Richmond St W. Suite 208
Toronto ON M5H 2L3

Re: Letter of Support for Dr. Geoffrey Liu's application for a Lung Cancer Canada – Geoffrey Ogram Memorial Research Grant

Dear Research Committee

As Research Director of the Princess Margaret Cancer Centre, University Health Network it is my pleasure to provide this letter of institutional support for Dr. Geoffrey Liu's application for a Lung Cancer Canada – Geoffrey Ogram Memorial Research Grant titled Canadian Cancers of the Lung in Light and Never Smokers Network Website.

Dr. Liu is a Senior Scientist at the Princess Margaret Cancer Centre (PM), UHN and a Professor of Medicine in Medical Biophysics, Pharmacology and Toxicology, Institute of Medical Science at the University of Toronto, and Professor of Epidemiology at the Dalla Lana School of Public Health at the University of Toronto. He also holds the M. Qasim Choski Chair in Translation Lung Cancer Research at PM. He is internationally recognized for lung cancer research and leads the Princess Margaret Lung-CALIBRE (Lung Cancer And Liquid biopsy, Informatics, Breathomics, Radiomics for Early detection) program. He also leads the Clinical-Outcome Studies of the International Lung Cancer Consortium (COS-ILCCO) and is the PI of the Canadian Rare Molecular Alteration Basket-umbrella Real-world Observational Study (CARMA-BROS). A substantial portion of his research involves improving methods for lung cancer screening and implementation, including participating as a main recruiting site for nationally and internationally funded research investigating what blood, breath, and radiomic biomarkers indicate a higher risk of lung cancer in individuals with various smoking histories.

On behalf of the institution, I confirm that the proposed research is feasible, and Dr. Liu has full support.

Sincerely,

Aaron Schimmer, MD, PhD, FRCPC
Director, Research
Senior Scientist, and Staff Physician,
Princess Margaret Cancer Centre
Professor, University of Toronto