UHN Princess Margaret Cancer Centre

September 25, 2025

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

Dear Selection Committee,

RE: Letter of Intent – Give A Breath Research Award
Lung TRACK: Monitoring lung cancer through liquid biopsy

I am writing to express my intent to submit our project, "Lung TRACK: Monitoring lung cancer through liquid biopsy," for consideration of the Give A Breath Research Award. This study will evaluate the accuracy and clinical impact of using liquid biopsy—blood-based cell-free whole genome sequencing (cfWGS) analysis—as a tool for cancer surveillance. Our aim is to complement or reduce reliance on routine CT imaging, improving the patient experience and potentially identifying disease progression earlier. Thanks to prior support from Lung Cancer Canada and the Ambition Alliance, we validated the TruSight Oncology 500™ liquid biopsy assay for clinical biomarker testing. This has already helped patients access targeted therapies faster and avoid invasive re-biopsies when tissue is insufficient.

We now propose to expand this technology's use beyond initial diagnostics. Currently, patients undergo frequent imaging to monitor disease, but scans are increasingly difficult to access, involve extra hospital visits, and can produce incidental findings that increase anxiety. Early data suggests that ctDNA may detect progression sooner and that prolonged ctDNA clearance correlates with improved outcomes. Using a tumor-informed assay tailored to each patient's tumor biology, this study will assess whether serial liquid biopsy can enhance or replace scan-based monitoring. This project will be led by Dr. Zhen (Jason) Fan, an oncology resident, prospective fellow, at the University of Toronto. With full support from our Thoracic Oncology team at Princess Margaret Cancer Centre, we will provide all necessary mentorship, infrastructure, biostatistical support, and matched funding through the Princess Margaret Cancer Foundation.

We sincerely thank you for your past support and look forward to continuing this impactful collaboration.

Sincerely yours,

Natasha B. Leighl, MD, MMSc, FRCPC, FASCO, FCAHS

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Title: Lung TRACK: Monitoring lung cancer through liquid biopsy
PI: Dr. Natasha Leighl
Co-applicant: Dr. Zhen (Jason) Fan

II. Summary of Proposed Research

Background

Lung cancer is the leading cause of cancer-related death in Canada, and most are diagnosed with advanced disease (1). Computed tomography (CT) scans performed every 2-3 months are the standard modality to assess disease stability in patients are receiving treatment. In Canada, including at the Princess Margaret Cancer Center (PMCC), there are increasing difficulties obtaining CT scans in a timely manner secondary to insufficient capacity, staffing shortages, and the rising number of patients. These factors contribute towards patient and provider anxiety and hinders clinical care (2,3).

Unlike other cancers, there are no validated blood-based tumor markers in lung cancer. Circulating tumor DNA (ctDNA) is gaining significant attention as a diagnostic and prognosticating tool for lung cancer patients (4). In prior studies, rising ctDNA was shown to precede or co-occur with radiographic progression in a retrospective analysis of a metastatic EGFR mutant population (5). At PMCC, we have expertise in utilizing whole genome sequencing (WGS) to develop tumor-informed cell-free DNA assays. This approach is highly personalized to the patient. We hypothesize that liquid biopsy using cfWGS is an accurate means to assess disease activity, when used in conjunction with CT scans. This may allow for earlier intervention, potentially improve patient outcomes, and possibly avoid CT scans for those whose cancer is controlled.

Objectives

Primary Objectives: (1) To assess the accuracy of serial cfWGS for disease monitoring

Secondary Objectives: (1) Describe the lead and turnaround times between ctDNA detection and cancer progression; (2) Assess impact of cfWGS detection on clinical management and treatment decision-making; (3) Assess patient preferences for a liquid biopsy-guided surveillance plan compared to standard of care (routine imaging); (4) Estimate the costs of liquid biopsy

Methods

The **Lung TRACK** study is an investigator-initiated, single-arm, prospective pilot study. We will enrol up to 33 patients with confirmed diagnosis of stage IV NSCLC that have achieved radiographic disease response or stability after at least 3 months of initial systemic therapy and are on ongoing treatment at The Princess Margaret/University Health Network (UHN) requiring routine imaging surveillance. We anticipate that 25 patients will have sufficient tissue needed for tumour-informed cfWGS testing.

Eligible patients will be approached in outpatient thoracic medical oncology clinics at PMCC. Consenting participants will undergo standard surveillance with CT scans every 3 months (+/-2 weeks) and a blood draw of 4 Streck™ tubes (40 mL of blood) at the same time of imaging for up to 12 months (**Figure 1, Appendix**). Blood plasma from two tubes of blood will be analysed using 30X plasma WGS. Blood buffy coat cells and FFPE tumour tissue will be analysed using the 80X tumor/30X normal WGS assay available at our Genomics department (6). This approach utilizes a

reference WGS sequence from the patient's baseline tumour biopsy to sample 1000s of mutations from across the genome, with limits of detection exceeding 10^{-5} in lung cancer due to the high mutation rate (7). The remaining 2 tubes will be banked at UHN Biobank for exploration with future assays developed at The Princess Margaret.

ctDNA results will be categorized as "clearance", "non-progressive", or "progressive" cancer. The genome-wide ctDNA variant allele frequency (ctVAF) is calculated as the total number of sequencing reads with mutations divided by the total number of reads overlapping each mutation site. Clearance will be defined as samples where disease is undetectable, i.e. the number of mutant reads detected in not statistically significant compared to a set of healthy controls. Non-progressive will be defined as a detectable ctVAF less than or equal to baseline levels at study entry. Progressive ctDNA results will correspond to increases in ctVAFs at levels higher than baseline. Clinically relevant thresholds have yet to be established, and this work will address this critical evidence gap. Imaging results as defined by RECIST v1.1 will be interpreted by independent radiologists and confirmed by the treating team (8).

Analysis

The primary objective will be evaluated by calculating the sensitivity, specificity, positive and negative predictive value and concordance between ctDNA and imaging results will be calculated and compared for up to 125 ctDNA-CT imaging pairs (25 patients x up to 5 timepoints). A Receiver Operator Curve will be generated to determine optimal VAF thresholds for disease progression.

Lead time will be calculated from time for first documented molecular progression to radiographic progression. Molecular turnaround time (i.e. time from blood draw to genomic result) and will be calculated. To assess influence on clinical decision-making, temporal relationships between time to next oncology visit, CT scan or subsequent clinician-initiated investigation, and subsequent line of treatment will be assessed based on each ctDNA-CT scan time point. Patients will be asked to complete the EQ5D-5L questionnaire, a validated and widely used questionnaire to assess health related quality of life and patient preference. Finally, cost data for ctDNA testing and radiology will be assessed.

III. Impact Statement

The Lung TRACK study will generate Canadian real-world data to evaluate the role of liquid biopsy as a complementary tool for cancer surveillance and an alternative to routine imaging in patients undergoing treatment for lung cancer. This work will identify the clinical benefits for patients, and the economic impact on Canada's publicly funded healthcare system, including cost savings through reduced imaging demands. These findings will help inform the design of future randomized trials and broader practice changes.

Liquid biopsy has the potential to enhance the patient experience while easing the burden on healthcare infrastructure. We propose using highly sophisticated technologies to generate a reference of mutations from the patient's own tumor, which will then inform blood-based assays that is used for each blood test. We expect concordance between ctDNA and imaging results in patients with stable or responding disease, supporting a shift toward blood-based monitoring in appropriate settings. This may improve access to precision oncology, reduce pressure on radiology services, and ultimately enhance patient outcomes.

This study will contribute to a robust business case for incorporating liquid biopsy into standard cancer surveillance pathways, while also helping to engage policy makers and funders. Longer-term, this work may guide the application of ctDNA and emerging technologies in early-stage disease and recurrence detection.

Personalized medicine using sophisticated genomic testing is at the forefront of modern cancer care. Incorporating liquid biopsy into routine care for patients with advanced NSCLC may reduce reliance on CT imaging, alleviate patient anxiety, and improve timely access to care. This study has the potential to set a new benchmark for patient-centered monitoring both nationally and internationally.

IV. Public, non-scientific summary

Lung cancer remains the deadliest cancer in Canada. We have gained a better understanding of how different genes or biomarkers drive cancer growth and how to match the most effective therapies that target these biomarkers. This has led to lung cancer patients living longer. While patients are on treatment, they undergo routine scans (imaging with computed tomography or CT scans) to monitor any changes in their cancer every 2-3 months as per guidelines. However, at the Princess Margaret Cancer Centre and nationally, there have been significant delays in accessing scans due to large demand, not enough equipment available, and staffing issues. Scans are also challenging for patients and caregivers who must take additional time off work, travel to hospital, and discovering incidental findings unrelated to the patient's cancer can often cause increased patient (and provider) anxiety. The dye used for CT scans is also associated with a risk of severe allergic reaction (0.04%).

"Liquid biopsy" is a blood test that can check for biomarkers that are found in cancer tissue. Despite its name, there is no biopsy in the conventional sense – it is a simple blood draw and uses highly sophisticated techniques to detect genetic material that is shed by the patient's cancer. Many studies, including in Canada, have shown that liquid biopsies are easier for patients, may provide faster results about cancer biomarkers and can accelerate the time to treatment. However, liquid biopsy tests are not funded in the Canadian healthcare system yet and patients must pay out of pocket to access them. Moreover, there has not been much research showing its use in the monitoring of disease activity within lung cancer.

Our study will use the patient's own tumor biopsy sample to help generate liquid biopsies tests. This means each liquid biopsy the patient completes will be highly personalized. These blood tests will occur at the same time as CT scans and results will be compared to see if they match. Other studies have already shown promising data, including for liquid biopsies to detect changes in patient's cancer before we can see them on CT scans. If liquid biopsy can indicate that the patient's cancer is stable or smaller, the patient may be able to avoid CT scans as part of monitoring. This study will explore the safety and value of this approach for patients with lung cancer, and assess its possible impact on our healthcare system, with the potential to change national and global practice in the future.

V. Budget

The Give A Breath Research Award will support the imaging review of all 25 patients for this study.

Staff	Salary	Benefits	FTE	Subtotal	Justification
Clinical research coordinator (2 yrs)	$ 85,000.00	$ 20,400.00	0.2	$ 42,160.00	Patient consent and blood draws
Research manager (2 yrs)	$ 87,000.00	$ 20,880.00	0.2	$ 43,152.00	Data and regulatory management
Senior biostatistician (1.5 yrs)	$ 125,000.00	$ 30,000.00	0.1	$ 23,250.00	Statistical analysis
Clinical fellow (2 yrs)				covered by other funding	
Services	**Unit Cost**	**Timepoints**	**No. of Patients**	**Subtotal**	**Justification**
Joint Department of Medical Imaging (JDMI) review	$ 250.00	5	25	$ 31,250.00	2 independent radiologist blinded review of imaging
Correlative studies program	$ 95.00	5	25	$ 11,875.00	Kit creation (Streck tubes) and transport to Dr Pugh Lab
ctDNA extraction	$ 58.00	5	25	$ 7,250.00	cfDNA extraction for assay
Whole genome transcriptome sequencing tissue	$ 4,341.00	1	25	$ 108,525.00	Panel generation
Whole genome sequencing plasma	$ 1,231.00	5	25	$ 153,875.00	Plasma ctDNA analysis
Biobank	$ 50.00	5	25	$ 6,250.00	Banking of 2 Streck tubes
TOTAL				$ 427,587.00	
Request				**$ 25,000.00**	
To be funded by PMCF				$ 402,587.00	

VI. Names of investigators and CCVs

Please see attached CVs:

Dr. Natasha Leighl – Principal Investigator

Dr. Zhen (Jason) Fan – Co-Applicant

Dr. Trevor Pugh – Co-Investigator

Dr. Patrik Rogalla – Co-Investigator

Appendix

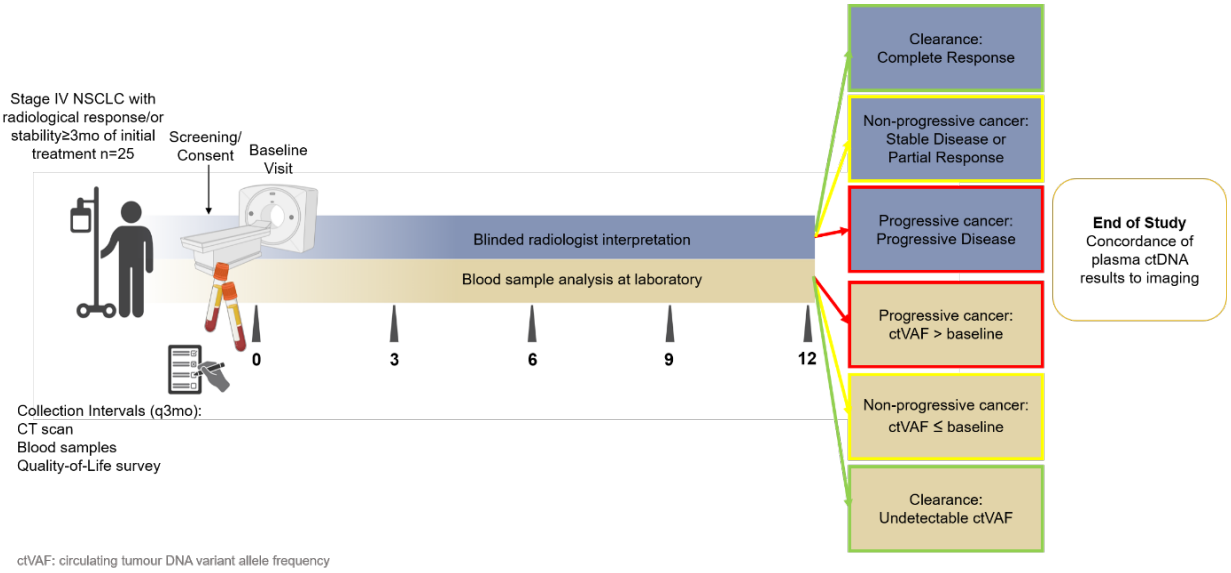

Figure 1. Study Schema.

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August 19, 2025

Lung Cancer Canada

RE: Statement of Support for Dr. Natasha Leighl – Give a Breath Research Award

Dear Award Review Committee,

I am pleased to write this statement of support for Dr. Natasha Leighl and her co-applicant Dr. Jason Fan's application for the Lung Cancer Canada Give a Breath Research Award entitled "Lung TRACK: Monitoring lung cancer through liquid biopsy." Dr. Leighl is the Division Head of Medical Oncology and the former Lung Cancer Site Group Leader which is comprised of research experts in the field, Drs. Frances Shepherd, Adrian Sacher, Geoffrey Liu, Penelope Bradbury, and Lawson Eng. Since joining our faculty as a member of the Division of Medical Oncology and Hematology at the Princess Margaret Cancer Centre (PMCC) in 2017, she has mentored several fellows in both research and clinical practice including the lead fellow of this project Dr. Fan. I am confident this proposal is aligned with the Lung Cancer Group's dedication to innovation for better experiences and outcomes for advanced stage lung cancer patients.

Dr. Leighl's group has been at the forefront of the liquid biopsy field in lung cancer. They will be conducting an observational trial for advanced stage lung cancer patients who are undergoing treatment to compare circulating tumour DNA (liquid biopsy) to routine standard of care CT scans. This work will demonstrate if liquid biopsy can be used in monitoring disease stability whilst patients are on treatment and potentially avoid a scan. This will help build the case for routine funding, access, and potentially faster treatment decision-making for Canada's lung cancer patients who do not have the time to wait for scans in an already overstretched healthcare system.

I have seen the productivity of Dr. Leighl's team ranging from liquid biopsies to real world evidence. I believe the financial support that this grant can provide would positively impact lung cancer patients' lives. On behalf of PMCC, I confirm the proposed research is feasible at our institution.

Yours sincerely,

Keith Stewart, MB ChB, FRCPC, MBA
Director, Princess Margaret Cancer Centre
Vice President, Cancer and Laboratory Medicine Program, University Health Network
Richard H. Clark Chair in Cancer Medicine
Vice President, Ontario Health, Toronto Central South Regional Cancer Program