UHN Princess Margaret Cancer Centre

January 30, 2024

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

Dear Selection Committee,

RE: Letter of Intent – Lung Ambition Award

Lung TRACK: Monitoring lung cancer through liquid biopsy

I am writing to express my intent to submit this project entitled "Lung TRACK: Monitoring lung cancer through liquid biopsy" for consideration of the Lung Ambition Award. In this study, we aim to assess the feasibility of using liquid biopsy – blood tests to assess circulating tumour DNA – as part of cancer surveillance and monitoring, with a view to decreasing the need for cancer imaging (computed tomography or CT scans).

Previously, thanks to Lung Cancer Canada and the Ambition Alliance, we validated the highly sensitive and specific TruSight Oncology 500™ (TSO 500™) liquid biopsy assay for clinical use in lung cancer patients. This assay covers 523 genes, including key lung cancer biomarkers in EGFR, ALK, ROS1, BRAF, NTRK1-3, RET, MET, KRAS, ERBB2 and STK11 genes with a specificity of ≥99.95% and sensitivity of ≥95%. This helps more patients obtain complete biomarker testing and access the best possible treatment faster than using regular cancer tissue and helps patients avoid repeat biopsy if the cancer tissue is not sufficient for biomarker testing.

Now, we wish to move this exciting technology into broader use for patients, beyond biomarker testing. Currently, patients with lung cancer are followed with repeat scans to assess whether their cancer treatment is controlling their disease. However, scans are limited in the Canadian healthcare system with longer wait times and less convenience and risks for patients including the risk of allergic reactions to dyes used in scans plus extra needles and time away from work or other activities. In this study, we hope to establish the potential for liquid biopsies or routine blood tests to understand whether a person's cancer is controlled or not, and potentially avoid a scan if the cancer is controlled. This project will be led by Dr. Zachary Coyne, a gifted junior investigator and clinical research fellow in our Thoracic Oncology Program here at the Princess Margaret Cancer Centre.

Our results will highlight the potential to move liquid biopsies into routine cancer monitoring in Canadian patients with lung cancer. This may improve timeliness of care along the lung cancer patient pathway, decrease costs through decreasing the need for frequent imaging and improve patient convenience.

I fully support this application, along with our entire Thoracic Oncology team at The Princess Margaret Cancer Centre. We will ensure that Dr. Coyne receives the training, supervision and support needed to ensure this project is a success within 12 months. In addition, we will provide matched funding through the Princess Margaret Cancer Foundation plus all biostatistical and project management support required to succeed.

We have been very fortunate to receive your support in the past, and hope we can continue to build on our progress.

Sincerely,

Natasha B. Leighl, MD, MMSc (Clin Epi), FRCPC FASCO

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Title: Lung TRACK: Monitoring lung cancer through liquid biopsy
PI: Dr. Natasha Leighl
Co-applicant: Dr. Zachary Coyne, Clinical Research Fellow

II. Summary of Proposed Research

Background:

Lung cancer remains the leading cause of cancer in Canada, and most patients present with advanced disease. With novel treatments including immunotherapy and targeted therapies, many patients are living longer, better lives [1]. When patients with advanced lung cancer are found to be benefiting from their current treatment, they have routine surveillance scans (imaging) every 2-3 months - computed tomography or CT scans – as recommended by guidelines [1]. However, this approach relies entirely on imaging to assess cancer control. In Canada, including at the Princess Margaret Cancer Centre, there are escalating delays in obtaining timely CT scans due to increased demand, insufficient capacity, and staffing issues. These all significantly increase patient (and provider) anxiety, and impact access to timely care and overall outcomes [2-3].

In other cancers, the use of circulating blood biomarkers has detected earlier recurrence beyond imaging alone, leading to timely interventions and potentially improved patient outcomes [4-6]. In non-small cell lung cancer (NSCLC), there is no blood-based biomarker test approved as part of routine surveillance. Liquid biopsy, a non-invasive blood test that detects circulating tumour (ct)DNA, has emerged in recent years as a faster alternative to conventional tissue biopsies for molecular testing for targeted therapies. These assays are safe and more convenient for patients [7]. Studies of ctDNA have demonstrated the ability to detect cancer returning several months before growth of cancer is found on imaging, leading to the potential to intervene earlier and potentially improve patient outcomes [8]. Both in early and late stage lung cancer, studies have shown the presence of ctDNA in blood for patients after treatment is associated with a higher risk of cancer progression [9-10]. In patients who have lung cancer surgery and experience return of their cancer, ctDNA can be detected in blood tests approximately 5-6 months before the cancer is found by imaging scans [11-13]. In patients with advanced cancer, there is a strong correlation between disappearance of ctDNA in blood with response to treatment, versus persistence or increase in ctDNA if a person's cancer is not responding to treatment. These findings underscore the potential utility of ctDNA for disease monitoring in patients with lung cancer [14-16]. We therefore hypothesize that liquid biopsy using ctDNA can be used as part of routine monitoring of lung cancer patients that would otherwise receive routine imaging surveillance alone.

Objectives:

Primary Objective: To assess the feasibility of incorporating plasma ctDNA into routine disease monitoring in patients with stage IV NSCLC that have achieved initial treatment benefit (response or cancer stability) after at least 3 months on drug treatments (chemotherapy, immunotherapy, targeted therapy).

Secondary objectives include:

1. Describe the lead time between ctDNA detection and cancer progression on imaging (CT);
2. Evaluate the concordance between liquid biopsy ctDNA and imaging (CT scan) results;
3. Assess the impact of ctDNA detection on clinical management and treatment decision-making;

4. Assess patient preferences for a liquid biopsy-guided surveillance plan compared to the current standard of care (routine imaging);
5. Estimate the costs and consequences of a liquid biopsy-guided surveillance plan compared to routine imaging from the perspective of the Canadian public health care system.

Methods:

The **Lung Track** study is an investigator-initiated, single-arm, prospective pilot study assessing the feasibility of this approach. We will enrol 25 patients with a diagnosis of stage IV NSCLC that have achieved radiological disease response or stability after at least 3 months (up to 12 months) of initial drug treatment (chemotherapy, immunotherapy or targeted therapy) and are on ongoing treatment at The Princess Margaret/University Health Network (UHN) with routine imaging surveillance.

Eligible patients will be approached in outpatient thoracic medical oncology clinics at The Princess Margaret (**Appendix, Figure 1**). Consenting participants will undergo standard surveillance with CT scan imaging every 3 months (+/-2 weeks) and an additional blood draw around the same time of imaging for up to 12 months as part of the study. Whenever possible, the blood draw will be scheduled when the patient is already having standard of care blood tests, to avoid patient inconvenience and repeat venipuncture (needle poke). A total of 4 Streck™ tubes (40 mL of blood) will be collected at each time point. Two tubes will be analysed in real time using the TruSight Oncology (TSO500™, Illumina Inc) ctDNA assay at our UHN Genome Diagnostics Laboratory, and 2 tubes will be banked at UHN Biobank for exploration with future assays developed at The Princess Margaret. Feasibility measures will include: 1. Patient compliance with study blood draws; 2. Any adverse effects from the liquid biopsy and routine imaging; 3. Estimated time and patient (and caregiver) burden required for each method; 4. Estimated costs for each, to be derived from UHN costing data; and 5. Plasma ctDNA concordance with CT imaging findings, specifically the rate of concordance and false negative and positive results. Patients will also be asked to complete the EQ5D-5L questionnaire, a validated and widely used questionnaire to assess patient preference and health related quality of life.

Analysis Approach:

ctDNA results will be categorized as progressive non-progressive cancer. Non-progressive ctDNA results will include results that are non-detectable, less than or equal to baseline levels at study entry. Progressive ctDNA results will include the emergence of new mutations or reported increases in ctDNA levels (per UHN laboratory standards) compared to baseline levels. Imaging results (stable, improved, worsened) will be interpreted by independent (blinded) radiologists and confirmed by the treating team. Data will be summarized in descriptive terms. For the up to 100 ctDNA-CT imaging pairs - 25 patients x up to 4 time points), sensitivity, specificity, positive and negative predictive value and concordance between ctDNA and imaging results will be calculated and compared.

III. Impact Statement

The Lung TRACK study will generate Canadian real-world data that support the potential of liquid biopsy as a complementary tool for surveillance and an alternative to routine imaging scans for Canadians with lung cancer on treatment. This information will provide supportive evidence of patient benefit with liquid biopsies and economic impact on our public system, including the potential for cost-savings through decreased need for imaging. These data will inform any future randomized studies or other evidence generation needed to change practice.

Liquid biopsy holds the potential to improve the patient journey and alleviate the current burden on the Canadian healthcare system. We anticipate that liquid biopsy results will align with imaging results, thus establishing a sustainable alternative of blood tests rather than imaging for patients with stable or responding cancer. Additionally, we believe this will enhance patient access to precision medicine, reduce burden on staff and resources, and ultimately improve patient outcomes. This feasibility study will help build the business case for implementation of liquid biopsy into the cancer surveillance algorithm as well as engage policy makers and funders. Future studies will move this or more sensitive technologies into early stage disease and detection of cancer recurrence.

Our study aims to transform the treatment journey for patients with advanced NSCLC by establishing liquid biopsy as an important complementary tool to routine imaging. By reducing the frequency of CT scans, this approach could alleviate patient anxiety, improve access to timely care, and optimize resource use in a strained healthcare system. This study has potential to pave the way for integrating liquid biopsy into routine monitoring at our institution and setting a new standard for care nationally and globally.

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 particular biomarkers. Precision medicine has led to lung cancer patients living longer. They undergo routine scans (imaging with computed tomography or CT) 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. To overcome this challenge, we are looking at an alternative, non-invasive way called a liquid biopsy to monitor changes in patients' cancer. Scans are also challenging for patients and caregivers who must take additional time off work, travel to hospital, and patients may even experience severe allergic reactions to the dye used with CT scans.

A liquid biopsy is a blood test that can check for biomarkers that are found in cancer tissue. 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 have to pay out of pocket to access them.

Our study will use liquid biopsies for patients with late-stage lung cancer undergoing treatment who require monitoring of their disease with CT scans. Blood tests will occur at the same time as scans and results will be compared to see if they match. We have established the liquid biopsy workflow in our laboratory and the laboratory can return real time results within a short period of time. If the liquid biopsy can indicate that the patient's cancer is stable or smaller, the patient may be able to avoid a CT scan 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 Ambition Award will support 25 patients from screening to study completion. Pilot data will be used to secure other sources of funding.

	Cost/unit	Units	No. of patients	Cost	Justification
Salaries					
Clinical research coordinator	$ 85.00	5	25	$ 10,625.00	Patient screening, consenting, blood draws, quality of life assessments
Research fellow	0.5 FTE	-	-	-	Salary support covered by Hold'em for Life Fellowship (University of Toronto)
Research project manager	$ 85.00	24	-	$ 2,040.00	Operational oversight including tracking accrual, milestones, data collection, team communications, manuscript preparation. 2hr/week over 1 year.
Biostatistician	$ 100.00	20	-	$ 2,000.00	Protocol development, statistical analysis, manuscript preparation. 20 hr to complete analysis.
Services					
Correlative studies program	$ 90.00	5	25	$ 11,250.00	Kit creation (Streck tubes)
cfDNA extraction from plasma samples	$ 180.00	5	25	$ 22,500.00	ctDNA for assay
TSO500 Assay	$2,450.00	5	25	$ 306,250.00	Assay runs and molecular reports
Other Costs					
Publication fees	$5,000.00	1	-	$ 5,000.00	Dissemination of findings
Total				**$ 359,665.00**	
Request				**$ 50,000.00**	
To be funded by Princess Margaret Cancer Foundation (Dr. Natasha Leighl Research Fund and OSI Pharmaceuticals Foundation Chair in Cancer Research)				$ 309,665.00	

VI. Team

PI: Dr. Natasha Leighl – please see attached CCV.

Co-applicant, lead study fellow: Dr. Zachary Coyne – please see attached CCV.

VII. Appendix

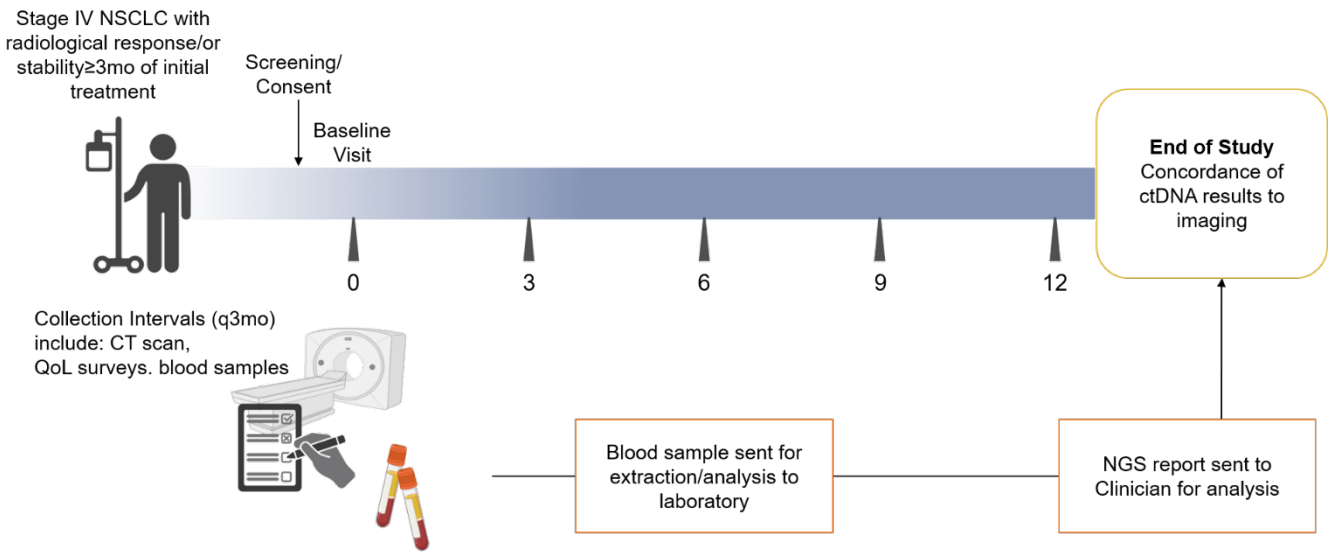

Figure 1. Lung TRACK study workflow. q3mo = every 3 months.

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January 30, 2025

Lung Cancer Canada

RE: Statement of Support for Dr. Natasha Leighl – Lung Ambition Awards

Dear Award Review Committee,

I am pleased to write this statement of support for Dr. Natasha Leighl and her co-applicant Dr. Zachary Coyne's application for the Lung Cancer Canada Lung Ambition Award entitled "Lung TRACK: Monitoring lung cancer through liquid biopsy." Dr. Leighl is the Lead Thoracic Medical Oncologist of the Lung Cancer Site Group 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. Coyne. I am confident this proposal is aligned with the Lung Cancer Group's dedication to innovation for better patient experiences and outcomes.

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 the Princess Margaret Cancer Centre, I confirm the proposed research is feasible at our institution. Thank you for your consideration.

Yours sincerely,

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