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September 30th, 2025

Lung Cancer Canada,
RE: Geoffrey Ogram Memorial Research Grant

Lung Cancer Canada,

Please find enclosed our application entitled: **"(AI-INSPIRES) Artificial Intelligence for Incident Nodule Screening on Prior Radiographic Exams: An Application to Lung Cancer Patients in Alberta"** that we are submitting for consideration for the Geoffrey Ogram Memorial Research Grant.

In 2025, more Canadians will die of lung cancer than any other cancer. This is due to lung cancers typically being diagnosed at an advanced stage when prognosis is extremely poor. When lung cancers are detected early, the prognosis and survival rates are greatly improved, which highlights the importance of early lung cancer detection initiatives. While screening for lung cancer with low-dose computed tomography (LDCT) is rolling out across Canada, some studies estimate that more than half of all lung cancers are diagnosed outside of screening programs. So despite the promise of screening, a considerable number of Canadians will not benefit from these programs and may still develop advanced lung cancers. Our study will directly address this critical need for innovative approaches to detect lung cancers early among individuals who may not meet current screening criteria, including never smokers, one of the core objectives of this grant.

Our project (**AI-INSPIRES**) aims to evaluate whether artificial intelligence can be used to detect lung cancers earlier on routinely collected chest radiographs (CXR). While LDCT is the preferred imaging modality for lung cancer screening, there's a growing interest that CXR may be viable when paired with AI image-interpretation tools. This will be the first study in Canada to comprehensively evaluate AI for early lung cancer detection using CXR and quantify the impact AI can have on shifting lung cancer diagnoses to earlier stages. Demonstrating that some lung cancers can be detected on CXR prior to an advanced diagnosis has the potential to reshape early lung cancer detection, reduce lung cancer mortality, and improve patient quality of life in Canada. Since CXR is available in nearly every healthcare setting, AI-enhanced interpretation could be implemented rapidly and at low cost, including in resource-limited regions where CT is unavailable. This study will provide the necessary evidence that AI can be a scalable technology to transform a pre-existing and common test into a powerful tool for early lung cancer detection outside of lung cancer screening programs.

Thank you for considering our application for the Geoffrey Ogram Memorial Research Grant. If you require any additional information from us, please do not hesitate to contact us at: matthew.warkentin@ucalgary.ca or atrembla@ucalgary.ca.

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TITLE: (AI-INSPIRES) Artificial **I**ntelligence for **I**ncident **N**odule **S**creening on **Pri**or **R**adiographic **E**xam**s**

BACKGROUND AND RATIONALE: Lung cancer is the leading cause of cancer death in Canada [1]. Most lung cancers are diagnosed at an advanced stage after the onset of symptoms with five-year survival less than 10% [2]. Early-stage diagnoses can greatly improve prognosis with five-year survival over 62% for early-stage lung cancers [2]. This highlights the importance of early lung cancer detection initiatives. Lung screening with low-dose computed tomography (LDCT) can significantly reduce lung cancer mortality [3,4]. However, not everyone will be eligible for lung screening programs since, where programs exist, eligibility is largely based on age and a heavy smoking history [5-6]. Up to 25% of lung cancers are diagnosed in patients with no history of smoking and who would be ineligible for screening [7]. Further, not all eligible individuals will choose to attend screening programs. Taken together, more than 50% of lung cancers are diagnosed outside of lung cancer screening programs [8].

Despite the promise of lung cancer screening in Canada, a considerable number of Canadians will not benefit from these programs, and many will develop lung cancers. There are several reasons why lung cancer screening has been limited to high-risk individuals with heavy smoking history. LDCT screening is not without risks, including false positives leading to unnecessary diagnostic interventions, incidental findings of unclear clinical benefit, and the potential for overdiagnosis [9]. In addition, the cost and resource utilization would be prohibitive to offer screening at a population level. Innovative approaches are needed for early lung cancer detection to further reduce lung cancer mortality for those who do not meet current lung cancer screening criteria, including those without a smoking history.

The detection of incidental pulmonary nodules during routine clinical care is an area of growing interest, particularly given the widespread use of chest radiographs (CXR). CXRs are commonly used as they are ordered for a wide range of clinical indications, relatively low cost, and confers minimal radiation exposure. However, small pulmonary nodules may not be noticed by radiologists, especially as nodule detection is not usually the primary indication for the exam. This missed opportunity for early lung cancer detection can result in delays in diagnosis with patients ultimately presenting later with more advanced disease. While LDCT is the preferred imaging modality for lung cancer screening, there's interest in leveraging a pre-existing and common test and optimizing its diagnostic sensitivity for detecting pulmonary nodules with AI-powered image-interpretation tools [10-13]. This also offers opportunities for lung screening in resource-limited areas, as CXR is more readily available than CT.

AIM AND OBJECTIVES: This study aims to investigate whether we can use AI to detect lung cancers earlier on routinely collected chest radiographs. The specific objectives include:

1. To perform automated pulmonary nodule detection using artificial intelligence on CXRs collected in the period before an advanced-stage lung cancer diagnosis.
2. To estimate how many advanced-stage lung cancer patients had potentially actionable pre-diagnostic clinical findings that were detected by AI and/or a clinical radiologist.
3. To estimate the early-stage lung cancer shift that would be achievable if previously unreported nodules were clinically investigated based on when the nodule was detected by AI.

METHODS: Data for this study will be collected from the Alberta Cancer Registry (ACR) and from the Diagnostic Imaging (DI) department of Alberta Health Services (AHS). From the ACR, we will identify all advanced-stage (Stage 3 and 4) lung cancers that were diagnosed over the previous 10 years in Alberta (2012 to 2022). Personal health numbers (PHN) will be securely shared between ACR and AHS DI to identify patients with digital CXRs completed between 1 and 3 years before their lung cancer diagnosis date. For all patients with prior CXRs, we will request the earliest and latest CXR during the pre-diagnosis window, for a maximum of two CXRs per patient (see **Figure 1A**). All CXRs will be stored as DICOM (Digital Imaging and Communications in Medicine) files and anonymized to remove any potential patient identifiers. For each patient, we will also have age at diagnosis, sex, zone of residency (urban/rural), cancer stage at diagnosis, and cancer topography and morphology.

<u>Objective 1:</u> Each CXR in our study will be analysed using a Health Canada approved and commercially-available AI software capable of performing automated pulmonary nodule detection on CXRs. The commercial AI system used in this study will be ClearRead Xray Detect from Riverain [14-17]. This system analyzes a CXR and generates a DICOM Structured Report (SR) that includes data for any pulmonary nodules detected by the AI algorithm and their location (i.e., coordinates). The nodule data in the DICOM SR will be extracted into tabular data (see **Figure 1B**). ClearRead Xray Detect also generates CXR images (including bone-supressed views) with bounding box overlays identifying the detected nodules. These images will be used for manual expert review. Each CXR will be accompanied by a clinical radiology report describing image findings. The radiology report and a JSON Schema (to define the desired data output structure) will be fed into a large language model (LLM) to extract any incidental pulmonary nodules that were reported by the radiologist and, if so, in what location (see **Figure 1B**). We will use a locally deployed instruction-tuned LLM (i.e., an AI assistant) running on the University of Calgary's high-performance compute (HPC) cluster to ensure data security and privacy.

<u>Objective 2:</u> Using the nodule data generated in Objective 1, we will estimate the number and proportion of lung cancer patients (and number of scans) that had an AI-detectable pulmonary nodule on their prior CXRs and whether those nodules were reported by the interpreting clinical radiologist. Any supposed nodule found by AI will be considered a positive finding. Similarly, any nodule mentioned in radiology report will be considered a positive finding for the interpreting clinical radiologist. We will construct a contingency table (see **Figure 2**) to evaluate the nodule findings and diagnostic performance of the AI model. Some nodules will be unreported by both AI and radiologists. No clinical actions can be taken on unreported nodules which reflects a realistic (but uncommon) event when interpreting CXR for non-specific symptoms. We will estimate and report the following diagnostic metrics: nodule detection rate (for AI, radiologist, and combined), nodule miss rate (where AI and radiologist disagree), false positive rate (after manual review by medical experts), false negative rate (based on reports), sensitivity, specificity, positive predictive value, negative predictive value, and agreement metrics (e.g., Cohen's kappa). Metrics will be reported stratified by patient demographics.

<u>Objective 3:</u> We will assess the potential for an early-stage shift in lung cancer diagnoses for patients with pulmonary nodules that are in the same location as the diagnosed lung cancer but were unreported by the interpreting radiologist (i.e., not clinically reported). This will be based on the counterfactual scenario where the AI pulmonary nodule detection technology had been available, deployed, and clinically actioned at the time of the CXR. We will estimate the diagnostic delay based on the date(s) of the CXR when the nodule was detected by AI and by simulating models of lung tumor progression. These models will be based on our understanding of lung cancer biology and the natural progression of the disease. We will report the counterfactual diagnosis date (see **Figure 1A**) and proportion of advanced lung cancers that could have been detected earlier if AI had been used for nodule detection.

SIGNIFICANCE OF THE WORK: CXR is one of the most common imaging studies globally, yet its potential for cancer detection has been limited. By applying AI to CXR interpretation, our research can transform a routine, inexpensive, and widely accessible test into a powerful tool for early lung cancer detection. This study will be the first comprehensive evaluation of AI applied to routinely collected CXR for early lung cancer detection in Canada. By leveraging an existing test, improving its diagnostic sensitivity, and expanding its reach to underserved populations and resource-limited settings, this study could transform the Canadian paradigm for early lung cancer detection. Our study offers a low-cost, scalable, and equitable pathway to earlier lung cancer detection to reduce lung cancer–related mortality, decrease the burden of complex late-stage care, and improve quality of life for patients and families.

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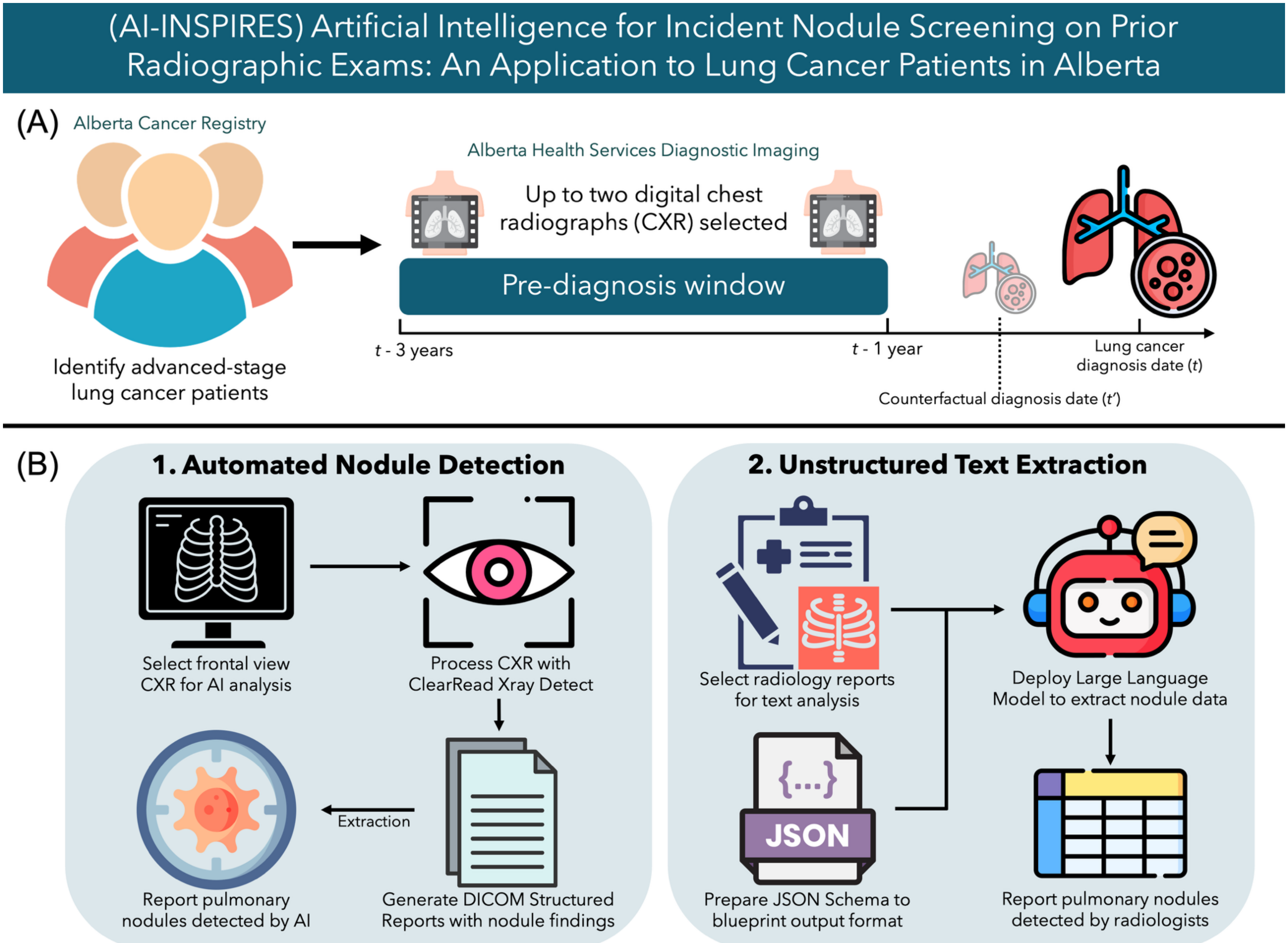

Figure 1: Schematic diagram for the AI-INSPIRES study. (A) Identification of the advanced-stage lung cancer patients from the Alberta Cancer Registry and selection of the chest radiographs in the window before a lung cancer diagnosis. **(B) Left:** Artificial intelligence (ClearRead Xray Detect) will be used to interpret chest X-rays and generate a Digital Imaging and Communications in Medicine (DICOM) Structured Report (SR) containing pulmonary nodule findings. The DICOM SR will be extracted into tabular data for reporting. **Right:** Unstructured clinical radiology text reports will be fed into a large language model (LLM) with a JavaScript Object Notation (JSON) Schema to extract structured data on pulmonary nodules, if reported.

Interpreting Clinical Radiologist
(Extracted from reports)

ClearRead Xray Detect
(Artificial Intelligence)

	Nodule	No Nodule	
Nodule	A	B	**AN+**
No Nodule	C	D	**AN-**
	RN+	**RN-**	**Total**

Legend:
- RN+ = Rad. Nodule Positive
- RN- = Rad. Nodule Negative
- AN+ = AI Nodule Positive
- AN- = AI Nodule Negative

Example Metrics:

$$\text{Sensitivity (Radiologist)} = \frac{A}{A + C} = \frac{A}{RN+}$$

$$\text{Nodule Detection Rate (AI)} = \frac{A + B}{A + B + C + D} = \frac{AN+}{Total}$$

Figure 2: Two-by-two contingency table comparing radiologist-detected pulmonary nodules and artificial intelligence-detected nodules on chest radiographs. Radiologist-detected nodules will be extracted from clinical radiology reports using large language models (LLM) and AI-detected nodules will be reported by ClearRead Xray Detect. Example metrics and their calculations are shown.

IMPACT STATEMENT

Our proposed research study will harness a pre-existing and widely used test, chest radiography (CXR), to create a transformative opportunity for early lung cancer detection. CXR is one of the most commonly performed imaging studies globally, yet its potential for cancer detection has been limited by low sensitivity and considerable inter-reader variability. By applying artificial intelligence to image interpretation, our research will directly address these limitations, optimizing the diagnostic sensitivity of CXR while improving consistency across readers. This represents a critical innovation: transforming a routine, inexpensive, and widely accessible test into a powerful tool for earlier and more reliable lung cancer detection.

Early lung cancer detection is pivotal as it changes the trajectory of the disease. By identifying cancers at a stage when curative treatment is possible, our research has the potential to reduce lung cancer–related mortality, decrease the burden of complex late-stage care, and improve quality of life for patients and families. This impact extends beyond those currently eligible for lung screening. Many individuals, especially never-smokers, are excluded from current screening criteria, yet they frequently undergo CXR in primary care for non-specific symptoms as the suspicion for lung cancer is lower. These patients represent an underserved and often overlooked group who represent a large proportion of lung cancer diagnoses, yet under current pathways are too often diagnosed at advanced stages. Our study directly addresses this gap, offering a scalable and equitable pathway to earlier detection for those most at risk of being missed. As CXR is already embedded in clinical workflows and available in nearly every healthcare setting, AI-enhanced interpretation could be implemented rapidly and at low cost, including in resource-limited regions where CT is unavailable. This research has the potential not only to reshape early detection in high-resource regions but also could extend lifesaving innovations to communities who would otherwise lack access.

This research study will also provide the first comprehensive evaluation in Canada of AI applied to routinely collected CXR for lung cancer detection. Demonstrating that pulmonary nodules can be identified prior to advanced-stage diagnosis would establish the evidence base required to shift clinical practice. In the short term, our research will generate high-impact knowledge, disseminated through leading international conferences and peer-reviewed publications, as well as through partnerships with patients and advocacy groups to ensure rapid uptake and awareness by key stakeholders. In the medium term, our team is uniquely positioned to translate findings into practice: our co-principal investigator leads the Alberta Lung Cancer Screening Program and the Alberta Thoracic Oncology Program, creating a direct pathway for integration into provincial and national care strategies. This provides an opportunity to follow-up this study with an implementation trial to demonstrate clinical utility prospectively in a real-world healthcare setting. Future studies may be required to demonstrate the cost-effectiveness of implementing such a tool, and our research group has considerable experience in this research area and are optimally situated to answer these important questions and translate our findings into meaningful clinical impact.

Ultimately, our research has the potential to exert sustained provincial and national impact. By leveraging an existing test, improving its diagnostic power, and expanding its reach to underserved populations and resource-limited settings, this study could transform the Canadian paradigm for early lung cancer detection. The result will be earlier diagnoses, reduced mortality, decreased care burden, improved patient quality of life, and a lasting contribution to the advancement of lung cancer research and care in Canada.

PUBLIC, NON-SCIENTIFIC SUMMARY

Lung cancer kills more people than any other cancer worldwide. Last year, 1 in 4 cancer deaths were due to lung cancer in Canada. One of the reasons for why lung cancer is so deadly is because it is usually diagnosed when it has spread to other parts of the body where the likelihood of survival is below 10%. However, when lung cancers are caught early, the survival improves considerably with around 62% of people surviving five years for cancers that have not yet spread.

Detecting lung cancers as early as possible through screening is crucial. Lung cancer screening is currently offered in several provinces and territories across Canada. However, to be eligible for screening you typically need to be older and with a heavy smoking history. Because of the narrowness of these eligibility criteria and less than optimal screening uptake, studies have shown that more than half of all lung cancers are detected outside of lung cancer screening programs. This highlights the importance of finding innovative ways to screen for early signs of lung cancer outside of organized programs.

Specialized X-ray technology, known as low-dose computed tomography (LDCT), is the preferred technology to look for lung cancers. However, there is growing interest to use chest X-rays given how commonly they are ordered by doctors for non-specific symptoms. That said, early signs of lung cancer may be missed when looking at X-rays because the images are much lower quality than LDCT and radiologists may be looking for other things since lung cancer is not usually the reason for ordering the X-ray. Today, new artificial intelligence (AI) tools are becoming available that may help to automatically locate these hard-to-find lung cancers on X-rays.

We will perform the first study in Canada to use AI to look for early signs of lung cancer using chest X-rays collected during the period before a person was diagnosed with lung cancer. Using over 14,000 X-rays from lung cancer patients in Alberta, we will retrospectively use AI to try and find these early signs of lung cancer that might have been visible before the lung cancer was diagnosed several years later. We will compare this with the reports created by the radiologists when they reviewed the X-rays to see if any early signs of lung cancer were missed. Using these data, we will be able to tell how many people could have potentially been diagnosed earlier if AI was available to help radiologists find signs of lung cancer earlier.

This study may lead to finding lung cancers earlier among individuals who may not qualify for lung cancer screening, including non-smokers. By showing that some lung cancers can be detected early on chest X-rays, our study has the potential to change lung cancer care in Canada. In the future, we may be able to use AI in the healthcare setting as a low-cost option for early lung cancer detection using X-ray images that are ordered for all types of reasons unrelated to the suspicion of lung cancer.

BUDGET

Project Title: (AI-INSPIRES) Artificial Intelligence for Incident Nodule Screening on Prior Radiographic Exams

Principal Applicants: Matthew T. Warkentin (Co-PI), Alain Tremblay (Co-PI)
Co-Applicants: Monica L. Mullin, Darren R. Brenner

Statement of Financial Need: As a postdoctoral fellow, securing this grant is critical as research funds are limited and external support is essential to sustain independent research activities. The financial support provided by this grant will allow me to perform the high-quality and leading-edge research described in this application which has the potential to transform the early detection of lung cancer in Canada. This grant will provide the resources necessary to purchase specialized software, access clinical and image data, and cover publication fees to ensure the findings of this work are made available to key stakeholders, all of which are not covered by fellowship or institutional funding. This support will allow me to successfully complete this project and start to build a foundation for long-term research independence. Securing external funding as a fellow is important because it demonstrates my ability to obtain competitive support and establishes a clear trajectory toward independence as a principal investigator.

ITEM	DESCRIPTION AND JUSTIFICATION	COST
Data and image access fees	The epidemiological data and images for this study will come from the Alberta Cancer Registry (ACR) and Alberta Health Services Diagnostic Imaging (AHS DI). From ACR, we will request all advanced stage (stage 3 and 4) lung cancers in Alberta from 2012 to 2022. The personal health numbers (PHN) for these participants will be securely shared with AHS DI to request the earliest and latest chest radiographs (CXR) in the one-to-three-year period prior to the lung cancer diagnosis date. This corresponds to 4,642 lung cancer participants, 7,190 studies (i.e., exams), and 14,015 CXR. AHS DI invoices $1.50 per study which comes to a total cost of $10,785 ($1.50 x 7,190).	$10,785
Software license fees	We will use a commercial AI tool (ClearRead Xray Detect from Riverain). This software is being purchased and licensed as part of a larger licensing agreement which will include other AI tools from this vendor. This budget expense will contribute proportionally to the purchase of ClearRead Xray Detect and licenses.	$4,000
Research analyst (0.15 FTE)	A Research Analyst (RA) costs approximately $60,000 per year, per the University of Calgary salary grid (costed as one RA at $23.07 to $34.01 rate / hour for 35 hours per week for 1.0 FTE and 26% for benefits). This budget item will contribute towards salary for an undergraduate (BSc) or graduate (MSc) level RA whose responsibilities will include managing data and images, running images through AI tools, and helping with analyses and manuscript writing. The RA will support the postdoctoral fellow (Co-PI) who will lead the work described herein.	$8,215
Open-access publication fees	Costs related to peer-reviewed journal fees for open-access publications to ensure our research is widely available to all interested stakeholders.	$2,000
TOTAL BUDGET		**$25,000**

September 2, 2025

Lung Cancer Canada
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RE: Statement of Support for Dr. Matthew Warkentin

To Whom It May Concern:

As Director of the Arnie Charbonneau Cancer Institute at the University of Calgary, I am writing in strong support of the application, *(AI-INSPIRES) Artificial Intelligence for Incident Nodule Screening on Prior Radiographic Exams: An Application to Lung Cancer Patients in Alberta*, submitted by Dr. Matthew Warkentin to Lung Cancer Canada's **Geoffrey Ogram Memorial Research Grant** opportunity. Dr. Warkentin, a postdoctoral associate with the Department of Oncology and the Arnie Charbonneau Cancer Institute, has shown significant progress during his postdoctoral training and I believe he has exceptional promise to successfully transition into an independent investigator position.

Among our institute's top priorities in screening, detection, and risk reduction research is a focus on the use of computational approaches, including artificial intelligence (AI), to improve screening for cancer. Dr. Warkentin's research aligns directly with this priority by furthering the development of innovative risk assessment approaches to enable earlier detection of lung cancer. This specific project will leverage one of the largest sets of pre-diagnostic chest X-rays for all advanced stage lung cancer patients in Alberta over the last decade to evaluate AI tools for automated pulmonary nodule detection on X-ray and estimate how many of these cancers might have been detectable earlier. This work has the potential to reduce lung cancer mortality and inspire change to the delivery of lung cancer care in Canada and beyond.

I confirm that this work is feasible within our institute and that the Arnie Charbonneau Cancer Institute is committed to supporting the growth of Dr. Warkentin's research in the area of lung cancer screening and detection in Canada. We have reviewed his proposal and are confident that it addresses an area of high need with the potential for significant impact, and that his approaches are methodologically sound. In addition, the proposed study will be supported by a strong collaborative and multidisciplinary environment for lung cancer research at the institute, as well as a partial salary contribution through philanthropic funding.

We are excited about Dr. Warkentin's proposed research and believe it has the potential to improve outcomes for individuals at high risk of lung cancer in Canada and beyond.

Sincerely,

Jennifer Chan, MD
Director, Charbonneau Cancer Institute
Cumming School of Medicine
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