TH-146: Cancer Associated Macrophage-Like (CAML) Cells to Enhance Detection of Early Stage Lung Cancer

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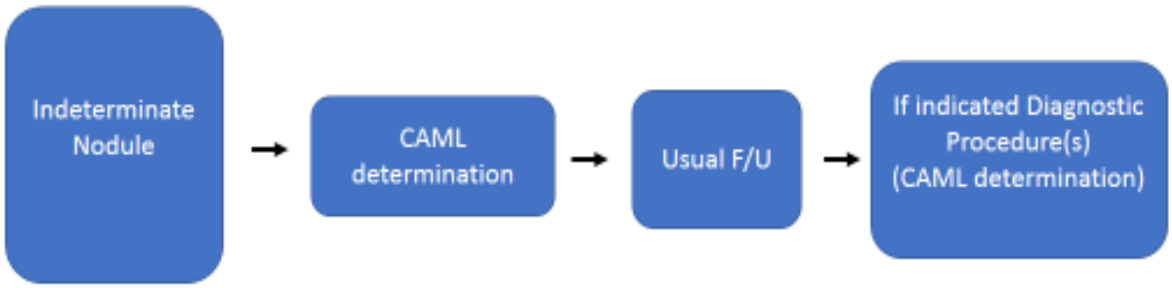
Schema



Primary endpoint: sensitivity/specificity of CAMLs

Contents

1.0 Introduction
1.1 Background and Hypothesis

Lung cancer screening

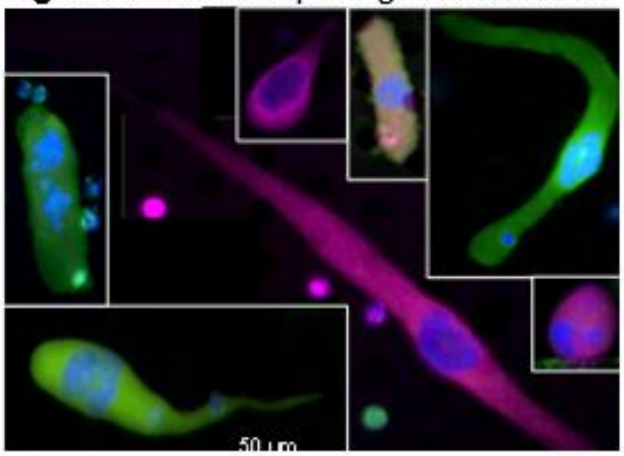
Lung cancer remains the major cause of cancer related death in the United States, with over 220,000 cases detected and 180,000 deaths.[i] The National Lung Screening Trial (NLST), for which the PI was a member of the endpoint verification committee, determined that low dose CT screening could decrease lung cancer death by 20% compared with CXR and is now recommended by all major professional groups and US Preventative Services Task Force.[ii] However, there are several problems with the current screening paradigm. Most critically, over 39% of screened subjects were determined to have positive screens with only 96.4% false positive. This very high false positive rate results in several critical problems including the requirement for further testing (scans, biopsies), the potential of loss to follow-up, the possibility of false negative biopsy and the resultant patient stress and anxiety. While lung nodules <0.8 cm are considered low-risk findings and nodules >3.0 cm high-risk, nodules between from 0.8-3.0 cm have been described as "indeterminate" and represent a management challenge.[iii] Therefore, there is a substantial need for a method to enrich the population of patients identified as likely to have malignancy and exclude those who have nodules not likely to have malignancy. The ideal test should be demonstrated to have high specificity and sensitivity. This is particularly important for patients with nodules of indeterminate size.

A number of publications have evaluated methods to predict which nodules harbor malignant disease. Location (upper lobe), characteristics of the nodule (specifically spiculation), age, female sex, number of nodules (fewer is more predictive) and carcinogen exposure have frequently been cited as predictive factors for malignancy.[iv] [v] A recent consensus statement by the International Association for the Study of Lung Cancer noted the variability in the very definition of indeterminate. [vi] In the NLST, screen positivity was defined by greatest nodule diameter of 4 mm or larger. In contrast, a European study (Dutch-Belgian Randomized Lung Screening Trial, NELSON) based screening interpretation on nodule volumetry and used a tiered approach.[vii] They classified nodules less than 50 mm3 (4.6-mm diameter) as negative, nodules greater than 500 mm3 (> 9.8-mm diameter) positive, and nodules 50 to 500 mm3 indeterminate. These indeterminate nodules underwent an early (3-month) follow-up LDCT to assess for growth; nodule volume doubling times were then used to distinguish between positive screens requiring additional diagnostic procedures and negative screens. Using this two-step approach, 2.6% of NELSON baseline screens were deemed positive, and a higher proportion of positive screens were due to lung cancer. An evaluation of >12,000 nodules by Mc Williams et al from two data sets was able to develop an algorithm with excellent discrimination between benign and malignant (ROC >0.90).[v] However, the above and similar experiences rely on continued follow-up, significant radiologic expertise and coordination. Further confusing matters, nodules discovered on subsequent scans in NELSON (and other studies) have a higher potential to be malignant regardless of size than those discovered on the initial scan.[viii]

The evaluation of patients with nodules generally consists of additional scanning as well as invasive procedures for nodules deemed suspicious. In the NLST, 28.4% of patients experienced a complication and with most of those (26.2%) considered "intermediate" or "major". 1.5% of patients died within 60 days of the most invasive diagnostic procedure. ***Critically, the prevalence of pulmonary nodules is dependent upon the population evaluated and appears to be substantially higher in the Veteran population.*** A recently published study reported a demonstration project in lung cancer screening at eight VA hospitals.[ix] Of the 2106 patients who completed screening, 1257 (59.7%) had positive test results, with 31 patients actually diagnosed with lung cancer. Therefore, the false positive rate was 97.5%. The investigators also evaluated the overall population potentially eligible for screening in the 8 centers and extrapolating to the entire VA population projected that there were almost 890,000 VA patients who would be candidates for lung cancer screening. This experience is informative in that it strongly indicates that screening in the VA/military population may be different than in the civilian population. There is a high degree of asbestos exposure in the military and there is some evidence that a very high proportion of patients with asbestos exposure will have pulmonary nodules. A Canadian study of 516 individuals with asbestos exposure found that 371 (71.9%) had pulmonary nodules.[x] The population that was evaluated in the VA demonstration project described above was heavily weighted towards male sex and had far more active smokers than in NLST. There was a much greater incidence of nodules requiring follow-up in the VA population (by a factor of 2). This indicates that full implementation of lung cancer screening with low dose CT followed by pulmonary (or other specialty referral) will demand far greater resources than projected by NLST. Many VA facilities do not appear to have adequate resources to implement current screening strategies. While there is high acceptance of the concept of screening in the VA population, in a survey of 106 (of 126 possible) VA facilities with pulmonary clinics, only 26.5% facilities were ideally prepared for lung cancer screening implementation. Furthermore, it is clear that potential for both positive tests (both false and true) is increased in the VA/military population. This will unquestionably be accompanied by an increased potential for diagnostic and therapeutic complications given the higher prevalence of smoking, age and comorbidities.

Cancer Associated Macrophage-Like (CAML) Cells

Figure 1. Four morphologies of CAMLs.



Creatv Microtech (Creatv) identified a previously unanalyzed cell in the blood of solid tumor patients, and named it CAMLs. [xi] They are specialized myeloid polyploid cells which emanate from primary tumor masses and transit the circulation of cancer (FIG 1) in a variety of malignancies which can be used to track cancer progression and evolution in response to therapy.[xii] CAMLs are absent in healthy controls and rare in persons with benign masses, Figure 2[xiii]. CAMLs have been identified in 14 types of solid tumors analyzed and prevalent in all stages, unlike circulating tumor cells (CTCs) which are relatively uncommon in lung cancer and non-metastatic disease. Creatv's CellSieve™ platform is a filter based system which has innovated liquid biopsies by its uniform pore size and distribution, with 180,000 pores. This allows for a low pressure filtration system for clean operation from whole blood with assays performed inside an encased filter holder (see details below, Methods).

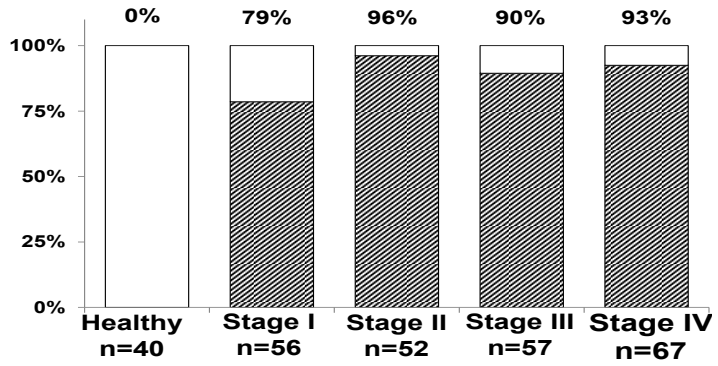


Figure 2. CAMLs only occur in cancer patients and some inflammatory illnesses, none in healthy control. CAMLs are found in high percentage even in stage I patients (n=272).

In approximately 10-20% of the patient samples, CAMLs are found to be in the process of engulfing CTCs and cellular debris (FIG 3). With CAMLs expressing proteomic and genomic markers associated with the primary tumor type, indicating engulfment of tumor/tumor debris

However, though seen by numerous groups, these cells have remained largely unstudied with their clinical and biological value in malignancies remaining uninvestigated.

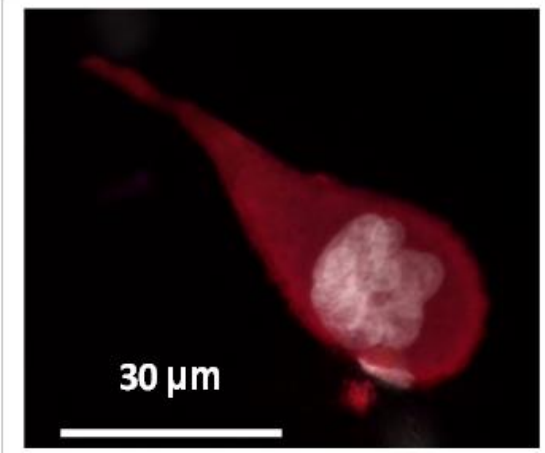
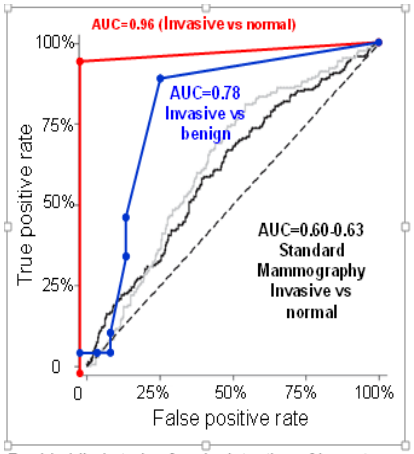


Figure 3

CAML from RCC patient in the process of engulfing a cell with the nucleus inside the CAML, but the cytoplasm is still partially outside. The CAML is stained for vimentin (brown).

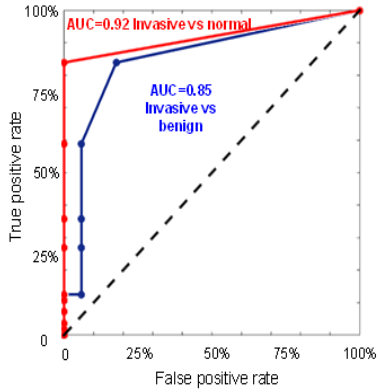
CAMLs consistently exist in stage I lung and undiagnosed breast cancer patients, making it an ideal target for early detection.

A double blinded study of breast cancer was conducted by Creatv MicroTech and Duke University on patients with suspicious mammography masses. In these patients, breast biopsies were performed in parallel with the detection of CAMLs from 7.5 mL of peripheral blood. The results demonstrated that CAMLs presence in blood had a significantly increased sensitivity and specificity versus mammography in individuals with cancer or non-cancerous masses (FIG 4).[xiv]



Double blind study of early detection of breast cancer based on CAMLs.

Figure 4



Single blind study of detection of lung cancer based on CAMLs.

Figure 5

Further, the study PI and co-PI performed a blinded preliminary comparison of 56 newly diagnosed ***lung cancer patients,*** 16 patients with benign conditions, and 40 healthy controls (FIG 5). Sensitivity of this study showed the number of patients (% positive): Stage I (63%), Stage II (86%), Stage III (92%), Stage IV 100%, unknown stage (100%); while the benign lung disease (18%) and healthy controls (0%). For malignant versus benign lung disease AUC=0.85, and for invasive versus health controls AUC=0.92. The current proposal will extend the above data to evaluate the prevalence and potential utility of CAMLs in individuals with pulmonary nodules to determine their use as a surrogate biomarker for cancerous nodules.

The prevalence and specificity of CAMLs in malignant disease is believed to be caused by immune inflammation and the specific microenvironment formed in cancerous and pre-cancerous legions. Typically giant polyploidy cells, like CAMLs, derive from common MPCs by either means of a pre-specified cascade of cellular differentiation (i.e. megakaryocytes or kupffer cells) or by an inflammatory response causing cell to cell fusion with nearby cells (Langhans or Foreign-body giant cells). Within the solid tumor mass, the commonly seen giant cancer associated polyploid cells are presumed to be caused by an aberrant inflammatory response caused during malignant growth, and the likely origin of CAMLs prior to dissemination into circulation. Further, because tumor derived giant polyploids are found in most early solid tumors, can negatively correlate with survival, and accumulate in pre-metastatic disease; it should be of little surprise that CAMLs in the blood

would have parallel clinical correlations. Additionally, while CTCs can act as a blood based surrogate to the tumor itself, CAMLs appear to act as a surrogate to the stromal microenvironment. Because stroma/immune inflammation is often larger than the tumor itself, and stromal genesis begins in both pre-cancerous and cancerous environments, it is not surprising that CAMLs would appear earlier and more commonly than actual CTCs.

1.2 Rational for the Study

While physicians have a clear path to follow for patients with low risk or high risk nodules, patients with indeterminate nodules do not have a defined method to predict their fate resulting in frequent scanning and invasive procedures. Screening by CT scans is faulty and unreliable with very high rate of false positives resulting in requirement for further tests and higher investment in resources. There is a need for a reliable screening method that would be predictive of the state of cancer. Circulating CAMLs have been shown to be of prognostic value in differentiating malignant and benign breast conditions[xiv, xxiv].

Our fundamental hypothesis is that CAMLs can substantially enrich for the presence of malignancy in the population of patients with pulmonary nodules. We also posit that parallel detection of CTCs has the potential to further enhance the ability to distinguish benign from malignant disease.

1.0 Objectives

2.1 Primary Objective

- Determine the prevalence of CAMLS in patients with pulmonary nodules.

2.2 Secondary Objectives

- Determine the positive and negative predictive value of CAMLS in patients with pulmonary nodules who undergo biopsy.
- Model combinations of clinical factors with the presence/absence of CAMLs to refine strategies for assessment of patients with pulmonary nodules. Evaluate whether these measures result in enhanced T-cell activity and/or NK cell function and number.

3.0 Study Design

3.1 Description of Study Design, Population and Duration of Study Therapy

This is a multi-site diagnostic study. Individuals who are diagnosed with indeterminate pulmonary nodules will be eligible. They will undergo standard evaluation and follow-up as determined by their pulmonary physician. In addition, they will have at least one blood draw to evaluate for the presence (and quantity) or absence of CAMLs.

Subjects will be drawn from pulmonary nodule clinics at the Fox Chase Cancer Center and the VAMC Philadelphia. Approximately 1200 pulmonary nodule patients are evaluated annually at Fox Chase. Approximately 200 pulmonary nodule patients/year with

indeterminate nodules (i.e. 0.8-3.0 cm) are seen each year at the VA Philadelphia. Patients who are seen in these clinics will be asked to complete a questionnaire that will include demographic information (age, sex, zip code, smoking history, occupational exposures, military history (where relevant). Medical history will be obtained from the medical records. This information will include diagnoses (e.g. COPD, CAD etc.), medications (steroids, inhalers etc), smoking and other pulmonary carcinogen history and other information. Radiologic information including location of nodule (lobe), size, characteristics (ground glass, solid, spiculation etc) will be recorded (Appendices A, B).

Patient's blood would be drawn at 2 time points- at the time of detection of indeterminate lung nodules, and at the time of biopsy or beginning of therapeutic procedure. Each blood sample will be 10 cc of blood into two tubes equaling 20 cc per blood draw. Two tubes of blood will be drawn for each sample: one CellSave tube will be sent to Creatv for further analysis and one CellSave will be processed at the FCCC protocol support lab (PSL). Detection of CAMLs will be performed using the CellSieve™ microfiltration system according to established criteria. The CellSieve™ microfilter (Fig. 6) has low fluorescent background, enabling detailed visualization and characterization of the cells on the filter, which led to the discovery of the CAMLs. Figure 6 shows a scanning electron micrograph (SEM) of a CellSieve™ microfilter. The characteristics of these microfilters and the benefits are summarized here.

Properties	**Benefits**
• Uniform pore size (7 µm diameter) and distribution	Pore size large enough to eliminate all red blood cells and 99.99% of white blood cells. Pore size small enough to capture all CTCs, CAMLs and cell clusters.
• 10 µm thick	Thin films minimize pressure on the cells. Cell morphologies are well maintained.
• High porosity (180,000 pores in a 9 mm diameter area	High porosity enables fast filtration, 5 mL/min. The 9 mm diameter filtration area minimizes time for imaging.
• Low auto-fluorescent background	Enables detailed images of cell features. Ability to quantify the staining intensity of markers of interest on the cells, such as PD-L1 and PD-L2.
• Very strong	No support needed; lies flat on glass slides.
• Lies flat on glass slides	Ease in preparing slides, and facilitates imaging by microscope.

The CellSieve™ low pressure filtration system is straightforward and offers clean operation (Fig. 6). The filter is held inside a filter holder, which also serves as the assay reaction well. Whole blood is placed into the input syringe and drawn through the filter into a waste syringe. 7.5 mL of whole blood diluted by 7.5 mL of prefixation buffer is filtered in 3 min. The assay steps (fixation, permeabilization, and staining), are all performed inside the holder. After staining, the filter is removed and mounted on a glass slide with a cover slip.

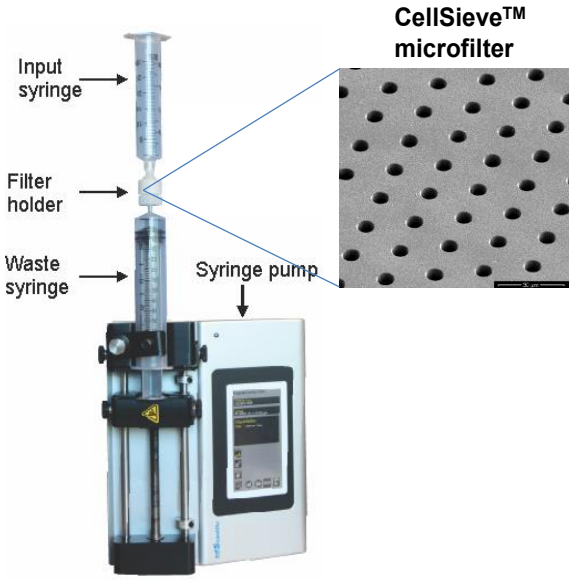


Figure 6. CellSieve™ filtration system. The microfilter is installed in a filter holder, which also serves as the assay reaction well.

The device is for Research Use Only. These products are not intended for in vivo or diagnostic use. Performance, safety, and effectiveness have not been established, and products are not approved by the FDA. Creativ MicroTech will comply with applicable requirements in 21 CFR 809.10©. The testing procedure is non-invasive and does not present significant risk, or intend to introduce energy into a subject. The testing is not used as a diagnostic procedure without confirmation by another procedure, medically established product or procedure. Thus, the device qualifies for IDE exemption.

4.0 Patient Selection Inclusion & Exclusion

4.1 Inclusion Criteria

4.1.1 Referral for a pulmonary nodule that has not yet been biopsied and that meets the definition of an "indeterminate" nodules (i.e. 0.8-3.0 cm).

4.1.2 No prior diagnosis of lung cancer or other invasive malignancy within the past 5 years.

4.1.3 No history of rheumatologic disease.

4.1.4 Age ≥ 18 years.

4.1.5 Ability to understand and willingness to sign a written informed consent and HIPAA consent document

4.2 Exclusion Criteria

4.2.1 Patients with active, known or suspected autoimmune disease.

4.2.2 Prior diagnosis of lung cancer or other invasive malignancy within the past 5 years.

4.2.3 Uncontrolled intercurrent illness that would increase the risk of toxicity or limit compliance with study requirements. This includes but is not limited to, uncontrolled infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

4.2.4 Known HIV-positive patients on combination antiretroviral therapy are ineligible because of the abnormal immune response that results from HIV disease (testing is not required).

4.2.5 Patients should be excluded if they are known to be positive for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV antibody) indicating acute or chronic infection (testing is not required).

4.2.6 Subjects with any history of interstitial lung disease or a history of > or = to grade 2 radiation pneumonitis.

4.3 Inclusion of Women and Minorities

Men and women, regardless of race, ethnic group or sexual orientation are eligible for this study.

4.4 Patient Registration

Participants may be registered from 8:00 am to 4:00 pm EST excluding holidays by emailing the Investigator-Sponsored Research Unit (ISRU) at: **FCCC.MONITOR@fccc.edu.** Eligible participants will be entered on study centrally once the following items have been received by email:

- Completed registration form
- Consent and HIPAA signature pages
- Eligibility checklist

For additional registration questions, please email **FCCC.MONITOR@fccc.edu**.
The FCCC ISRU will notify the site by email once registration is confirmed and the sequence number has been assigned. Participants must be registered and have received a sequence number prior to blood draw.

Exceptions to the current registration policies will not be permitted.

5.0 Study Plan

5.1 Duration of study

The study duration is anticipated to be three years. Patients would be registered during the first 2 years and followed for a maximum of 3 years since the beginning of the study. Patient who is registered towards the end of 2nd year will be followed for 12 months, i.e, end of the study.

5.2 Duration of Follow up

Patients will be in the study from the time of enrollment until the follow up. Follow up is the time when a CT scan and nodule assessment is done after the biopsy. Patients will be followed for a minimum of one year from accrual (last patient accrued) to a maximum of three years (patient accrued at the beginning of study).

5.3 Criteria for Discontinuation

Patients will be removed from study when any of the following criteria apply:

- Patient decided to withdraw from the study.
- Sponsor-investigator decides to remove patient from the study due to non-compliance
- The study is discontinued

The reason for study removal and the date the patient was removed must be documented in the medical record and case report form.

6.0 Laboratory Studies

These studies will be performed at Creatv Microtech. The outcomes of the study are determination of the prevalence, positive and negative predictive value of CAMLs in pulmonary nodules.

7.0 Study Calendar

Study	Enrollment	Scan 2[1]	Scan 3[1]	Biopsy or other diagnostic/therapeutic procedure[1]	Follow up
Informed consent	x				
Medical History	x			x	
Physical exam	x				
Smoking history	x				

Occupational and other exposures	x				
Medications	x				
PFTs[1]	x				
CT chest	x				x
CT/PET or PET[1]					x
CAML	x			x	
Nodule(s) measurement	x	x	x	x	x
Nodule characteristics	x	x	x	x	x

[1] If clinically indicated

8.0 Measurement of Lung Nodules

Bidimensional measurements of lung nodules will be performed. Measurements may be done by radiologist or pulmonary physician from CT scans with 5 mm (or less) cuts, using lung windows in the axial plane.

9.0 Statistical Considerations

Aim 1: Demographic and clinical characteristics of the study population will be summarized using standard methods (e.g., means, standard deviations, medians, binomial proportions, frequencies, two-sided confidence intervals). The proportion of patients with presence of CAMLs (CAML+) at the initial screen, with 95% two-sided confidence intervals, will be tabulated for the entire population. These statistics will also be used to summarize the presence of CAMLs at the time of an invasive follow-up procedure. The concordance of CAML results measured at two time points within the same individual will be evaluated using Cohen's Kappa.

Aim 2: Positive Predictive Value (PPV), Negative Predictive Value (NPV), sensitivity and specificity of CAMLs at the initial screen (along with two-sided 95% confidence intervals (CI)) will be computed for the entire study population. Patients with biopsy confirmed lung cancer during the entire duration of the study since initial CAML test will be defined as "diseased"; otherwise, they will deemed "disease free". We conservatively estimate that we will be able to accrue 1,000 patients with pulmonary nodules. We anticipate that ~35 and ~965 patients will be CAML+ CAML- at the initial screen, respectively. The expected accuracy of PPV and NPV estimates are presented in table 1.

Table 1. Accuracy of PPV and NPV estimates.

PPV or NPV estimate	Two-sided 95% CI for PPV	Two-sided 95% CI for NPV
0.5	±0.166	±0.032
0.7	±0.152	±0.029

0.9	±0.099	±0.019

Aim 3: We will use logistic regression models to assess the utility of presence/absence of CAMLs after accounting for clinical factors and nodule characteristics. The primary analysis will be at the patient level, since this approach is most consistent with the potential future application of a validated CAML test in the clinic. The dependent variable will be a binary indicator of patient disease status as described for Aim 2 (1=diseased, 0=disease free). Independent variables will include presence/absence of CAMLs as well as factors previously identified in the literature as important predictors of lung cancer status including age, gender, smoking status, lesion diameter, spiculation, family history of lung cancer, emphysema, clear borders, and exposure to asbestos or other common pulmonary carcinogens.[xv] [xvi] [xvii] When more than one lesion is detected in the same patient, lesion-specific covariate values (e.g., nodule diameter, spiculation) for that patient will be based on the nodule with highest risk of lung cancer. Continuous covariates may be modelled using restricted cubic splines to account for non-linear effects. As recommended by Pepe et al, Seshan et al and Vickers et al , the significance of the association between CAML test results and cancer status controlling for previously established clinical and radiological characteristics will be assessed using a Wald statistic from the multivariable logistic regression model (two-sided, 5% type I error). [xviii] [xix] Table 2 displays detectable differences between CAML+ and CAML– patients from these multivariable [xx]models, under a number of conditions.[xxi] These estimates assume data are available from 1,000 patients with suspicious nodules (35 CAML+ and 965 CAML-), and approximately 3.5% of patients will subsequently have biopsy-confirmed lung cancer.

Table 2. Detectable differences in proportion with lung cancer between CAML+ and CAML – patients.

Squared multiple correlation between CAML status and other independent variables in the model	Detectable difference in the proportion with lung cancer between CAML+ and CAML – patients	Power
0.0	0.111	80%
0.1	0.118	80%
0.2	0.127	80%
0.3	0.138	80%

Table 3. Two-sided 95% confidence intervals for varied AUCs

AUC	Lower Bound	Upper Bound
0.80	0.71	0.89
0.85	0.77	0.93
0.90	0.83	0.97

0.95	0.90	1.00

Receiver Operating Characteristic (ROC) curves and area under the ROC curve (AUC), with associated 95% two-sided confidence intervals, will be created to summarize the predictive accuracy of the model. Given the anticipated sample size, the upper and lower bounds for 95% two-sided confidence intervals for a range of possible AUCs are presented in Table 3.[xxii] In addition, the performance of the model will be evaluated using leave-one-out cross validation.

In secondary analyses, we will test second-order interactions between presence/absence of CAMLs and other covariates to explore whether test performance differs among subsets of the population defined by demographic, clinical and nodule characteristics.

In exploratory analyses we will conduct nodule-specific analyses using methods similar to those described above. In this case, the dependent variable will be a binary indicator of nodule disease status (1=cancer detected, 0=cancer not detected). To account for the fact that some subjects may have multiple nodules, the logistic models will be fit using generalized estimating equation methods (GEE) (and robust variance estimates will be used for inference.[xxiii] The power estimates in Table 2 are based on the assumption that there will be only 1 nodule per patient. Given that some subjects will have multiple nodules, the actual power of these exploratory analyses will likely exceed the stated estimates.
We will also evaluate the value of adding CAMLs to previously defined algorithms for evaluation of pulmonary nodules and the ability of CAMLs to potentially replace other known variables.

Trial feasibility: The trial calls for a total of 1000 evaluable patients accrued over 2 years. To assess the feasibility of this accrual rate, we examined the number of potentially eligible patients seen in the FCCC pulmonary clinic for FY 2017 (7/1/2016 to 6/30/2017). We found that there were over 1200 patients referred for evaluation of pulmonary nodules. The exact size of these nodules has not been captured in the data base, but the majority are within the indeterminate range. At the VA Philadelphia, the pulmonary nodule clinic performs over 1500 bronchoscopies/year and sees over 200 patients/year with pulmonary nodules measuring .8-3.0 cm. Therefore, between the two institutions, we feel confident that we will be able to enroll 1000 patients with indeterminate nodules within 24 months of activation.

10.0 Data and Safety Monitoring Plan

10.1 Monitoring Plan

This study does not involve any intervention, thereby posing minimal risk to the patient. The patient's visit will be as needed for standard of care and no visit is needed specifically for this study. Therefore, sponsor investigator will be responsible for conduct of the study. Investigator sponsored research unit (ISRU) will be conducting spot check of the study to ensure timely entry of patient and related study data.

10.2 Data & Safety Monitoring Board (DSMB)

The study is purely observational with no interventions. It does not involve more than minimal risk to the patients, and will not be reviewed by DSMB.

11.0 Administrative

This study will be conducted in accordance with local, state and Federal regulations and according to accepted good clinical practice guidelines.

11.1 Data Reporting

Patients will be registered in OnCore and patient data will be entered at each site in electric case report forms in electronic data capture system RedCap that will be password protected. The FCCC Study Monitor will request case report forms to be completed within 2 weeks of the protocol visit. Participating sites are responsible to respond to queries prior to the next scheduled monitoring visit.

All patient information will be stored in an EDC system accessible only to the study team members for the purpose of entering, reviewing and analyzing data. Any paper records, such as case report files, produced will be stored in a secure location. Confidentiality of the patient data will be maintained at all time.

Patients registered in the trial will be assigned a registration number. If needed, data will transferred in a de-identified manner between institutional encrypted emails only.

11.2 Retention of Records

All the study related records will be collected form the participating sites as per contract and retained at Fox Chase Cancer Center for 3 years after the trial ends.

11.3 Informed Consent

The IRB approved informed consent documents must be signed by the patient, or the patient's legally authorized representative, before his or her participation in the study. The case history for each patient shall document that informed consent was obtained prior to participation in the study. A copy of the informed consent documents must be provided to the patient or the patient's legally authorized representative. If applicable, they will be provided in a certified translation of the local language.

Original signed consent forms must be filed in each patient's study file or medical record with a copy in the study file.

12.0 References

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ON STUDY FORM

Confidential

On Study Form

Record ID	_____
Sequence Number	_____
ON STUDY FORM	
Date:	_____
Institution	○ FCCC ○ VA
Demographics:	
Age:	_____
Sex:	○ M ○ F
Racial Group:	☐ Caucasian ☐ African-American ☐ Hispanic ☐ Asian ☐ Other
Residence: Number of Years	
NE US	_____ (# of years)
Central US	_____ (# of years)
SE US	_____ (# of years)
West US	_____ (# of years)
SW US	_____ (# of years)
NW US	_____ (# of years)

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Unaccounted years (calculated)	_____
Other (specify)	_____
Education:	◯ < High School ◯ High School Diploma ◯ Some College ◯ College ◯ Post-College

Tobacco History:

Cigarettes:	◯ Never ◯ Current ◯ Past
Age of first use:	_____
Peak use (packs per day):	◯ < 0.25 ◯ 0.25 ◯ 0.50 ◯ 0.75 ◯ 1.00 ◯ 1.25 ◯ 1.50 ◯ 1.75 ◯ 2.00 ◯ >2.00
Age at last use:	_____
Number of years since last use:	_____ (# of years)

Exposures:

Asbestos exposure:	◯ No ◯ Yes
Occupational (specify)	_____
Hobby (specify)	_____
Residential (specify)	_____
Random exposure:	◯ No ◯ Yes
If yes, specify:	_____
Agent Orange:	◯ No ◯ Yes
Other Occupational Exposure:	◯ No ◯ Yes

Medical History:	
Family History;	☐ Lung cancer ☐ Head and Neck Cancer ☐ Bladder Cancer ☐ Esophageal Cancer ☐ Other (specify)
Other cancer, please specify:	_____
Personal Medical History:	☐ COPD ☐ Reactive airways disease ☐ CAD ☐ Other pulmonary disease ☐ History of pneumonia
Height (cm):	_____ ((cm))
Weight (Kg):	_____ ((Kg))
Calculated BMI:	_____
Pulmonary Function Tests	
FEV1 (liters)	_____ (liters)
FEV1 (% pred)	_____ (% pred)
FEV1/FVC	_____
DLCO	_____ (numeric field)
DLCO % Predicted	_____ (% pred)

Scan:	
Date of Scan:	_____
Characteristics of Nodule(s):	
Nodule 1 Location:	◯ RUL ◯ RML ◯ RLL ◯ LUL ◯ LLL ◯ Lingula
Density:	◯ Solid ◯ Semisolid
Size (cm):	_____ ((cm))
Contour	◯ Smooth ◯ Spiculated ◯ Ground glass
If nodule is part solid/ground glass: % solid.	_____ (% solid)
Calcification	◯ Not present ◯ Diffuse ◯ Central ◯ Laminated ◯ Popcorn ◯ Present, Not otherwise specified
Fat	◯ Not present ◯ Present
Satellite nodules	◯ Not present ◯ Present
Do you need to add another Nodule?	◯ Yes ◯ No
Nodule 2 Location:	◯ RUL ◯ RML ◯ RLL ◯ LUL ◯ LLL ◯ Lingula
Density:	◯ Solid ◯ Semisolid
Size (cm):	_____ ((cm))
Contour	◯ Smooth ◯ Spiculated ◯ Ground glass

If nodule is part solid/ground glass: % solid.	_____ (% solid)
Calcification	◯ Not present ◯ Diffuse ◯ Central ◯ Laminated ◯ Popcorn ◯ Present, Not otherwise specified
Fat	◯ Not present ◯ Present
Satellite nodules	◯ Not present ◯ Present
Do you need to add another Nodule?	◯ Yes ◯ No
Nodule 3 Location:	◯ RUL ◯ RML ◯ RLL ◯ LUL ◯ LLL ◯ Lingula
Density:	◯ Solid ◯ Semisolid
Size (cm):	_____ ((cm))
Contour	◯ Smooth ◯ Spiculated ◯ Ground glass
If nodule is part solid/ground glass: % solid.	_____ (% solid)
Calcification	◯ Not present ◯ Diffuse ◯ Central ◯ Laminated ◯ Popcorn ◯ Present, Not otherwise specified
Fat	◯ Not present ◯ Present
Satellite nodules	◯ Not present ◯ Present
Do you need to add another Nodule?	◯ Yes ◯ No
Nodule 4 Location:	◯ RUL ◯ RML ◯ RLL ◯ LUL ◯ LLL ◯ Lingula

Density:	◯ Solid ◯ Semisolid
Size (cm):	_____ ((cm))
Contour	◯ Smooth ◯ Spiculated ◯ Ground glass
If nodule is part solid/ground glass: % solid.	_____ (% solid)
Calcification	◯ Not present ◯ Diffuse ◯ Central ◯ Laminated ◯ Popcorn ◯ Present, Not otherwise specified
Fat	◯ Not present ◯ Present
Satellite nodules	◯ Not present ◯ Present
Do you need to add another Nodule?	◯ Yes ◯ No
Nodule 5 Location:	◯ RUL ◯ RML ◯ RLL ◯ LUL ◯ LLL ◯ Lingula
Density:	◯ Solid ◯ Semisolid
Size (cm):	_____ ((cm))
Contour	◯ Smooth ◯ Spiculated ◯ Ground glass
If nodule is part solid/ground glass: % solid.	_____ (% solid)
Calcification	◯ Not present ◯ Diffuse ◯ Central ◯ Laminated ◯ Popcorn ◯ Present, Not otherwise specified
Fat	◯ Not present ◯ Present
Satellite nodules	◯ Not present ◯ Present

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CAML (Cancer-Associated Macrophage-Like Cells) testing results:	
CAML Date:	_____
CAML cells present?	○ Present ○ Absent
CAML size	_____ (microns)
CAML number	_____ (numeric field)
CAML Comments	_____ (free text field)
CTCs present?	○ Present ○ Absent
CTC number	_____ (numeric field)
Apoptotic CTC	_____ (numeric field)
EMT CTC	_____ (numeric field)
CEVC present?	○ Present ○ Absent
CEVC number	_____ (numeric field)

FOLLOW UP FORM

Confidential

Follow Up Form

Record ID	_____
Date	_____
Institution	◯ FCCC ◯ VA
Cigarettes:	◯ Never ◯ Active ◯ Quit since last time
Peak use (packs per day):	◯ < 0.25 ◯ 0.25 ◯ 0.50 ◯ 0.75 ◯ 1.00 ◯ 1.25 ◯ 1.50 ◯ 1.75 ◯ 2.00 ◯ >2.00
Age at last use:	_____
Number of years since last use:	_____ (# of years)

Medical History:

Family History: Change since last visit?	◯ Yes ◯ No
Family History:	☐ Lung cancer ☐ Head and Neck cancer ☐ Bladder cancer ☐ Esophageal cancer ☐ Other
Other cancer, please specify:	_____
Personal Medical History: Change since last visit?	◯ Yes ◯ No
Personal Medical History:	☐ COPD ☐ Reactive airways disease ☐ CAD ☐ Other pulmonary disease ☐ History of pneumonia
Height (cm):	_____ ((cm))
Weight (Kg):	_____ ((Kg))

Calculated BMI	_____
Pulmonary Function Tests	
FEV1 (liters)	_____ (liters)
FEV1 (% pred)	_____ (% pred)
FEV1/FVC	_____
DLCO	_____ (numeric field)
DLCO % Predicted	_____ (% pred)
Scan:	
Date of Scan	_____
Characteristics of Nodule(s):	
Nodule 1: Location:	◯ RUL ◯ RML ◯ RLL ◯ LUL ◯ LLL ◯ Lingula
Density:	◯ Solid ◯ Semisolid
Size (cm):	_____ ((cm))
Contour:	◯ Smooth ◯ Spiculated ◯ Ground glass
If nodule is part solid/ground glass: % solid.	_____ (% solid)

Calcification	◯ Not present ◯ Diffuse ◯ Central ◯ Laminated ◯ Popcorn ◯ Present, Not otherwise specified
Fat	◯ Not present ◯ Present
Satellite nodules	◯ Not present ◯ Present
Do you need to add another Nodule?	◯ Yes ◯ No
Nodule 2 Location:	◯ RUL ◯ RML ◯ RLL ◯ LUL ◯ LLL ◯ Lingula
Density:	◯ Solid ◯ Semisolid
Size (cm):	_____ ((cm))
Contour:	◯ Smooth ◯ Spiculated ◯ Ground glass
If nodule is part solid/ground glass: % solid.	_____ (% solid)
Calcification	◯ Not present ◯ Diffuse ◯ Central ◯ Laminated ◯ Popcorn ◯ Present, Not otherwise specified
Fat	◯ Not present ◯ Present
Satellite nodules	◯ Not present ◯ Present
Do you need to add another Nodule?	◯ Yes ◯ No
Nodule 3 Location:	◯ RUL ◯ RML ◯ RLL ◯ LUL ◯ LLL ◯ Lingula
Density:	◯ Solid ◯ Semisolid

Size (cm):	_____ ((cm))
Contour:	◯ Smooth ◯ Spiculated ◯ Ground glass
If nodule is part solid/ground glass: % solid.	_____ (% solid)
Calcification	◯ Not present ◯ Diffuse ◯ Central ◯ Laminated ◯ Popcorn ◯ Present, Not otherwise specified
Fat	◯ Not present ◯ Present
Satellite nodules	◯ Not present ◯ Present
Do you need to add another Nodule?	◯ Yes ◯ No
Nodule 4 Location:	◯ RUL ◯ RML ◯ RLL ◯ LUL ◯ LLL ◯ Lingula
Density:	◯ Solid ◯ Semisolid
Size (cm):	_____ ((cm))
Contour:	◯ Smooth ◯ Spiculated ◯ Ground glass
If nodule is part solid/ground glass: % solid.	_____ (% solid)
Calcification	◯ Not present ◯ Diffuse ◯ Central ◯ Laminated ◯ Popcorn ◯ Present, Not otherwise specified
Fat	◯ Not present ◯ Present
Satellite nodules	◯ Not present ◯ Present
Do you need to add another Nodule?	◯ Yes ◯ No

Nodule 5 Location:	◯ RUL ◯ RML ◯ RLL ◯ LUL ◯ LLL ◯ Lingula
Density:	◯ Solid ◯ Semisolid
Size (cm):	_____ ((cm))
Contour:	◯ Smooth ◯ Spiculated ◯ Ground glass
If nodule is part solid/ground glass: % solid.	_____ (% solid)
Calcification	◯ Not present ◯ Diffuse ◯ Central ◯ Laminated ◯ Popcorn ◯ Present, Not otherwise specified
Fat	◯ Not present ◯ Present
Satellite nodules	◯ Not present ◯ Present
Biopsy:	
Biopsy:	◯ Yes ◯ No
Results:	◯ Benign ◯ Malignant
Specify:	◯ NSCLC ◯ SCLC ◯ Squamous ◯ Non-Squamous
CAML (Cancer-Associated Macrophage-Like Cells) testing results:	
CAML Date:	_____
CAML cells present?	◯ Present ◯ Absent
CAML size	_____ (microns)
CAML number	_____ (numeric field)

CAML Comments	_____ (free text field)
CTCs present?	◯ Present ◯ Absent
CTC number	_____ (numeric field)
Apoptotic CTC	_____ (numeric field)
EMT CTC	_____ (numeric field)
CEVC present?	◯ Present ◯ Absent
CEVC number	_____ (numeric field)