Negative: IPN Lung Cancer Detection

By “Coach Vance” Trefethen

***Resolved: The United States federal government substantially reform the use of Artificial Intelligence technology***

Case Summary: The AFF plan does “something” to promote lung cancer detection technology (getting all hospitals to use it?). It’s a new medical procedure that should increase early detection of lung cancer and save lives. IPN = Indeterminate Pulmonary Nodules. These are small objects found in the lungs that may or may not be indicators of developing lung cancer. Many of them are benign (harmless) but some percentage of them do indicate the beginnings of cancer (malignant). Doctors read CT (Computed Tomography) scans (like glorified X-rays) to view these IPNs but it’s hard to tell whether they’re benign or malignant. If you operated on everyone immediately who has an IPN, you would waste huge amounts of money and take drastic medical risk with unnecessary surgery because most of them don’t have cancer. But if you wait too long until the nodules grow, then the cancer becomes too advanced to be treated successfully, leading to increased death rates. The new technology uses AI to read thousands of scans and compare them to known outcomes of past patients to develop a better “feel” for which IPNs are dangerous and which are not. More accurately predicting whether a patient’s IPN indicates cancer or not will reduce unnecessary surgery on patients who don’t need it and increase survival rates by intervening early on patients who do have lung cancer.
 NEG position is that the Status Quo is already going to roll out IPN AI as soon as it’s ready, but it’s not quite ready yet. There are still some final studies and clinical trials that need to be finished. Even AstraZeneca, a company that makes this new test, doesn’t advocate immediately mandating all hospitals use it. They’re going thru pilot projects in Europe to get it working properly and prove its success. Besides that, there are other early cancer detection methods that are also rolling out that are as good or better. So, lives will be saved with early cancer detection even with a Negative ballot. No need to rush something into production that isn’t ready.

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TOPICALITY 3

1. Status Quo policy, not reform 3

Link: GO2 Foundation is doing the AFF Plan: IPN Lung Cancer detection across the country, once studies are concluded 3

GO2 Foundation and the IPN Task Force are preparing training and implementation strategies right now 3

INHERENCY 4

1. Better system coming #1: MCED (Multi-Cancer Early Detection tests) 4

MCED does early detection of lung cancer PLUS lots of other types of cancer (so, it’s better than AFF’s plan) 4

Faster availability than the AFF Plan: MCED limited initial launch is underway now and expecting full FDA approval any day now 4

2. Better system coming #2: the RNA blood test 4

It doesn’t involve artificial intelligence because it doesn’t need to: It’s a blood test that’s much easier to rollout 4

Blood RNA test will have very high accuracy at spotting cancer in lung nodules 5

Inherency Impact: No lives lost with a Negative ballot. The Status Quo will get as good or better results than AFF plan on early lung cancer detection 5

SOLVENCY 5

1. Results not validated 5

No AI lung cancer detection model has received widespread external validation or clinical acceptance 5

2. No standards in the Plan 6

AFF Plan just fiats it without setting usage standards. But standards are absolutely critical to success 6

3. More study needed 6

Astra Zeneca (company that makes the AFF Plan technology) doesn’t advocate the Plan! They’re conducting a study in Europe now because they still have to work out a lot of details 6

At least 2 specific things need more study: 1) Volumetric timing and 2) Standardized benchmarks 7

Long list of reasons why a lot more study is needed and things that need to be studied 7

Dr. Massion Study concludes: It has great potential but needs further study and clinical trials 8

4. Not covered by insurance 9

Medicare won’t cover it until Congress approves it. Private insurers won’t cover it until it is recommended by USPSTF 9

Without insurance coverage, cancer screening is much less likely to be done 9

DISADVANTAGES 9

1. Harmful Overdiagnosis & Overtreatment 9

Why rushing ahead without more study is bad: Early cancer detection can create negative net benefits - Risk of overdiagnosis and overtreatment 9

Negative: IPN Lung Cancer Detection

TOPICALITY

 1. Status Quo policy, not reform

Link: GO2 Foundation is doing the AFF Plan: IPN Lung Cancer detection across the country, once studies are concluded

PR Newswire 2021. “GO2 Foundation for Lung Cancer Expands Early Detection Efforts to Include Incidental Pulmonary Nodules (IPN) to Save More Lives” <https://www.biospace.com/article/releases/go2-foundation-for-lung-cancer-expands-early-detection-efforts-to-include-incidental-pulmonary-nodules-ipn-to-save-more-lives/> (accessed 23 Dec 2021)

"GO2 Foundation's new IPN initiative will give health care providers additional tools to diagnose lung cancer early, when it's more treatable and even curable." To broadly implement the new IPN initiative, GO2 Foundation is working with its 850 Center of Excellence (COE) health care facilities throughout the country to identify best practices on IPN management and provide guidance to sites who have not yet adopted this approach. As part of its early detection offerings, GO2 Foundation has developed a [thoracic oncology business model](https://c212.net/c/link/?t=0&l=en&o=3192086-1&h=677200848&u=https%3A%2F%2Fgo2foundation.org%2Ffor-professionals%2Fthoracic-oncology-business-model-tool%2F&a=thoracic+oncology+business+model) that includes both lung cancer screening and IPN management and is designed to help teams financially plan to build and grow their programs. Many innovative and pioneering COEs are already demonstrating clinical impact with their IPN programs.

GO2 Foundation and the IPN Task Force are preparing training and implementation strategies right now

PR Newswire 2021. “GO2 Foundation for Lung Cancer Expands Early Detection Efforts to Include Incidental Pulmonary Nodules (IPN) to Save More Lives” <https://www.biospace.com/article/releases/go2-foundation-for-lung-cancer-expands-early-detection-efforts-to-include-incidental-pulmonary-nodules-ipn-to-save-more-lives/> (accessed 23 Dec 2021)

In addition, GO2 Foundation is proud to be partnering with Biodesix who is providing strategic guidance, as well as collaborating with COE experts to form an IPN Task Force. The IPN Task Force is creating a toolkit that will include IPN education, program implementation, growth/optimization, as well as exploring research opportunities to study patients who are diagnosed incidentally with the goal of providing further evidence for lung cancer risk factors.

INHERENCY

1. Better system coming #1: MCED (Multi-Cancer Early Detection tests)

MCED does early detection of lung cancer PLUS lots of other types of cancer (so, it’s better than AFF’s plan)

British Journal of Cancer 2021 ([Allan Hackshaw](https://www.nature.com/articles/s41416-021-01498-4#auth-Allan-Hackshaw) (with Cancer Research UK & University College London Cancer Trials Centre, London).  [Sarah S. Cohen](https://www.nature.com/articles/s41416-021-01498-4#auth-Sarah_S_-Cohen) and Heidi Reichert (with EpidStrategies, A Division of ToxStrategies, Inc., USA).   [Anuraag R. Kansal](https://www.nature.com/articles/s41416-021-01498-4#auth-Anuraag_R_-Kansal), [Karen C. Chung](https://www.nature.com/articles/s41416-021-01498-4#auth-Karen_C_-Chung) and [Joshua J. Ofman](https://www.nature.com/articles/s41416-021-01498-4#auth-Joshua_J_-Ofman) (are with GRAIL, an MCED development company). British Journal of Cancer is a  twice-monthly professional [medical journal](https://en.wikipedia.org/wiki/Medical_journal) publishing papers by clinicians and scientists. ) 21 Aug 2021 “Estimating the population health impact of a multi-cancer early detection genomic blood test to complement existing screening in the US and UK” <https://www.nature.com/articles/s41416-021-01498-4> (accessed 8 Nov 2021)(brackets added)

In the US, an estimated 189,498 breast, lung, colorectal and cervical cancers are found through current recommended screening, with 8,057,657 false positives (Figs. [1](https://www.nature.com/articles/s41416-021-01498-4#Fig1) and [2a](https://www.nature.com/articles/s41416-021-01498-4#Fig2), Table [1](https://www.nature.com/articles/s41416-021-01498-4#Tab1)). The TP:FP [true positive to false positive] ratio is therefore 1:43 **[END QUOTE**] (to detect one person with any of these four cancers, 43 people without these cancers may have diagnostic investigations following a screen-positive result). The estimate of 189,498 represents 15% of all cancers (CDR). [**THEY GO ON TO WRITE QUOTE**:] Using an MCED blood test in addition to current recommendations could detect an extra 422,105 cancers (Fig. [2a](https://www.nature.com/articles/s41416-021-01498-4#Fig2), Table [1](https://www.nature.com/articles/s41416-021-01498-4#Tab1)), including 95,262 breast, cervical, colorectal and lung cancers, and 326,843 other cancers, such as head and neck, liver, bladder, stomach, ovary, oesophagus and lymphoma and lung cancer in low-risk individuals (Fig. [2a](https://www.nature.com/articles/s41416-021-01498-4#Fig2)).

Faster availability than the AFF Plan: MCED limited initial launch is underway now and expecting full FDA approval any day now

Reuters news service 2021. “FTC Challenges Vertical Merger Involving Cancer Screening Tests” 6 Apr 2021 <https://uk.practicallaw.thomsonreuters.com/Document/Ic6d00b0a961e11ebbea4f0dc9fb69570/View/FullText.html?transitionType=Default&contextData=(sc.Default)&firstPage=true> (accessed 11 Nov 2021)

Grail is one of a number of firms racing to develop multi-cancer detection (MCED) tests. Grail's test, Galleri, is poised for an initial limited launch for use in specific circumstances in 2021, and Food and Drug Administration (FDA) approval is anticipated shortly thereafter.

2. Better system coming #2: the RNA blood test

It doesn’t involve artificial intelligence because it doesn’t need to: It’s a blood test that’s much easier to rollout

American Association for Cancer Research 2019. (authors were: Andrew V. Kossenkov, Rehman Qureshi, Noor B. Dawany, Jayamanna Wickramasinghe, Qin Liu, R.Sonali Majumdar, Celia Chang, Sandy Widura, Trisha Kumar, Wen-Hwai Horng, Eric Konnisto, Gerard Criner, Jun-Chieh, J. Tsay, Harvey Pass, Sai Yendamuri, Anil Vachani, Thomas Bauer, Brian Nam, William N. Rom, Michael K. Showe and Louise C. Showe ) A Gene Expression Classifier from Whole Blood Distinguishes Benign from Malignant Lung Nodules Detected by Low-Dose CT, CANCER RESEARCH, Jan 2019 <https://cancerres.aacrjournals.org/content/79/1/263> (accessed 23 Dec 2021) (brackets added)

We have now demonstrated that RNA from whole blood, easily collected in PAXgene RNA stabilization tubes, can also be mined for gene expression information that distinguishes malignant from benign lung nodules. This minimally invasive, 2.5-mL [milliliter] blood collection system allows samples to be collected not only at major medical centers, but wherever blood is routinely drawn. The RNA stability at room temperature for 5 days means that no special storage system is required to maintain sample integrity, thereby facilitating sample collection and subsequent transfer to a central testing facility even from remote locations. The quality of the RNA makes it amenable to analysis on a wide variety of platforms including a variety of sequencing platforms that require high-quality RNA.

Blood RNA test will have very high accuracy at spotting cancer in lung nodules

American Association for Cancer Research 2019. (authors were: Andrew V. Kossenkov, Rehman Qureshi, Noor B. Dawany, Jayamanna Wickramasinghe, Qin Liu, R.Sonali Majumdar, Celia Chang, Sandy Widura, Trisha Kumar, Wen-Hwai Horng, Eric Konnisto, Gerard Criner, Jun-Chieh, J. Tsay, Harvey Pass, Sai Yendamuri, Anil Vachani, Thomas Bauer, Brian Nam, William N. Rom, Michael K. Showe and Louise C. Showe ) A Gene Expression Classifier from Whole Blood Distinguishes Benign from Malignant Lung Nodules Detected by Low-Dose CT, CANCER RESEARCH, Jan 2019 <https://cancerres.aacrjournals.org/content/79/1/263> (accessed 23 Dec 2021)

We now report that the gene expression in whole blood, collected using PAXgene RNA stabilization tubes, can distinguish benign from malignant lung nodules detected by LDCT with high accuracy on independent validation and also report the successful transition of this pulmonary nodule classifier (PNC) from the microarray developmental platform to the NanoString nCounter platform.

Inherency Impact: No lives lost with a Negative ballot. The Status Quo will get as good or better results than AFF plan on early lung cancer detection

Duplicating effort doesn’t help anything and diverting resources away from Status Quo projects won’t get you a net savings of lives. Vote Negative and let the Status Quo roll out two methods that are better than the AFF Plan. You don’t need the AFF Plan to save lives from lung cancer. A NEG ballot will do it as well or better.

SOLVENCY

1. Results not validated

No AI lung cancer detection model has received widespread external validation or clinical acceptance

[Canadian Journal of Respiratory, Critical Care, and Sleep Medicine](https://www.tandfonline.com/journals/ucts20)2020. (written by Stephen Lam, [Heather Bryant](https://www.tandfonline.com/author/Bryant%2C%2BHeather), [Laura Donahoe](https://www.tandfonline.com/author/Donahoe%2C%2BLaura), [Ashleigh Domingo](https://www.tandfonline.com/author/Domingo%2C%2BAshleigh), [Craig Earle](https://www.tandfonline.com/author/Earle%2C%2BCraig), [Christian Finley](https://www.tandfonline.com/author/Finley%2C%2BChristian), [Anne V. Gonzalez](https://www.tandfonline.com/author/Gonzalez%2C%2BAnne%2BV), [Christopher Hergott](https://www.tandfonline.com/author/Hergott%2C%2BChristopher), [Rayjean J. Hung](https://www.tandfonline.com/author/Hung%2C%2BRayjean%2BJ), [Anne Marie Ireland](https://www.tandfonline.com/author/Ireland%2C%2BAnne%2BMarie), [Michael Lovas](https://www.tandfonline.com/author/Lovas%2C%2BMichael), [Daria Manos](https://www.tandfonline.com/author/Manos%2C%2BDaria), [John Mayo](https://www.tandfonline.com/author/Mayo%2C%2BJohn), [Donna E. Maziak](https://www.tandfonline.com/author/Maziak%2C%2BDonna%2BE), [Micheal McInnis](https://www.tandfonline.com/author/McInnis%2C%2BMicheal), [Renelle Myers](https://www.tandfonline.com/author/Myers%2C%2BRenelle), [Erika Nicholson](https://www.tandfonline.com/author/Nicholson%2C%2BErika), [Christopher Politis](https://www.tandfonline.com/author/Politis%2C%2BChristopher), [Heidi Schmidt](https://www.tandfonline.com/author/Schmidt%2C%2BHeidi), [Harman S. Sekhon](https://www.tandfonline.com/author/Sekhon%2C%2BHarman%2BS), [Marie Soprovich](https://www.tandfonline.com/author/Soprovich%2C%2BMarie), [Archie Stewart](https://www.tandfonline.com/author/Stewart%2C%2BArchie), [Martin Tammemagi](https://www.tandfonline.com/author/Tammemagi%2C%2BMartin), Jana L. Taylor, [Ming-Sound Tsao](https://www.tandfonline.com/author/Tsao%2C%2BMing-Sound), [Matthew T. Warkentin](https://www.tandfonline.com/author/Warkentin%2C%2BMatthew%2BT) and [Kazuhiro Yasufuku](https://www.tandfonline.com/author/Yasufuku%2C%2BKazuhiro))14 Oct 2020 “Management of screen-detected lung nodules: A Canadian partnership against cancer guidance document” <https://www.tandfonline.com/doi/full/10.1080/24745332.2020.1819175> (accessed 23 Dec 2021) (brackets added)

A deep learning model for predicting lung cancer risk in repeat screening LDCT [low-dose computed tomography] was recently published using data using the PanCan screening study for validation. Decision-making with both models is based on cancer probability. Optimal thresholds and management responses are yet to be determined in prospective studies. Recently, many similar artificial intelligence machine learning nodule malignancy models have been published, but to date none have received widespread external validation and clinical acceptance.

2. No standards in the Plan

AFF Plan just fiats it without setting usage standards. But standards are absolutely critical to success

[Canadian Journal of Respiratory, Critical Care, and Sleep Medicine](https://www.tandfonline.com/journals/ucts20)2020. (written by Stephen Lam, [Heather Bryant](https://www.tandfonline.com/author/Bryant%2C%2BHeather), [Laura Donahoe](https://www.tandfonline.com/author/Donahoe%2C%2BLaura), [Ashleigh Domingo](https://www.tandfonline.com/author/Domingo%2C%2BAshleigh), [Craig Earle](https://www.tandfonline.com/author/Earle%2C%2BCraig), [Christian Finley](https://www.tandfonline.com/author/Finley%2C%2BChristian), [Anne V. Gonzalez](https://www.tandfonline.com/author/Gonzalez%2C%2BAnne%2BV), [Christopher Hergott](https://www.tandfonline.com/author/Hergott%2C%2BChristopher), [Rayjean J. Hung](https://www.tandfonline.com/author/Hung%2C%2BRayjean%2BJ), [Anne Marie Ireland](https://www.tandfonline.com/author/Ireland%2C%2BAnne%2BMarie), [Michael Lovas](https://www.tandfonline.com/author/Lovas%2C%2BMichael), [Daria Manos](https://www.tandfonline.com/author/Manos%2C%2BDaria), [John Mayo](https://www.tandfonline.com/author/Mayo%2C%2BJohn), [Donna E. Maziak](https://www.tandfonline.com/author/Maziak%2C%2BDonna%2BE), [Micheal McInnis](https://www.tandfonline.com/author/McInnis%2C%2BMicheal), [Renelle Myers](https://www.tandfonline.com/author/Myers%2C%2BRenelle), [Erika Nicholson](https://www.tandfonline.com/author/Nicholson%2C%2BErika), [Christopher Politis](https://www.tandfonline.com/author/Politis%2C%2BChristopher), [Heidi Schmidt](https://www.tandfonline.com/author/Schmidt%2C%2BHeidi), [Harman S. Sekhon](https://www.tandfonline.com/author/Sekhon%2C%2BHarman%2BS), [Marie Soprovich](https://www.tandfonline.com/author/Soprovich%2C%2BMarie), [Archie Stewart](https://www.tandfonline.com/author/Stewart%2C%2BArchie), [Martin Tammemagi](https://www.tandfonline.com/author/Tammemagi%2C%2BMartin), Jana L. Taylor, [Ming-Sound Tsao](https://www.tandfonline.com/author/Tsao%2C%2BMing-Sound), [Matthew T. Warkentin](https://www.tandfonline.com/author/Warkentin%2C%2BMatthew%2BT) and [Kazuhiro Yasufuku](https://www.tandfonline.com/author/Yasufuku%2C%2BKazuhiro))14 Oct 2020 “Management of screen-detected lung nodules: A Canadian partnership against cancer guidance document” <https://www.tandfonline.com/doi/full/10.1080/24745332.2020.1819175> (accessed 23 Dec 2021) (brackets added) (A “phantom” is a model or dummy that is used to calibrate the scanner. A standardized phantom is an identical one that is used across the industry so that everyone is measuring the accuracy of their equipment by the same standard.)

LDCT image quality can significantly influence determination of nodule type and measurement of size and growth. A high standard of image quality is of importance in a LDCT lung cancer screening program.

Key messages

1. Adherence to strict standards in personnel training and qualification, CT equipment, image acquisition, image processing and storage parameters is critical for accurate and reproducible measurement of lung nodules and to ensure a low dose protocol is used to minimize radiation exposure. 2. We recommend lung cancer screening sites conform to the RSNA [Radiological Society of North America] QIBA [Quantitative Imaging Biomarker Alliance] Small Lung Nodule Volume Assessment and Monitoring in Low-Dose Screening Profile using a standardized phantom.

3. More study needed

Astra Zeneca (company that makes the AFF Plan technology) doesn’t advocate the Plan! They’re conducting a study in Europe now because they still have to work out a lot of details

Astra Zeneca corporation 2021. (international biopharmaceutical company) “New collaboration between AstraZeneca and Aidence supports early diagnosis of lung cancer using artificial intelligence” July 2021 <https://www.astrazeneca.com/media-centre/articles/2021/new-collaboration-between-astrazeneca-and-aidence-supports-early-diagnosis-of-lung-cancer-using-artificial-intelligence.html> (accessed 23 Dec 2021)

**Veye Lung Nodules** – an AI solution that automatically detects IPNs from lung CT scans and provides information regarding the nodule’s type, size and growth. In addition to providing benefits for patients, Veye Lung Nodules AI supports the improvement of patient outcomes by detecting possible early-stage lung cancer and lowering the risk of misdiagnosis. It can also improve efficiency and quality of care by enabling faster detection, reporting information, reducing unnecessary follow-ups and acting as a ‘second pair of eyes’ for radiologists—all of which are associated with potential cost savings.
**Veye Clinic** – an application that facilitates follow-up for patients with identified IPNs based on established clinical guidelines to ensure timely diagnosis and treatment.
We will fund a pilot phase of implementing these solutions in 2021, before expanding to a planned 25-30 European hospitals next year. An external Steering Committee has been established to support the collaboration which will include developing a protocol to optimise the early lung cancer detection early detection pathway through collaboration with scientific societies, establishing lung nodule clinics, supporting improved patient communication for follow-up and educating HCPs [health care providers] and patients.

At least 2 specific things need more study: 1) Volumetric timing and 2) Standardized benchmarks

[Canadian Journal of Respiratory, Critical Care, and Sleep Medicine](https://www.tandfonline.com/journals/ucts20)2020. (written by Stephen Lam, [Heather Bryant](https://www.tandfonline.com/author/Bryant%2C%2BHeather), [Laura Donahoe](https://www.tandfonline.com/author/Donahoe%2C%2BLaura), [Ashleigh Domingo](https://www.tandfonline.com/author/Domingo%2C%2BAshleigh), [Craig Earle](https://www.tandfonline.com/author/Earle%2C%2BCraig), [Christian Finley](https://www.tandfonline.com/author/Finley%2C%2BChristian), [Anne V. Gonzalez](https://www.tandfonline.com/author/Gonzalez%2C%2BAnne%2BV), [Christopher Hergott](https://www.tandfonline.com/author/Hergott%2C%2BChristopher), [Rayjean J. Hung](https://www.tandfonline.com/author/Hung%2C%2BRayjean%2BJ), [Anne Marie Ireland](https://www.tandfonline.com/author/Ireland%2C%2BAnne%2BMarie), [Michael Lovas](https://www.tandfonline.com/author/Lovas%2C%2BMichael), [Daria Manos](https://www.tandfonline.com/author/Manos%2C%2BDaria), [John Mayo](https://www.tandfonline.com/author/Mayo%2C%2BJohn), [Donna E. Maziak](https://www.tandfonline.com/author/Maziak%2C%2BDonna%2BE), [Micheal McInnis](https://www.tandfonline.com/author/McInnis%2C%2BMicheal), [Renelle Myers](https://www.tandfonline.com/author/Myers%2C%2BRenelle), [Erika Nicholson](https://www.tandfonline.com/author/Nicholson%2C%2BErika), [Christopher Politis](https://www.tandfonline.com/author/Politis%2C%2BChristopher), [Heidi Schmidt](https://www.tandfonline.com/author/Schmidt%2C%2BHeidi), [Harman S. Sekhon](https://www.tandfonline.com/author/Sekhon%2C%2BHarman%2BS), [Marie Soprovich](https://www.tandfonline.com/author/Soprovich%2C%2BMarie), [Archie Stewart](https://www.tandfonline.com/author/Stewart%2C%2BArchie), [Martin Tammemagi](https://www.tandfonline.com/author/Tammemagi%2C%2BMartin), Jana L. Taylor, [Ming-Sound Tsao](https://www.tandfonline.com/author/Tsao%2C%2BMing-Sound), [Matthew T. Warkentin](https://www.tandfonline.com/author/Warkentin%2C%2BMatthew%2BT) and [Kazuhiro Yasufuku](https://www.tandfonline.com/author/Yasufuku%2C%2BKazuhiro))14 Oct 2020 “Management of screen-detected lung nodules: A Canadian partnership against cancer guidance document” <https://www.tandfonline.com/doi/full/10.1080/24745332.2020.1819175> (accessed 23 Dec 2021) (brackets added) (A “phantom” is a model or dummy that is used to calibrate the scanner. A standardized phantom is an identical one that is used across the industry so that everyone is measuring the accuracy of their equipment by the same standard.)

A recent study in Canada showed both Computer-Aided-Diagnostic (CAD) technology-based volume derived mean diameter and volume based nodule malignancy risk prediction models have excellent discrimination and calibration in the baseline screening LDCT, with similar areas under the receiver-operating-characteristic curves of 0.947.External validation studies showed that although malignancy risk prediction models using mean diameter and volume have similar discrimination, the calibration of the models using nodule volume is not as good as models using mean 2-D diameter measurement.A preliminary study in Canada also suggests the PanCan nodule malignancy risk calculator that uses mean diameter measurement may be more efficient in triaging screenees to a diagnostic pathway than the EU-NELSON volumetric protocol after the baseline screening LDCT with a significantly higher positive predictive value. A randomized trial comparing the clinical utility of volumetric measurement with volume doubling time versus 2-D diameter change to determine the timing of the next imaging study or biopsy and cancer detection rate investigation is needed. Currently, preference can depend on local practice and availability of CAD software until additional data are available. On-going work to use a standardized phantom to benchmark volumetry software packages is important as different software packages can result in widely different recall rates.

Long list of reasons why a lot more study is needed and things that need to be studied

[Journal of Thoracic Oncology](https://www.sciencedirect.com/science/journal/15560864) 2019 (authors were: [Luis M.Seijo MD, PhD](https://www.sciencedirect.com/science/article/pii/S1556086418335019%22%20%5Cl%20%22%21) [Nir Peled MD, PhD](https://www.sciencedirect.com/science/article/pii/S1556086418335019#!) [Daniel Ajona PhD,](https://www.sciencedirect.com/science/article/pii/S1556086418335019#!) [MattiaBoeriPhD](https://www.sciencedirect.com/science/article/pii/S1556086418335019#!), [John K.FieldPhD,](https://www.sciencedirect.com/science/article/pii/S1556086418335019#!) [Gabriella SozziPhD,](https://www.sciencedirect.com/science/article/pii/S1556086418335019%22%20%5Cl%20%22%21) [Ruben PioPhD,](https://www.sciencedirect.com/science/article/pii/S1556086418335019%22%20%5Cl%20%22%21) [Javier J.Zulueta MD PhD](https://www.sciencedirect.com/science/article/pii/S1556086418335019%22%20%5Cl%20%22%21), [Avrum Spira MD MScl](https://www.sciencedirect.com/science/article/pii/S1556086418335019#!),[Pierre P.Massion MD,](https://www.sciencedirect.com/science/article/pii/S1556086418335019#!) [Peter J.Mazzone MD MPH](https://www.sciencedirect.com/science/article/pii/S1556086418335019%22%20%5Cl%20%22%21), [Luis M.MontuengaPhD](https://www.sciencedirect.com/science/article/pii/S1556086418335019#!)) Biomarkers in Lung Cancer Screening: Achievements, Promises, and Challenges, March 2019 <https://www.sciencedirect.com/science/article/pii/S1556086418335019> (accessed 23 Dec 2021)

Individual risk needs to be refined, and screening criteria need to be modified to have an impact on lung cancer–related mortality. Orphan images of [IPNs](https://www.sciencedirect.com/topics/medicine-and-dentistry/lung-nodule) stand to improve our success differentiating benign from malignant with a robust biomarker at our disposal. There is also a clear unmet need for prognostic molecular and clinical markers for patients with screening-detected early-stage tumors. Although some believe that testing a new biomarker would be comparable to the gargantuan effort embodied by the [NLST](https://www.sciencedirect.com/topics/medicine-and-dentistry/national-lung-screening-trial), we believe that less complex and more affordable validation is possible in the setting of established lung cancer screening programs. There is plenty of room for improvement. We need to promote studies integrating promising candidate biomarkers, including molecular and image-based biomarkers, and the use of artificial intelligence technologies to help in selection of the most appropriate combinations. Head-to-head comparisons of biomarkers in specific clinical scenarios would also be welcome. Deep mining of the troves of data provided by ongoing screening efforts with new mathematical and computational models based on machine learning will surely help. This will require a systematic collection of patient samples in the context of screening. Finally, ways to prove the cost-effectiveness of the new tests, as well as to overcome the potential hurdles to get the approval by regulatory agencies, need to be considered in the list of challenges that we face ahead in the development of molecular biomarkers in screening. Although the logistics and expense of such an effort may seem daunting at first, we believe that the long-term outcome may prove highly efficient.

Dr. Massion Study concludes: It has great potential but needs further study and clinical trials

American Journal of Respiratory and Critical Care Medicine 2020. (authors were: Dr. [Pierre P. Massion MD, lead author, along with](https://www.atsjournals.org/author/Massion%2C%2BPierre%2BP) [:](https://www.atsjournals.org/doi/full/10.1164/rccm.201903-0505OC#aff2) [Sanja Antic](https://www.atsjournals.org/author/Antic%2C%2BSanja), [Sarim Ather](https://www.atsjournals.org/author/Ather%2C%2BSarim)[3](https://www.atsjournals.org/doi/full/10.1164/rccm.201903-0505OC#aff3), [Carlos Arteta](https://www.atsjournals.org/author/Arteta%2C%2BCarlos), [Jan Brabec](https://www.atsjournals.org/author/Brabec%2C%2BJan), [Heidi Chen](https://www.atsjournals.org/author/Chen%2C%2BHeidi), [Jerome Declerck](https://www.atsjournals.org/author/Declerck%2C%2BJerome), [David Dufek](https://www.atsjournals.org/author/Dufek%2C%2BDavid), [William Hickes](https://www.atsjournals.org/author/Hickes%2C%2BWilliam), [Timor Kadir](https://www.atsjournals.org/author/Kadir%2C%2BTimor), [Jonas Kunst](https://www.atsjournals.org/author/Kunst%2C%2BJonas), [Bennett A. Landman](https://www.atsjournals.org/author/Landman%2C%2BBennett%2BA), [Reginald F. Munden](https://www.atsjournals.org/author/Munden%2C%2BReginald%2BF), [Petr Novotny](https://www.atsjournals.org/author/Novotny%2C%2BPetr), [Heiko Peschl](https://www.atsjournals.org/author/Peschl%2C%2BHeiko), [Lyndsey C. Pickup](https://www.atsjournals.org/author/Pickup%2C%2BLyndsey%2BC), [Catarina Santos](https://www.atsjournals.org/author/Santos%2C%2BCatarina), [Gary T. Smith](https://www.atsjournals.org/author/Smith%2C%2BGary%2BT), [Ambika Talwar](https://www.atsjournals.org/author/Talwar%2C%2BAmbika), and [Fergus Gleeson](https://www.atsjournals.org/author/Gleeson%2C%2BFergus)) 15 July 2020 “Assessing the Accuracy of a Deep Learning Method to Risk Stratify Indeterminate Pulmonary Nodules” <https://www.atsjournals.org/toc/ajrccm/202/2> (accessed 23 Dec 2021)(brackets added)

Computer-aided risk stratification using machine learning (ML) classification of benign and malignant nodules could potentially address some of these limitations, and the availability of large datasets and increasingly powerful computational resources has made the development of such techniques feasible. Such techniques work directly with the image and patient clinical data, negating the need to first describe the morphology or measure the size of the nodule. Prior ML work on previous datasets has shown that such tools have the potential to outperform conventional risk models, but their performance has not been evaluated on multiple independent datasets, including incidentally detected nodules in smokers and nonsmokers. Moreover, the published literature lacks external validation, including data acquired using heterogeneous CT technology and protocols from a variety of clinical practices. Our study offers such a level of clinical validation, which is required for future clinical trials and ultimately for clinical practice.
**END QUOTE. LATER IN THE ARTICLE THEY GO ON TO WRITE QUOTE**:
The work presented here has limitations. Although we compared the performance of LCP-CNN with that of relevant clinical risk models, we did not report its potential to change clinical decision-making. Because some clinical parameters were missing, not all risk models could be run on all datasets. In the future, comparisons with multiple models would be desirable ([52](https://www.atsjournals.org/doi/full/10.1164/rccm.201903-0505OC), [53](https://www.atsjournals.org/doi/full/10.1164/rccm.201903-0505OC)). [**END QUOTE**] Because of the smaller size of the VUMC dataset (n = 116), the difference in AUC was not significant (P = 0.082), although all VUMC reclassification results were significant. As discussed above, despite the differences in disease prevalence and patient populations across the three validation datasets, the same linear calibration between the LCP-CNN and risk was used for all the results shown in [Figure 3](https://www.atsjournals.org/doi/full/10.1164/rccm.201903-0505OC); however, the results may be further optimized by a population-specific calibration. For example, although the reclassification of VUMC and OUH datasets was very good, on the NLST, 3.5% of controls were incorrectly classified as intermediate risk compared with Brock, because of the low prevalence of disease. The OUH dataset did not capture the patients’ history of cancer, which is necessary to calculate the Mayo risk scores, although patients who had received a cancer diagnosis in the last 5 years were excluded. Therefore, in calculating the Mayo scores, it was assumed that the OUH patients had no history of cancer. Although the results are at the nodule level rather than the patient level, the VUMC dataset only had one nodule per patient, and the mean number of nodules per patient in the OUH dataset was 1.08. In summary, using an ML method as a diagnostic algorithm, our LCP-CNN model provided a significant improvement in AUC over the clinically validated risk models (Brock and Mayo). Furthermore, it achieved a strong improvement in DLRs in both clinical validation sets, which included different patient populations. [**AND FINALLY THEY CONCLUDE QUOTE**] Our model is intended to be improved over time as data collections are added and structured curation efforts continue. Although more stringent clinical validations on additional (external and independent) datasets are needed, our results suggest that it may be possible to address a major problem in the management of individuals presenting with IPNs by using an ML-derived prediction model.

4. Not covered by insurance

Medicare won’t cover it until Congress approves it. Private insurers won’t cover it until it is recommended by USPSTF

The Prevent Cancer Foundation 2021. (United States-based non-profit organization; one of the leading US health organizations devoted to the early detection and prevention of cancer) “Multi Cancer Early Detection – Coverage and Legislation” <https://www.preventcancer.org/multi-cancer-early-detection/coverage-and-legislation/#coverage-act> (accessed 7 Nov 2021)

Under current law, Medicare coverage of preventive services is limited to tests for which Congress has explicitly authorized coverage.  Private insurers cover screening tests that receive an “A” or “B” recommendation from the U.S. Preventive Services Task Force (USPSTF).

Without insurance coverage, cancer screening is much less likely to be done

National Academy of Sciences, Institute of Medicine 2002. (Committee on the Consequences of Uninsurance Board on Health Care Services ) “Care Without Coverage: Too Little, Too Late.” <https://www.ncbi.nlm.nih.gov/books/NBK220636/> (accessed 23 Dec 2021)

According to several large population surveys conducted within the past decade, adults without health insurance are less likely to receive recommended preventive and screening services and are less likely to receive them at the frequencies recommended by the United States Preventive Services Task Force than are insured adults. The 1992 National Health Interview Survey (NHIS) documented receipt of mammography, CBE, Pap test, fecal occult blood test (FOBT), sigmoidoscopy, and digital rectal exam by adults under 65 (Potosky et al., 1998). Those with no health insurance had significantly lower screening rates compared to those with private coverage *and* compared to those with Medicaid for every service except sigmoidoscopy.

DISADVANTAGES

1. Harmful Overdiagnosis & Overtreatment

Why rushing ahead without more study is bad: Early cancer detection can create negative net benefits - Risk of overdiagnosis and overtreatment

Dr Ruth Etzioni, Roman Gulati, and Dr. Noel S Weiss 2021 (All 3 are with Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle. Etzioni – PhD. Gulati – M.S. Weiss – MD, DrPH) Multicancer Early Detection: Learning From the Past to Meet the Future 27 Aug 2021 <https://academic.oup.com/jnci/advance-article/doi/10.1093/jnci/djab168/6358734> (accessed 11 Nov 2021)

Furthermore, even if benefit can be established, a central lesson of single-cancer screening is that the value of early detection can be a double-edged sword. For many cancers, earlier detection and treatment is more likely to result in cure, yet for some cancers, it can also lead to overdiagnosis and overtreatment. As a consequence, evaluation of both benefit and harm of a novel early detection technology is required before it can be recommended for general use in the population.