# Old Habits Die Hard: Managing Lung Nodules With Size Alone Is Not Sufficient

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# Disclosures

| Name | Disclosures |
|---|---|
| Steve C. Springmeyer MD | Employee & shareholder at Biodesix Inc. |
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| Trevor J. Pitcher Ph.D | Employee & shareholder at Biodesix Inc. |

# Introduction

- Management of lung nodules requires an estimate of cancer risk (pCA) to follow guidelines.
- The pCA can be derived from various calculators or clinical judgement.
- Nodule size is used in all the calculators and some guidelines recommendations (Table 1). Nodule size was equaled as the most important factor in the Integrated Classifier (IC), a proteomic biomarker test [1].
- We noted that in clinical use, the IC was being used in patients with smaller nodules and more advanced age [2].
- Here we investigate those observations in more detail. We compare distribution of size within two nodule cohorts [3,4] to clinical use data to examine how physicians are ordering a blood-based biomarker in clinical use.
- We hypothesis that physicians are using nodule size alone, instead of pCA, to determine which patients will benefit from testing.

**Table 1. Nodule Calculators for Cancer Risk (pCA)**

Nodule Size is Primary Measure

- **LungRADS**- based on nodule size alone
- **Fleischner**- combines low-moderate and high-risk nodules and then classifies by nodule size alone
- **NCCN**- similar to Fleischner

Nodule Size combined with multiple factors

- **Mayo (SPN calculator)**
- **VA**
- **Many others**


1. Tanner N, Springmeyer S, Porter A et al. CHEST. 2021; 159(3): 1283-1287.
2. Pritchett M, Sigal BW, Bowling MR, et al. AJRCCM 2020;201:A4465
3. Gould M, Donington J, Lynch W et al. *CHEST*. 2013; 143(5 Suppl): e93s-e120s.
4. Silvestri GA et al. Chest. 2018 Sep;154(3):491-500

# Methods

**Testing Overview:** The blood-based biomarker (Nodify Lung, Biodesix Inc., Boulder, CO)-

- 1st: The antibody test [AB] (Nodify CDT™ Test, Biodesix Inc. Boulder, CO)
  - Panel of 7 autoantibodies against tumor associated antigens elevated in lung cancer [5].
- 2nd: Integrated classifier [IC] test (Nodify XL2® Test, Biodesix Inc., Boulder, CO)
  - Proteomic classifier that combines the ratio of two plasma proteins and five clinical factors to identify likely benign lung nodules [4].

**Clinical Sample Sets:**

- Samples from the PANOPTIC study (NCT01752114) [4] and Biodesix Clinical Use Samples (Commercial use) meeting Clinical Use (CU) criteria were evaluated by the combined AB/IC testing strategy.
  - ≥40 years of age
  - Nodule diameter 8-30mm
  - No history of cancer
  - Pre-test risk ≤ 65% by the Mayo Swensen model [6] and MD assessment

**Pre- and Post-Test Risk calculation:**

- Pre-test risk calculated using the Mayo Swensen model [6].
- Post-test risk calculated using positive likelihood ratios for the Ab test [5] or negative likelihood ratios for the IC test.

**Nodule Size Groups:**

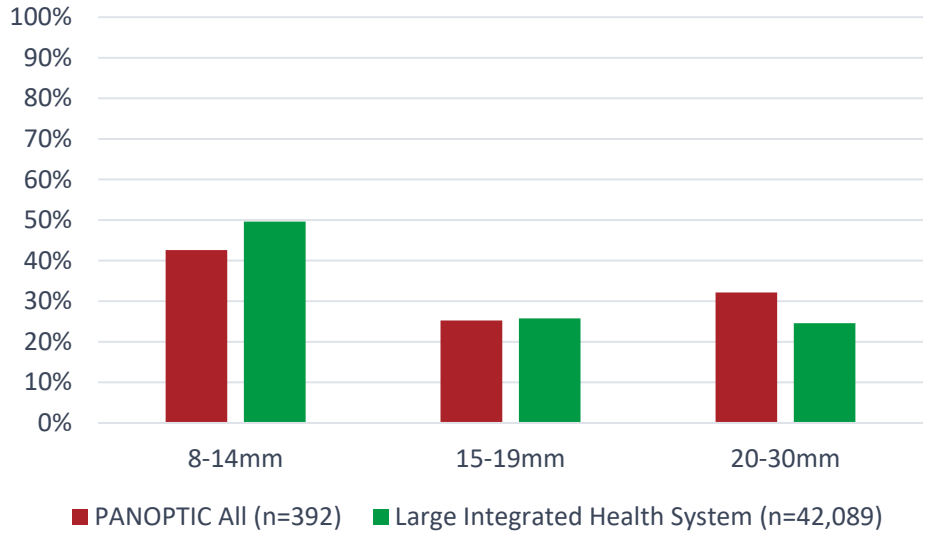
- Distribution of lung nodule sizes observed in the Clinical Use Cohort was compared to the distribution observed in the PANOPTIC study and the those observed in a large healthcare system [3]. Three size ranges were chosen based on when biopsy procedures or further imaging change in clinical utility. These are Group A: 8-14 mm, Group B: 15-19 mm, and Group C: 20-30 mm.

3. Gould M, Tang T, Liu I et al. *AJRCC*. 2015; 192(10): 1208-1214
4. Silvestri GA et al. Chest. 2018 Sep;154(3):491-500
5. Healy et al. Journal of Cancer Therapy 2017 (8): 506-517
6. Swensen SJ et al. Arch Intern Med. 1997 Apr 28;157(8):849-55

# Results: Distribution of Nodule Size

## PATIENTS RECEIVING AB/IC TESTING HAVE SIGNIFICANTLY SMALLER NODULES (P<.0001) THAN THE EXPECTED DISTRIBUTIONS OF PATIENTS THAT WOULD MEET ELIGIBILITY CRITERIA

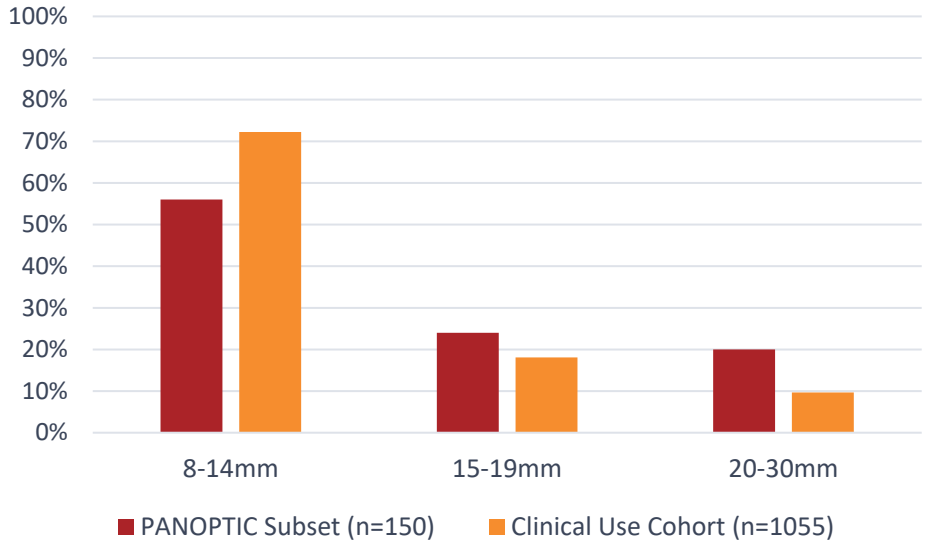
Expected Distribution of Nodules in two Cohorts:
All Nodules 8-30mm




Nodule size among the 3 groups are similar between PANOPTIC trial and the large integrated health system [3].

- Expected distribution for 8-30mm nodules
- 2 datasets are statistically different, but PANOPTIC had data for pCA calculations and may be more representative of nodule patients referred for evaluation

Expected Distribution of Nodule Size:
Nodules 8-30mm, 5-65% pCA




Comparison of PANOPTIC subset and Clinical Use Cohort with a 5-65% pCA.

- The Clinical Use Cohort has a significantly larger portion of the smaller nodules in Group A: 8-14 mm (p<.0001) compared to the expected number.
- Nodule size is the only clinical factor that significantly varied from the expected distributions in the three groupings.

3. Gould M, Tang T, Liu I et al. *AJRCC*. 2015; 192(10): 1208-1214.

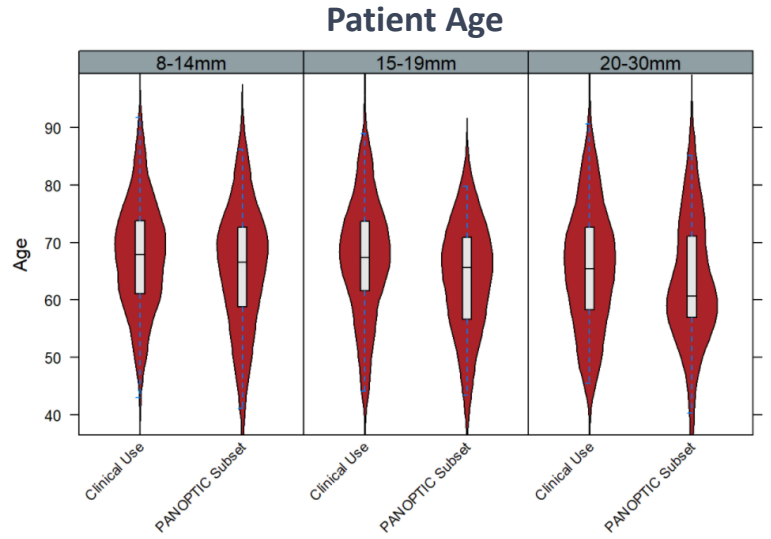
# Patient Demographics Table

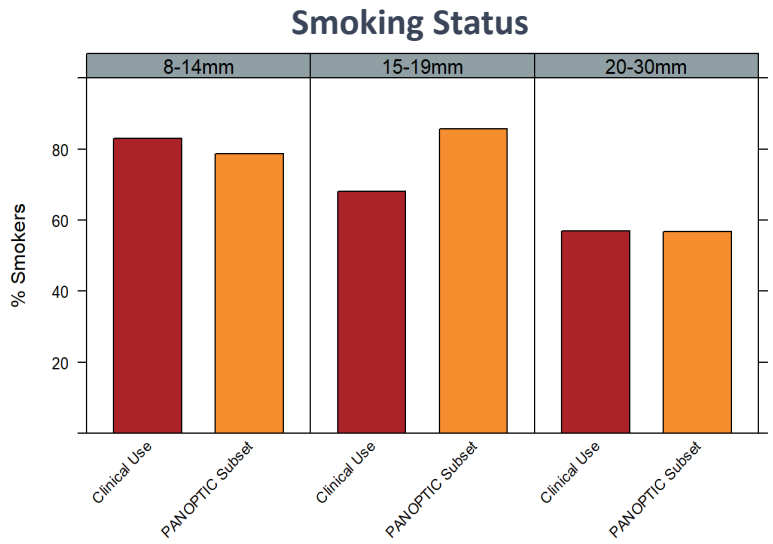
## PATIENT DEMOGRAPHICS IN THE PANOPTIC SUBSET (n =150) AND CLINICAL USE COHORT (n =1055) WERE NOT STATISTICALLY DIFFERENT AMONG EACH SIZE GROUP

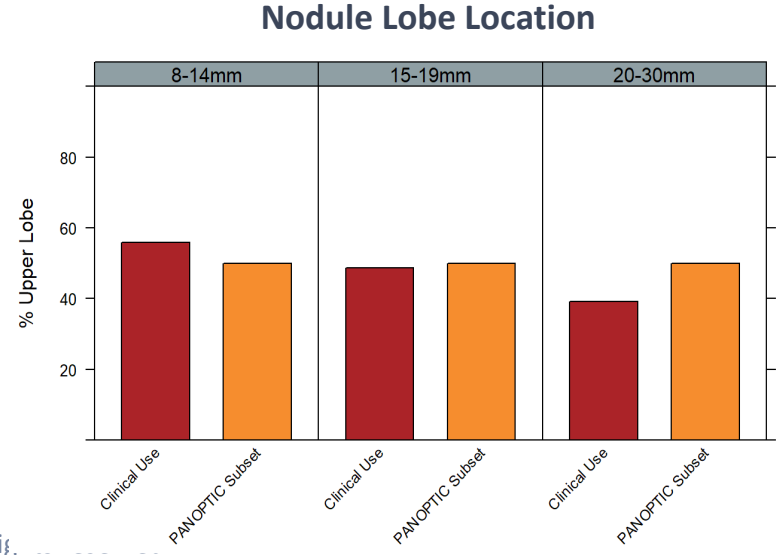
| | 8-14mm | | 15-19mm | | 20-30mm | |
|---|---|---|---|---|---|---|
| **Size Group** | **PANOPTIC Subset** | **Clinical Use Cohort** | **PANOPTIC Subset** | **Clinical Use Cohort** | **PANOPTIC Subset** | **Clinical Use Cohort** |
| **Number of Patients** | 84 | 762 | 36 | 191 | 30 | 102 |
| **Age, years** | | | | | | |
| **Mean (SD)** | 65.8 (10.3) | 67.7 (9.5) | 63.8 (9.0) | 67.3 (10.2) | 63.1 (10.3) | 65.7 (10.3) |
| **Median (Range)** | 66.6 (45.1) | 67.9 (52.2) | 65.6 (36.4) | 67.4 (52.3) | 60.7 (44.8) | 65.4 (45.2) |
| **Former/Current Smoker, % (N)** | 78.6% (N=66) | 83% (N=632) | 85.7% (N=30) | 68% (N=130) | 56.7% (N=17) | 57% (N=58) |
| **Lung Nodule Size** | | | | | | |
| **Mean (SD)** | 10.9mm (2.01) | 10.3mm (1.9) | 16.1mm (1.3) | 16.5mm (1.4) | 23.5mm (3.0) | 22.5mm (3.0) |
| **Median (Range)** | 11.0mm (6) | 10mm (6) | 15.5mm (4) | 16mm (4) | 22mm (10) | 21.5mm (10) |
| **Upper Lobe, % (N)** | 50% (N=84) | 56% (N=425) | 50% (N=18) | 49% (N=93) | 50% (N=15) | 39% (N=40) |
| **Spiculated, % (N)** | 22.6% (N=19) | 31% (N=239) | 30.6% (N=11) | 24% (N=46) | 20.0% (N=6) | 8% (N=8) |

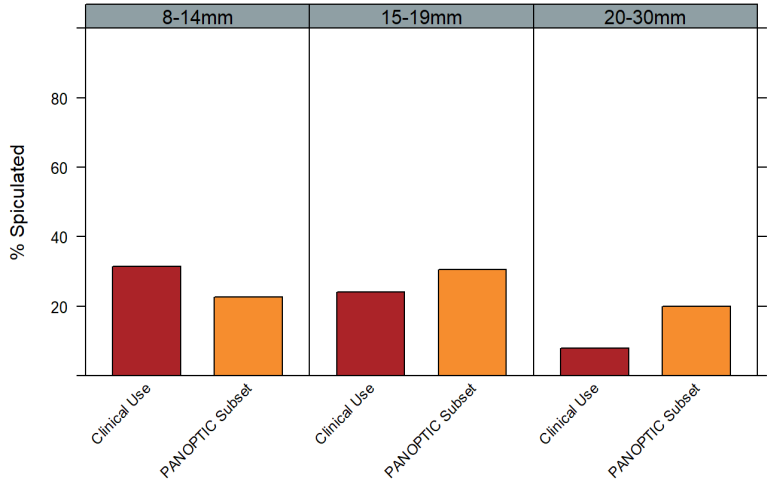
# Results: Other Patient Demographics by Size Groups

## PATIENT DEMOGRAPHICS IN THE PANOPTIC SUBSET (n =150) AND CLINICAL USE COHORT (n =1055) WERE NOT STATISTICALLY DIFFERENT AMONG EACH SIZE GROUP



# Results: pCA Classification Changes (CC) by Group

Combined CC in the Clinical Use Cohort is 425 of 1055 patients (40%)

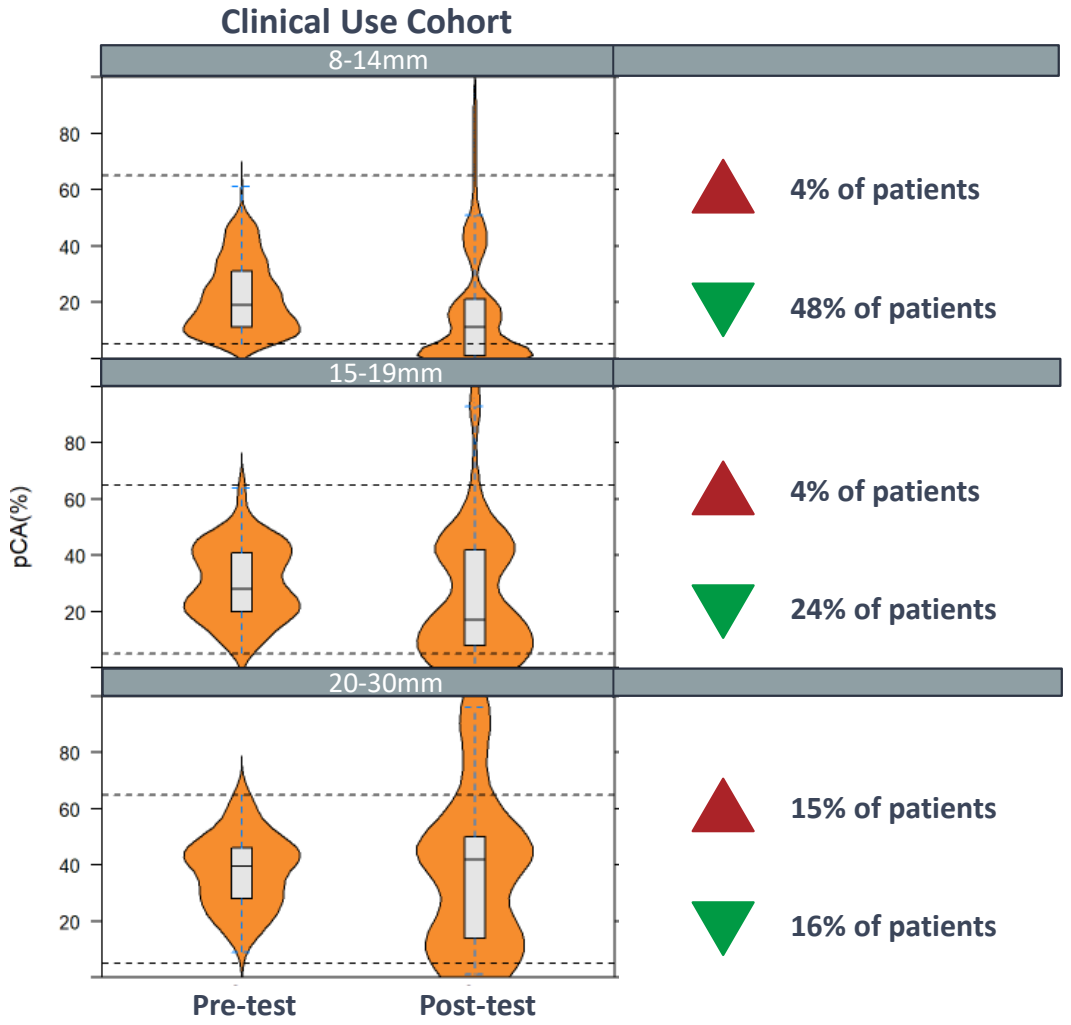
- Smaller nodules (Group A) have a lower pCA and a higher CC at 48% with the Integrated Classifier.
- Larger nodules (Group C) have a modestly higher pCA at 38% and higher CC with the Autoantibody testing at 15%.

**Note:** the CC to <5% for 24% and 16% of Group B and Group C nodules suggests IC testing will be beneficial

| Autoantibody and Integrated Classifier Testing in 8-30mm Nodules Separated in to Three Groups By Size Alone | | | | |
|---|---|---|---|---|
| **Group (mm)** | **A (8-14)** | **B (15-19)** | **C (20-30)** | **Total** |
| **Nodules 5-65% pCA (% of total)** | 762 (72%) | 191 (18%) | 102 (10%) | 1055 |
| **Average % Pre-test pCA** | 21% | 30% | 38% | 24% |
| **Autoantibody Positive (%)** | 83 (11%) | 20 (10%) | 23 (23%) | 126 (12%) |
| **Classification Change >65% (%)** | 27 (4%) | 8 (4%) | 15 (15%) | 50 (5%) |
| **Integrated Classifier Nodules Tested** | 677 | 167 | 74 | 918 |
| **Classification Change <5% (%)** | 323 (48%) | 40 (24%) | 12 (16%) | 375 (41) |
| **Classification Change Combined (%)** | 350 (46%) | 48 (25) | 27 (26%) | 425 (40%) |

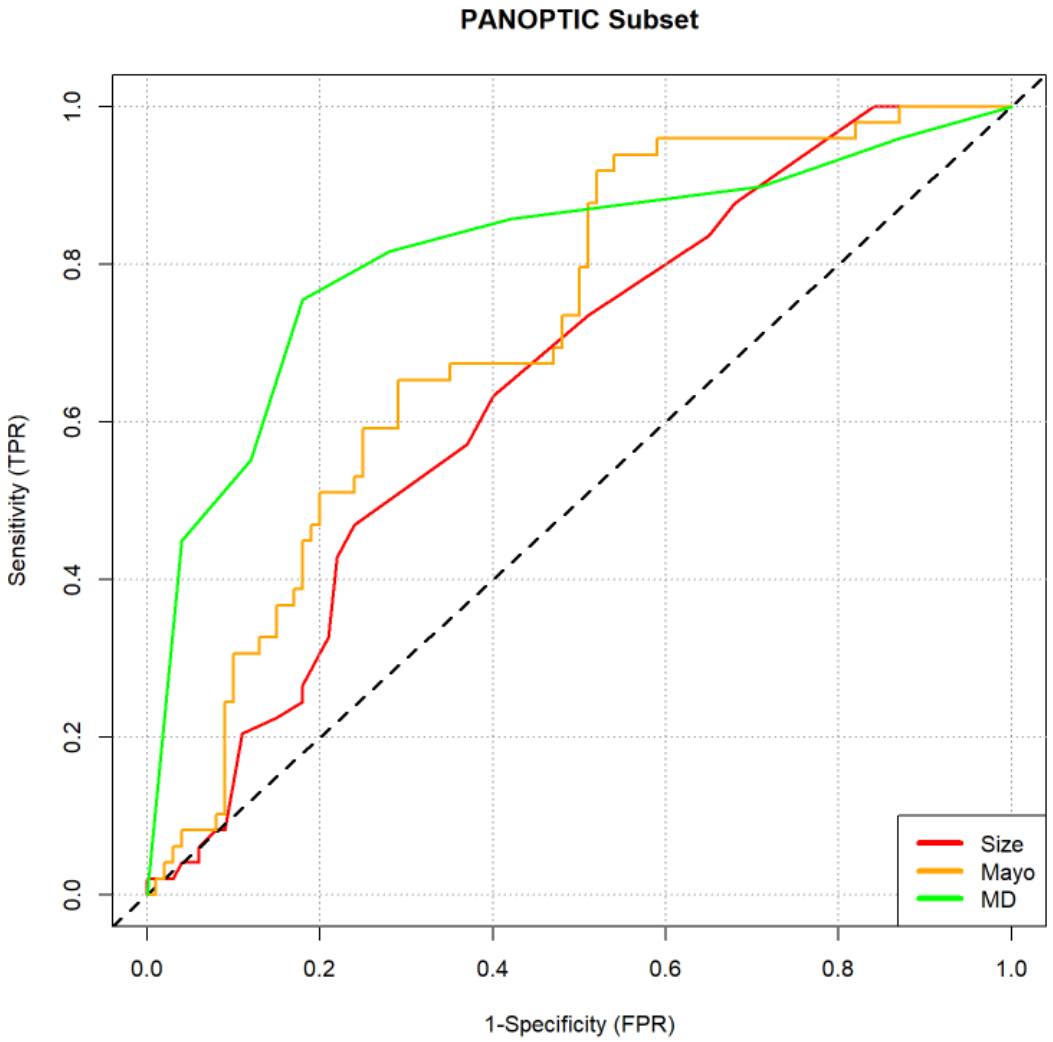
# Results: pCA Classification Changes (CC) by Group

**Pre-test and post-test diagrams for pCA classifications of the Clinical Use Cohort (n =1055).**




Note: patients in all groups are reclassified into the very low (<5% pCA) or high (>65% pCA) risk group using the antibody/integrated classifier testing.

# Comparison of Nodule Size Alone to Other Assessments




- Physician assessed Risk (MD) and the Solitary Pulmonary Nodule Calculator (Mayo) have higher AUC than Nodule Size alone
- AUC for each:
  - Nodule Size: 0.65 AUC
  - Solitary Pulmonary Nodule Calculator: 0.72 AUC
  - Physician Assessed Risk: 0.81 AUC

This suggests that using nodule size alone (not considering other factors) is insufficient information for management.

# Conclusions

1. Combined Antibody/Integrated Classifier Testing is confirmed to reclassify 40% of patients from low to moderate into the very low (<5% pCA) or high (>65% pCA) risk group.
2. Lung nodule groups (15-19mm & 20-30mm) have lower than expected testing rates as compared to published studies. This suggests a preference for biopsy, over-confidence in the pCA using nodule size alone, or other clinical observations not measured.
3. Nodule size alone does not predict benign vs. malignant nodules with as much accuracy as holistic risk assessments such as physician pCA or the Ab-IC testing.
4. Combined Antibody/Integrated Classifier testing continues to show meaningful reclassification across all 8-30 mm nodules (40% of patients being reclassified). This beneficial classification change has continued clinical utility in 15-30 mm nodules.

# Appendix