The Challenge of Early-stage Cancer Detection

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Background: Cancer is the second leading cause of death globally, accounting for an estimated 9.7 million deaths in 2023. According to statistics presented by the International Agency for Research on Cancer, the annual reported cancer incidence worldwide was 19,976,499 cases, which for the population over 50 years of age is equal to an incidence of 1.1% annually. Cancer detection is complicated by the variations associated with the location of the neoplasms, the structure of the cancer cell itself, and the tissue origin. In addition, the prevalence of most cancers in the general population is typically only 0.05-0.2%, and this further complicates the predictive value of the detection method. To overcome these detection challenges, various approaches are used. The traditional first approach is an imaging study (ultrasound, CT, MRI, PET) targeting the suspected cancer location. However, these modalities often do not have sufficient resolution to detect cancer in its earliest stages.

A promising approach for cancer detection is an analysis of gene mutations known to be associated with cancer using circulating DNA or RNA as the target. Such a test must be 100% specific for the cancer the test is attempting to detect, however, the theoretical maximum specificity of these tests is no more than 99.6% [1]. The 0.05-0.2% cancer prevalence in the population yields only a 10-30% positive predictive value (PPV1) (Figure 1), and the sensitivity of a circulating DNA/RNA cancer gene detection method is relatively low for early-stage cancers.

Another approach to the problem of early-stage cancer detection is based on a unique feature of epithelial cancer cells. It utilizes a highly sensitive and very specific proprietary early-stage cancer biomarker called CA-62. The negative predictive value (NPV) of CA-62 is dramatically higher for early-stage cancers than other detection methods. We predict that part of the patients with elevated CA-62 levels that are re-tested with CA-62 in the 1-6 months window post their initial test ("secondary screening"), will test negative on the secondary screening, mainly as a result of earlier comorbidities, improper patient preparation, drug or hormone therapies or blood collection inconsistencies (PPV2; see formula1 below) by as much as 40-80% vs. the initial CA-62 screening data. (Figure 2). Alternatively, the secondary screening of the patients with elevated CA-62 levels could be performed with a circulating DNA/RNA method.

Method: A blind clinical study was conducted using the CA-62 marker in the prospective screening of 1,000 employees over the age of fifty from three facilities with elevated cancer risk. Within the testing cohort, there were ten patients with confirmed cancer diagnoses, twelve patients in remission following cancer treatment, and 208 with diseases reported potentially to cause false-positive CA-62 results. Only forty-three employees had no comorbidity in their medical records. CA-62 was measured in all these patients. Statistical analysis was performed using MedCalc software.

Results: In multiple blind studies, CA-62 has confirmed its diagnostic utility for the early-stage detection of the six most common epithelial carcinomas (non-small cell lung cancer, prostate cancer, breast cancer, ovarian cancer, colorectal cancer, renal cell carcinoma). The CA-62 biomarker is specific for epithelial cancers (stomach cancer, cervical cancer, endometrial cancer, melanoma, etc.) as well. These cancers account for more than 90% of all cancer cases worldwide. In blind prospective studies for early-stage cancers, which have a prevalence of 0.57% in the general population over the age of 50, and 90-93% sensitivity at the 95% specificity of the CA-62 assay were confirmed [2-6].

CA-62 screening of the 1000 employees described above with CA-62, showed a 100% negative predictive value (NPV) and a 15.9% positive predictive value (PPV). Elevated CA-62 levels were found in 63 employees, 10 of them having been previously diagnosed with cancer, corresponding to a 15.9% PPV (93% sensitivity and 95% specificity) (PPV1; Figure 1). Most of the remaining employees with elevated CA-62 levels were diagnosed with non-cancerous diseases (cysts, ulcers, polyps, and obstructive pulmonary disease) during follow-up medical testing. Interestingly, elevated CA-62 levels were not found in all employees who had the same diseases in medical records except four out of eight employees with asthma. The employees with cancer in remission did not show elevated CA-62 levels.

Secondary screening of patients that initially tested positive for CA-62 could substantially improve PPV (PPV2) (Figure 2). We usually advise repeat CA-62 testing in 30-60 days in patients found to have elevated levels of CA-62 who had not previously been diagnosed with cancer and were asymptomatic. Various medical conditions and treatments (e.g., early pregnancy, stem cell procedures, and recent immunizations) have been found to cause temporary elevations of serum CA-62 levels in the absence of cancer. The high NPV of CA-62 offers significant value for multicancer screening, providing confidence in the absence of cancer within a wide range of prevalences (Figure 3).

Formula 1 of PPV2 calculation:

PPV2 = 100 * (PPV1 * Sensitivity) / (PPV1 * Sensitivity + ((1 - PPV1) * (1 - Specificity))

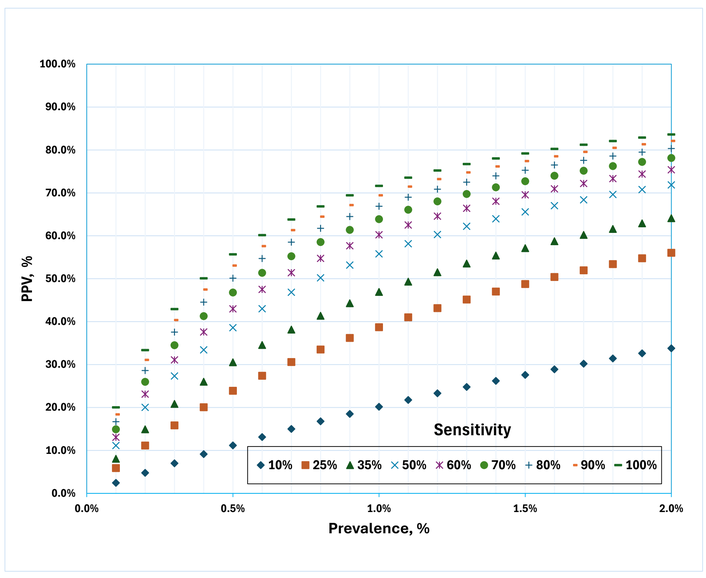

Figure 1. Positive predictive value (PPV1) at 99.6% specificity and prevalence up to 2% and various sensitivities.

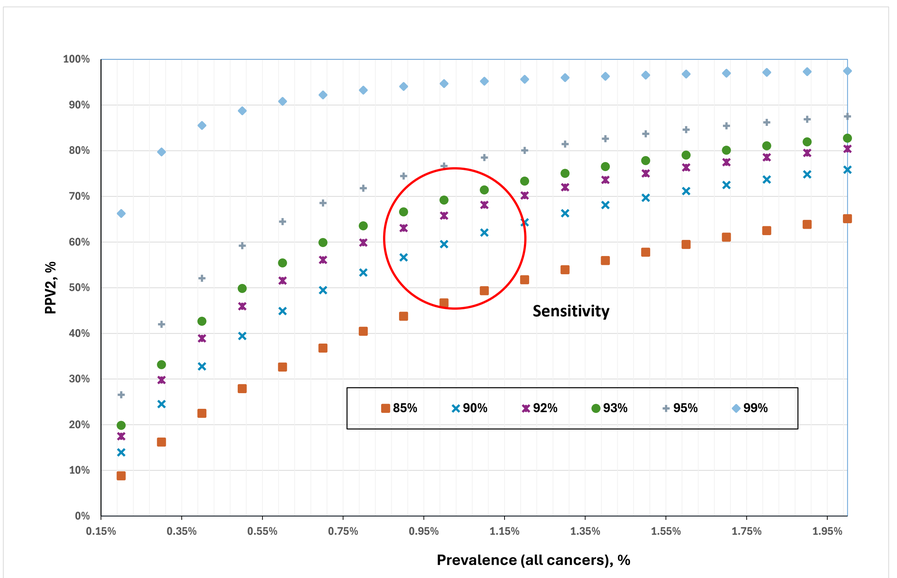

Figure 2. Positive predictive values (PPV2) at 95% specificity and prevalence (all cancers) up to 2% and various sensitivities in the secondary study.

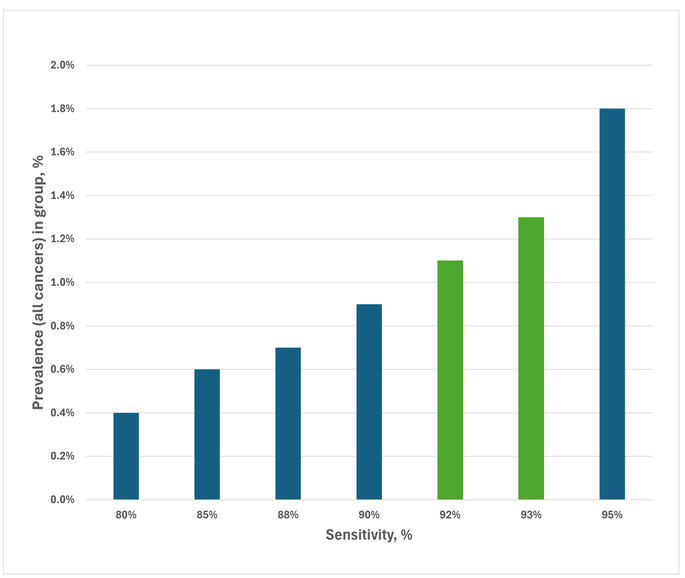

Figure 3. Dependence of negative predictive value (NPV) on prevalence (all cancers) at different sensitivity.

Conclusions:

- The CA-62 test is relatively simple to perform and is a very affordable screening test for early-stage cancer.
- CA-62 can facilitate the screening of patients at elevated risk for cancer.
- Implementation of a "secondary testing" program with CA-62 will no doubt decrease the number of patients previously found to have elevated CA-62 levels requiring additional cancer screening and improve PPV (PPV2) up to 40-80%.

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