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Improving cancer risk assessment and prognosis: the role of Multianalyte Assays with Algorithmic Analyses

A report by The Economist Intelligence Unit

Key points:

- Multianalyte Assays with Algorithmic Analyses (MAAAs) are tests that combine two or more biomarkers into an algorithm to generate a disease risk assessment or prognostic result. They potentially offer better performance than single biomarkers.
- MAAAs have been adopted for use in Eastern Countries such as China, but to this point, Western Countries, particularly European and North American countries, have not embraced these algorithms. We explore the use of these algorithms in areas where they have been incorporated into screening and testing protocols and discuss potential reasons why there has been less uptake for use in other places.
- We suggest three actions that need to occur in order to facilitate the adoption of MAAAs into clinical care. These are to 1) improve the targeting of MAAAs through better guidance, 2) promote MAAAs as a screening tool in primary care, and 3) continue to evaluate the costs and benefits of MAAAs in clinical practice.

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Introduction

Biomarker testing and Multianalyte Assays with Algorithmic Analysis (MAAA)

Biomarker testing, via a blood or urine test, uses molecules, genes or other characteristics to identify cancer risk, determine prognosis, and monitor disease progression. Over the past decade there have been a rising number of tests that combine two or more biomarkers into an algorithm to generate a result. These combined tests are called Multianalyte Assays with Algorithmic Analysis, or MAAA for short. This combination of two or more markers with an algorithm improves performance compared to single biomarkers.[1-5]

MAAAs can be used at a variety of stages of the patient disease management pathway, ranging from screening and risk assessment, through to prognosis and therapy selection.[5] They can be used to determine which patients should be more actively screened and followed. Then, once a diagnosis is made by tissue biopsy, MAAAs can be used to help determine which therapy the tumour will likely respond to, as well as how aggressive the cancer treatment needs to be. In summary, MAAAs help focus resources on who should be screened most frequently and treated more aggressively when a cancer is identified.

The combination of two or more markers with an algorithm improves performance compared to single biomarkers.[1-5]

MAAAs are not evenly spread across all cancers. There are many in use for prostate cancer (e.g. phi, 4KScore® and Mi-Prostate Score) and ovarian cancer (e.g. OVA-1®, OVERA, and ROMA), but fewer or none for other cancers. Only a few tests are commonly used on a global scale.[1] MAAAs are also being developed for non-cancer conditions, such as preeclampsia, acute coronary syndrome and sepsis.[5]

Adoption of MAAAs is more common in East Asia than in US and Europe

MAAAs have been adopted in many Asian countries. In some countries, such as China, Risk of Ovarian Malignancy Algorithm (ROMA)—an algorithm that combines CA125 with HE4 and menopausal status to calculate a risk of malignancy—is found in medical guidelines as an option for patient assessment. Other biomarkers, such as AFP and PIVKA-II, are also commonly used together for Liver Cancer assessment.

MAAAs can improve the patient experience by reducing waiting times for appointments, scans, and biopsies.

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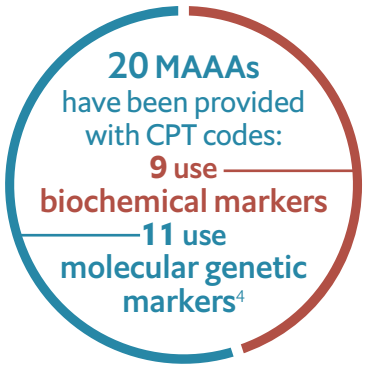
Second Military Medical University in Shanghai

Prof Tian Yang, Associate Professor of the Second Military Medical University in Shanghai, confirmed that in China, MAAAs are used frequently for liver cancer treatments—they "can improve the patient experience by reducing waiting times for appointments, scans, and

biopsies". He suggests that biomarkers are much cheaper in China than in Western countries, making the technology more accessible and cost-efficient. Prof Chunxue Bai, Director of the Zhongshan Hospital, Fudan University, agrees that the low-price is one of the biggest enablers for the adoption of biomarkers in China.

However, in most Western and Latin American countries, the number of MAAAs used clinically remains modest. As Dr Luiz Maltoni, Executive Director of the National Cancer Foundation in Brazil remarks, "the development and use of genomics is more advanced in treatments and drugs than in diagnostics and prognostics". Only a few MAAAs have been cleared by the Food and Drug Administration (FDA), although some manufacturers have achieved coverage for MAAAs despite not obtaining FDA approval first, or ever in some cases.[6] Twenty MAAAs have been provided with current procedural terminology (CPT) codes: 9 use biochemical markers and 11 use molecular genetic markers.[4]



One of the reasons for their limited use in the West is that MAAAs and other combination tests are often proprietary in nature. The algorithm component, which brings all the constituent parts of the test into a personalised risk score, is often complex and unique to a private laboratory or manufacturer—this can lead to the higher costs noted by Professors Tian Yang and Chunxue Bai.

To illustrate how MAAAs can contribute to the assessment and management of cancer, we present below three short case studies of their use in three cancers: ovarian, liver and lung. While MAAAs are relatively common in ovarian cancer, they are less established in liver cancer, where they are mostly used to augment the use of imaging technology. In lung cancer, the last decade has seen the establishment of biomarker testing for screening at the centre of best practice.

MAAAs in practice: three case studies

Ovarian cancer: differentiating between malignant and benign tumours

Ovarian cancer is the fifth leading cause of cancer deaths of women worldwide.[7] In more than 70% of cases, it is diagnosed at an advanced phase, so prognosis remains poor overall, with a 5-year survival rate of just 46%.[8]

The use of biomarkers is relatively well established in ovarian cancer. Historically, clinicians used the single biomarker cancer antigen-125 (CA-125). However, due to its relatively imperfect diagnostic sensitivity and specificity[9], laboratories and diagnostic manufacturers have introduced several algorithms to improve risk assessment. Many of these included Human Epididymis Protein 4 (HE4), a biomarker that adds information to CA125 measurement alone.[10]

A four-marker panel (using CA125 and HE4 alongside two other biomarkers: E-CAD, and IL-6) performed significantly better than CA 125 alone or CA125 with HE4.[11] The four-marker panel had the highest ROC AUC (Receiver Operating Characteristic, Area Under the Curve), a graphical plot that compares true positives vs false positives: the higher the score, the greater the proportion of true positives.

MAAAs, such as the four-panel marker described above, are used in ovarian cancer to help differentiate between malignant and benign tumours. MAAAs currently in use include the Risk of Malignancy Index (RMI), OVA1, OVERA, and ROMA. The RMI incorporates CA-125, ultrasound features, and menopausal status, while the others use a combination of blood biomarkers and/or ultrasound.[2] A recent review found that the best biological diagnostic tools today for ovarian cancer are the RMI or ROMA algorithms.[12]

Liver cancer: enabling early diagnosis to a currently underserved population

Liver cancer is estimated to be the sixth most commonly diagnosed cancer and the fourth leading cause of cancer deaths globally.[13] There is no standard or routine screening test for liver cancer, and while imaging techniques such as ultrasound and PET scans are useful for diagnosis, they are expensive and hence unsuitable as a basis for a screening programme.[14] Ultrasound also has relatively low sensitivity in the detection of liver cancer.[15]

Blood biomarkers have been proposed as a screening alternative for liver cancer. They are non-invasive, safe, convenient and cheap, and can be measured repeatedly with ease, in order to monitor disease progression.[16] There are three main algorithms that have been developed for liver cancer: the GALAD score[17], the HES algorithm[18] and the ASAP model.[19] They are all based on a combination of serological diagnostic biomarkers for liver cancer in clinical practice.[20]

PIVKA-II in particular has long been used in Japan, where it is covered by Japan's national health insurance, along with other biomarkers.[21,22] The US is following Japan's example here, for the FDA has recently granted Breakthrough Device Designation for a new GALAD score—based on AFP, AFP-L3, and PIVKA-II—to support earlier diagnosis of liver cancer.[23]

This combination of biomarkers can be used alongside imaging technology, and sometimes help avoid unnecessary (and expensive) advanced ultrasonography investigations.[24] "Traditionally, what is recommended for liver cancer is ultrasound plus AFP", Dr Madeleine Eternity Labio, of the Makati Medical Center, informed us. "Now, we are beginning to add PIVKA as well. The test is increasing early detection when combined with the other tests; we are using it both for diagnostics and for monitoring ongoing treatment."

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Dr Madeleine Eternity Labio, Makati Medical Center

While the MAAAs all offer advantages over single biomarkers, the best model with highest diagnostic accuracy remains controversial, due to the complex nature of liver cancer.[20]

Lung cancer: guiding treatment decisions and supporting patient-centred care

Over the last decade, the treatment of patients with advanced non–small cell lung cancer (NSCLC) has become increasingly based on blood biomarkers. So much so that a recent summary of lung cancer guidelines suggested that all patients with NSCLC, regardless of clinical characteristics, should undergo molecular testing.[6] These include, at a minimum, testing for EGFR mutation, ALK and ROS1 rearrangements, BRAF mutation, and PD-L1 IHC.[6]

Similar to ovarian and liver cancer, numerous studies have shown that combining biomarkers performs better than single biomarkers. For example, a combination of six serum tumour markers performed better than any tumour marker considered individually.[25] The combination improved sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV). Their addition also improved the performance (i.e. increased the ROC AUC) of an algorithm that included tumour size, age and smoking status.[25]

On the back of these and similar findings, various prognostic algorithms have been developed for lung cancer. Serum proteomic signature tests, for example, are blood-based tests that can be used to help identify aggressive cancer.[26] They allow for the stratification of advanced NSCLC patients into groups that would benefit from intensive treatment strategies.[27] Establishing such a timely, patient-specific prognosis promotes shared decision-making through improved treatment strategies and better informed patient management.

A second example of a risk-stratification algorithm is the LCBP (Lung Cancer Biomarker Panel) study in China.[28] The algorithm integrates blood biomarker testing with CT scans to improve the early and accurate diagnosis and prognosis of high-risk patients with suspected lung cancer. The algorithm demonstrates excellent discrimination, allowing for the stratification of patients with different levels of lung cancer risk. The LCBP is an example of an algorithm that is designed for a particular demography and is applicable to high-risk Chinese populations.[28]

Limited uptake in the West

Barrier 1: Screening programmes have not traditionally used biomarkers

The use of MAAAs is greater in Asia than in Europe and North America. Physicians in Asia are already used to working with biomarkers, and so the adoption of MAAAs seems natural. For example, national screening programmes for gastric cancer can be found in Japan, South Korea, China and Singapore[29], and there are government funded screening programmes for liver cancer in Taiwan and Japan.[30] There are also ongoing research programmes to push for yet wider adoption of biomarker-based screening programmes. The Taizhou Longitudinal Study in China, for example, has shown the promise of biomarkers in the early detection of stomach, oesophageal, colorectal, lung, and liver cancer.[31]

The relative scarcity of similar biomarker-based screening programmes in Europe and North America means that healthcare professionals in US and Europe tend to be less enthusiastic about MAAAs. This is often the case even when the MAAA is formally recommended. For example, while the Oncotype DX test has been incorporated into U.S. breast cancer clinical guidelines, less than half of eligible women receive it.[32]

Barrier 2: Physicians remain hesitant because of a lack of experience with MAAAs

Recent research in the US on the use of a specific MAAA—Oncotype DX—identified three categories of barriers to adoption. First, organizational factors, such as departmental structure, Oncotype DX marketing, and medical and insurance guidelines. Second, the influence of interpersonal factors, such as oncologists' normative beliefs and peer use of Oncotype DX. Third, intrapersonal factors, such as oncologist attitudes, perceived barriers, and research gaps. Although oncologists largely held positive attitudes about the MAAA, they reported challenges with interpreting scores for treatment decisions and explaining test results to patients.[32]

There are other reasons why some physicians may remain hesitant. Given the multiple types of genetic alterations possible, and the fact that tests may fail due to technical reasons.[6] There may also be shortages of local availability of tests, and delays in obtaining results (turnaround times).[33] Finally, clinicians need to know which biomarker to prioritise, which requires education and experience.[6] All of these issues means that the average post-launch delay in clinical uptake of a test is 4.5 years.[34]

Barrier 3: The evidence base is perceived to be weak

The evidence base for MAAAs is still developing, and currently their use is best focussed on specific populations for which there is good evidence. Dr Maltoni remarks that "today MAAAs don't have sufficient clinical trials to justify screening programs using the technology. Instead, they are more effective in well-selected patients with pre-identified risk conditions." Professor Colon-Franco describes the importance of moving beyond studies that compare sensitivity and specificity to single biomarkers, and towards trials that track outcomes important to patients. "There's very little knowledge about the full effect on real health outcomes like mortality, morbidity and quality of life." Dr Almhanna agrees; "we need randomized studies. I want to see prospective trials, to prove they are really changing outcomes"

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>
> *Dr Luiz Maltoni,*
> *National Cancer Foundation, Brazil*

While it is hoped that MAAAs can reduce the reliance on other tests, particularly invasive tests and biopsies, they are not yet at this stage. "Today, MAAAs are not able to replace other tests", remarks Dr Maltoni, "but in very specific cases they may reduce the number of tests done; for example from every 6 months to every year". He goes on to explain that "history shows us that cancer technologies have always been complementary, not substitutes—CT did not replace X-Ray, MRI did not replace CT".

Barrier 4: Costs remain a concern, particularly if they fall on the patient

A final barrier mentioned by interviewees is cost. The development and validation of MAAAs is more costly than single markers. A laboratory or manufacturer developing MAAAs will need to evaluate the analytical performance of each maker individually, and the performance of the combination of markers for the generation of the composite score.[4] MAAAs can therefore be relatively costly to develop, and consequently, to deliver.

"There are costs associated with running the test; oftentimes the test must be sent to a specialist laboratory", remarks Professor Jessica Colon-Franco, Assistant Professor at the Department of Pathology, Medical College of Wisconsin, in the US. "If we can start offering tests locally (ideally in-house), and not just in specialist laboratories, this will help bring costs down." Dr Labio agrees, remarking that "In the Philippines, most of the costs are out of the pocket, none of the costs are subsidised by the government, so there is a huge economic burden for patients."

Looking ahead

MAAAs promise the opportunity of improved risk assessment, prognosis and a better patient experience. While they need evaluating in real world settings for their impact on patients' outcomes and quality of life, their adoption in Asia shows their usefulness alongside imaging and other technologies. However, elsewhere in the world, the update of MAAAs remains stalled. We describe here three developments that would support their use.

1) Improve the targeting of MAAAs through better guidance

Healthcare professionals need to be supported in the process of using patient history to identify high-risk patients that would benefit from MAAAs. "Panels [such as MAAAs] are more effective on pre-selected patients, those with a family history of cancer and other risk factors", remarks Dr Maltoni. There therefore needs to be better guidance on when and how to use MAAAs.

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Dr Luiz Maltoni,
National Cancer Foundation, Brazil

In many Western countries, a perceived paucity of evidence is obstructing their incorporation into guidelines. It may be that institutions in the US, Europe and elsewhere need to familiarise

themselves better with evidence from Asia-Pacific. Dr Labio, who is a member of the team to set guidelines for liver cancer, remarks that a stronger evidence base will lead to stronger guidance, and that "once we have better and more robust guidelines we could advocate for some type of reimbursement."

2) Promote MAAAs as a tool for primary care practitioners

"If we want to prevent and detect cancer early, we should be speaking with clinical practitioners and primary care physicians", suggests Dr Maltoni. In the near future, he argues, risk assessment tools should be part of their practice, not of oncologists. When patients get to an oncologist they tend to already be diagnosed. The most effective use of risk assessment may therefore be in primary care.

Dr Labio agrees with the need to promote screening in primary care. "Physicians are not screening enough. We know who the high-risk populations are, but for many reasons we are not screening them. We definitely need to improve all the diagnostic tools we have to make them more accessible and precise."

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3) Evaluate the costs and benefits of MAAAs in clinical practice

There needs to be suitable investment in research and clinical trials to strengthen the evidence-base to support the adoption of MAAAs in clinical practice. Many of the current trials are run by owners of the algorithms, which can lead physicians to be sceptical of the results. When manufacturers fund such trials, they need to ensure that protocols are registered at a trial registry at the beginning of the trial; such transparency will help increase confidence amongst potential users.

Trials are a costly business. "You cannot do trials just to test biomarkers", suggests Dr Almhanna. "Rather than doing a large trial just for biomarkers, they need to be added to other cancer clinical trials." Studying MAAAs within the context of a wider patient pathway will better reveal their impact in real-world, clinical practice.

Closing remarks

MAAAs play an important role as an adjunct to screening to identify high risk patients who need more aggressive evaluation and follow-up monitoring. They can be used to monitor for cancer recurrence and help establish what treatment will be most suitable for a patient. However, uptake is slow outside of Asia.

We suggest three developments that would support the assessment and adoption of MAAAs. Taken together, the three developments would form a virtuous circle: improved targeting would lead to greater use, the development of an evidence base, and incorporation into guidance, which would further increase their use in practice.

While MAAAs are slowly gaining traction in the West, greater awareness of their use in China, Japan, South Korea, Taiwan and elsewhere in Asia-Pacific would allow healthcare systems, institutions and professionals to learn from their experience. The evidence base shows that MAAAs perform better than single biomarkers—the challenge for practitioners in the West is to learn where best to incorporate their use alongside other technologies in the patient pathway.

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- **Prof Tian Yang,**
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