Dia:gram

EDITION 2017 Vol 2

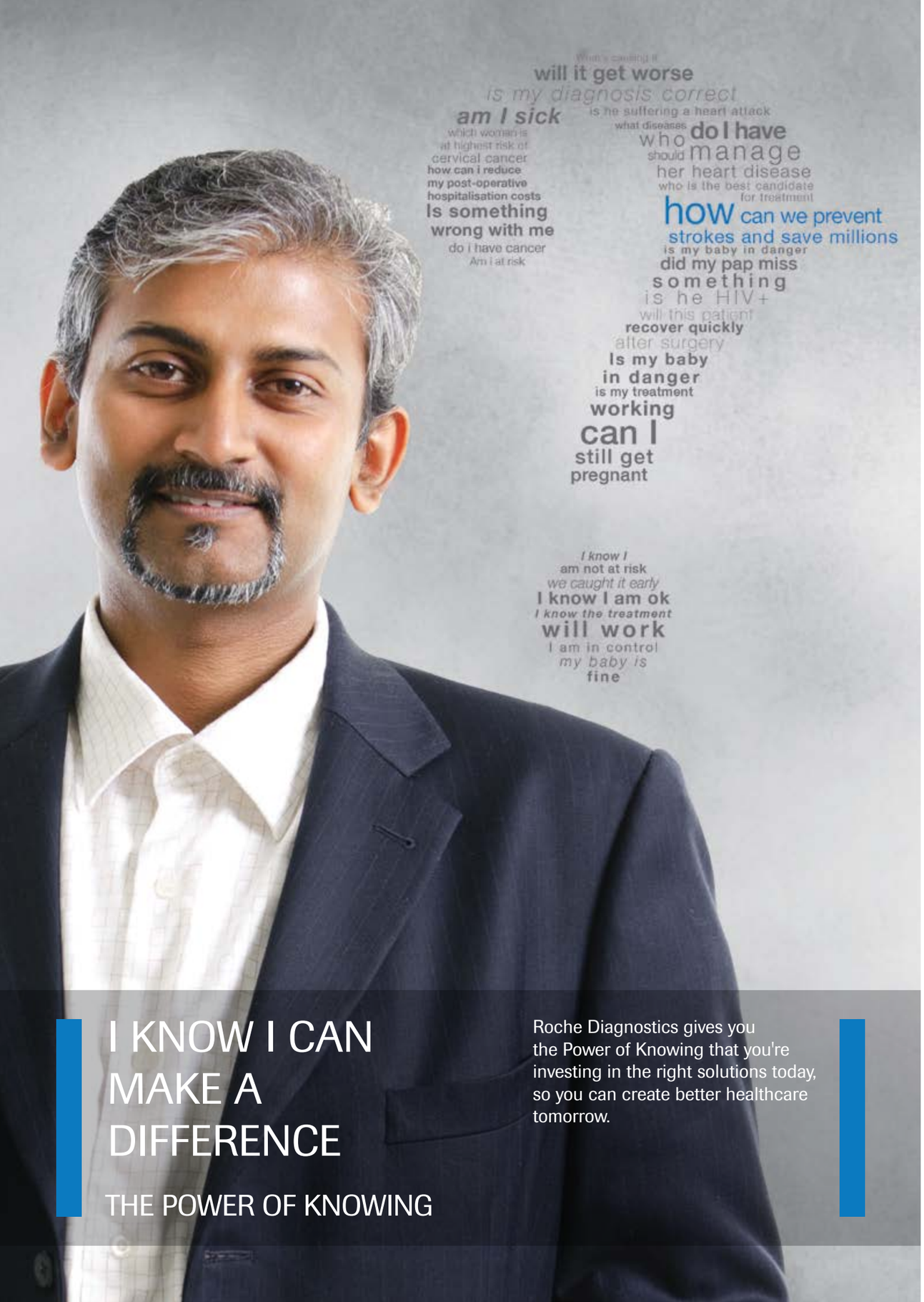
Breaking silos to unlock the value of diagnostics

The promise of liquid biopsy

Driving personalised care in cancer management

Advancing family planning in Asia

Professor Chii-Ruey Tzeng



Note from the editor

Dear Readers,

Since the launch of Dia:gram at the end of 2016, we have received overwhelming feedback from the healthcare community in Asia Pacific. With our second issue we've once again embarked on an inspiring journey, uncovering interesting and thought provoking stories along the way from our conversations with leading voices in the field of diagnostics. We've interviewed healthcare leaders from Australia, Japan, Malaysia and Thailand to showcase the breadth of exciting developments across our diverse region.

As patient-centric diagnostic innovation continues to shape our industry, we have examined what value really means in this shifting landscape, and how laboratories can demonstrate it. From liquid biopsies to newer biomarkers – the information provided by these tests is changing both the pathologist and the patient's relationship with care providers. This is driving a new culture of collaboration and shared decision-making, all in the service of better outcomes for patients.

It is a truly interesting time as we chart a new and exciting path.

Rachael Bylykbashi
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Dia:gram

Edition 2017, Vol. 2

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The promise of liquid biopsy

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DR. PATHMANATHAN RAJADURAI

In this interview with **Dia:gram** magazine, ***Dr. Pathmanathan Rajadurai***, Senior Consultant Pathologist and Laboratory Director at Subang Jaya Medical Centre (SJMC) in Malaysia talks about the significance of liquid biopsy testing for non-small cell lung cancer with Epidermal Growth Factor Receptor (EGFR) mutations. SJMC was among the first facilities in the region to adopt liquid biopsy, and Dr. Pathmanathan reflects on how the molecular targeting of oncogenic mutations is central to personalised care.

Over the last five years, the number of new lung cancer cases has been rising steadily in Malaysia[1], and Asia Pacific as a whole[2]. Fifty one percent of the world's lung cancer cases occur in Asia[3].

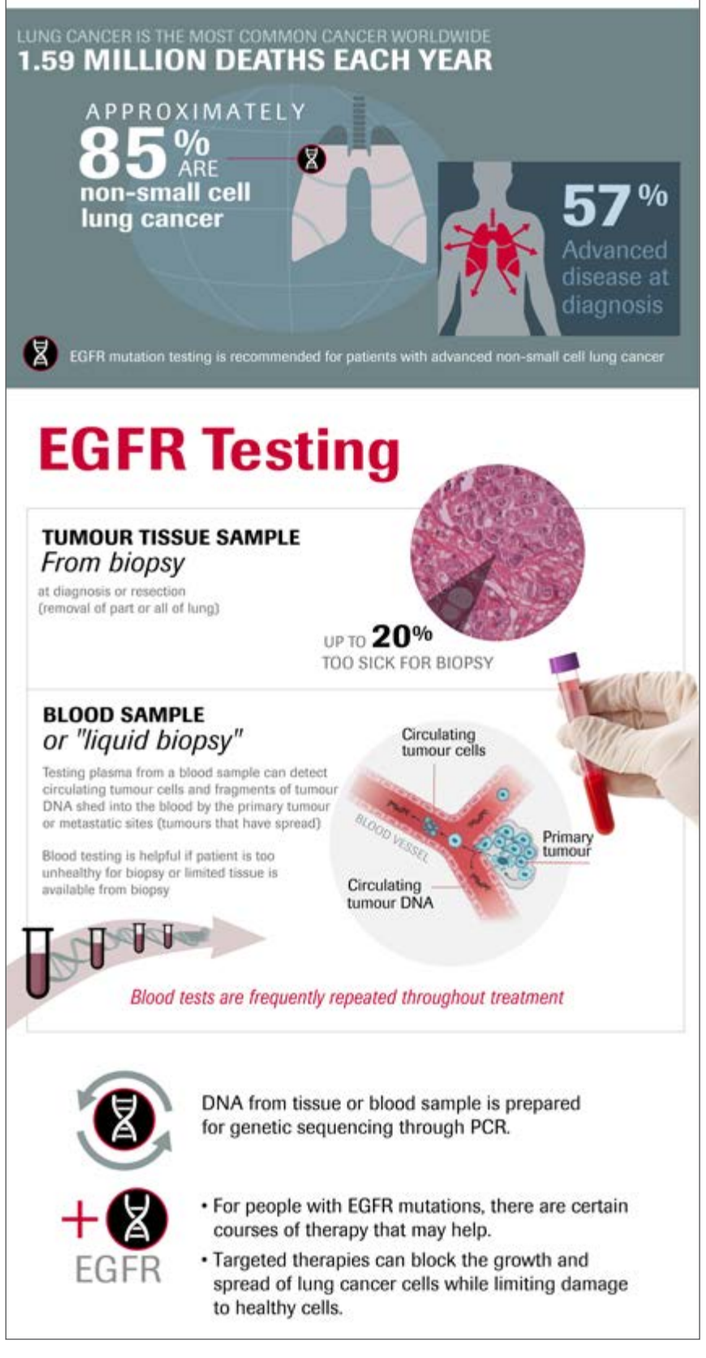
However, it is not only the increasing burden that concerns Dr. Pathmanathan but also the complexities associated with late stage diagnoses and the emergence of early resistance to treatment that impact patient survival rates. Which is why Dr. Pathmanathan's recent research explores driver mutations in the multiethnic Malaysian population[4].

Markers such as EGFR can be used to predict treatment response to EGFR tyrosine kinase inhibitors, which are crucial to slowing or stopping cell growth in these type of tumours.
Dr. Pathmanathan had previously used traditional tissue sampling, but soon realised that this collection method was not always feasible, particularly in cases where the disease had significantly advanced, the quality of the tissue yield did not meet standards, or the tumour was located in an inaccessible region where extraction could pose a risk to the patient.

In such cases, Dr. Pathmanathan said, liquid biopsy has proved to be a viable alternative for many of his lung cancer patients. Liquid biopsy allows pathologists to gain a wide range of information about a tumour through a blood sample – critical for treatment planning.

"We started by comparing liquid biopsies of lung cancer with the tissue biopsies and found that the information you get is a lot more than you would get from the tissue biopsy alone. With liquid biopsy, you can serially examine the patient through a semi-quantitative index which can look at the rise and the fall of these DNA fragments, provided they carry a sensitising mutation," said Dr. Pathmanathan. "We looked at about 150 samples and were surprised at how good the technique was. The kind of concordance that we got was staggering."
Dr. Pathmanathan explained that liquid biopsy allows a physician to monitor not

Testing for EGFR mutations in non-small cell lung cancer



only a subpopulation of tumour cells but what is happening in the patient's entire body for early detection of emerging resistance. "In that sense, it's been a game changer," he said.

Experts at the 2017 American Society of Clinical Oncology (ASCO) Annual Meeting discussed the use of liquid biopsy to better understand cancer biology, guide treatment, and limit some of the risks associated with more traditional methods of diagnostics[5]. Patients with melanoma, breast, colorectal, and non-small cell lung cancer should have repeated biopsies each time the cancer recurs or grows despite treatment, so that treatments are adjusted to match the evolving genomic makeup of the tumour according to National Comprehensive Cancer Network (NCCN) guidelines[6].

Genomic changes occur as the cancer grows and spreads. New changes may lead to cancer recurrence or resistance to treatment. A liquid biopsy allows doctors to keep easier track of new mutations and plan for targeted treatment.

Clinical utility of liquid biopsy

Awareness of liquid biopsy is high among clinicians in Malaysia, according to Dr. Pathmanathan. "There are many physician education programmes, forums, and local advisory boards devoted specifically to the subject of precision cancer care and related technologies," he said.

Still, there are a number of barriers to the adoption of liquid biopsy, including price, international certification, and care team integration. On the point of cost, Dr. Pathmanathan said that his hospital has encountered a bit of a 'chicken and egg' situation. The recruitment of patients has been slow, primarily because of the cost of the test. If there was greater patient volume, then the hospital would be able to lower costs.

"Overall, I think there is a huge acceptance among oncologists and primary physicians. Our volumes for liquid biopsy have gone up slowly but steadily. Slowly because of the cost, but steadily because everyone understands the importance of liquid biopsy for the depth of information it provides," said Dr. Pathmanathan.

One way that the government is trying to help subsidise the costs of targeted therapies is by working to add companion diagnostics as part of the Blue Book formulary so that the patient can access such tests with certain subsidies[7]. Dr. Pathmanathan believes that public sector support for testing along with more patient education will have a noticeable impact on bringing liquid biopsy to a mainstream clinical setting.

Liquid Biopsy: Mainstay of the future

Today, liquid biopsy in Malaysia, and in most clinical settings in the world, is primarily used for tracking EGFR mutations in lung cancer cases. However, Dr. Pathmanathan shared that he also applies liquid biopsy testing for the identification of KRAS and NRAS mutations in colon cancer patients[8].

Future applications for the use of liquid biopsy testing for prostate and breast cancer are just on the horizon in Dr. Pathmanathan's opinion. There are studies currently underway to assess the impact of liquid biopsies on breast cancer management from initial detection to resistant metastatic disease stage[9].

"There is a thrust to address cases where the tumour burden is high or the cancer incidence is high," said Dr. Pathmanathan. "For cancers with poor prognosis, it is about picking them up earlier with a good test that will allow for earlier detection. For cancers in general, it is about the ability to detect disease progression or treatment resistance long before it would trigger clinical symptoms or appear on imaging scans. This is a big promise for liquid biopsy."

Future role of the pathologist

Dr. Pathmanathan remembers being warned by professors and colleagues to avoid the field of pathology when he graduated in 1978. He reflects that in those days, they called it a dying discipline on 'life support'.

A quarter of a century later, Dr. Pathmanathan has not only thrived as a pathologist but is constantly redesigning his role on the care management team. In the era of liquid biopsy and more advanced molecular testing, he believes that pathologists will take on a more central, stabilising role by bringing evidence-based knowledge to decision-making.

> *"There is huge acceptance among oncologists and primary physicians for liquid biopsy."*

"Pathologists should play a pivotal role in diagnosis, as well as the prognostics of the tumour and pre-characterising it with driver mutations. They have to become an integral part of the multi-disciplinary care management team," said Dr. Pathmanathan. "This is really how cancer treatment is advancing, so the pathologist is central to adding noticeable value and cost savings in this new era of therapy," he adds.

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[2]Kan Chan Siang, Chan Kok Meng John. (2016). A review of Lung Cancer research in Malaysia. Med J Malaysia Vol 71 Supplement 1
[3]World Health Organization. (2012). GLOBOCAN: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012
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Taking control of cervical cancer

How the 'power of knowing' shaped one woman's journey

DANG THI PHUONG NGA

Dia:gram speaks to 41-year old ***Dang Thi Phuong Nga*** from Ho Chi Minh City in Vietnam. A primary school teacher and mother of two boys, Nga talks about the emotional rollercoaster she went on when doctors told her about her abnormal Pap smear results and how she found inner strength during this ordeal. She hopes her story will encourage more women to go for regular health screenings.

The first thing one notices about Dang Thi Phuong Nga is her smile. Shy at first, it slowly unravels to reveal the real Nga and in the process lights up her face.

Sitting at a café in a bustling neighbourhood in Ho Chi Minh City, Nga is drinking sweet local coffee, engrossed in conversation, and smiling. Anyone watching would think she's having an everyday conversation.

But this is far from a typical conversation. "I remember the call from the doctor's office at Van Hanh Hospital. He said my annual Pap smear results showed some abnormalities," Nga says.

"My first thought is that there's been a mistake because my Pap test results came back okay last year," she states.

However, there was a niggling doubt that maybe her doctor wasn't wrong. She had been experiencing some irritation and abnormal fluid discharge for a while.

It's when the doctor said that she would need to get a colposcopy that it hit Nga. "I had never heard this term before so it took me sometime to understand what the doctor was saying. I was nervous about having a colposcopy and in the days leading up to the procedure tried my hardest to get on with my daily routine." But the thought of what could be was always at the back of her mind.

Reluctantly, Nga went for a colposcopy which showed she had CIN2. On receiving the results, Nga's doctor referred her to Tu Du Hospital, Ho Chi Minh City's largest Obstetrics & Gynaecology (O&G) hospital.

"This was at a time in my life when I didn't know much about cancers but enough to know that any abnormality in the cervix is a cause for concern," says Nga.

"The doctor didn't use the word cervical cancer at this point, so I thought maybe if I don't think about the word cancer it won't be true," she tries to explain.

Despite regularly undergoing cancer screenings, Nga feels she was unprepared mentally. Since she had never considered herself to be at risk, the situation she found herself in came as quite a shock. "It didn't matter how familiar I was with the risk factors or the signs and symptoms of cervical cancer, nothing could have prepared me for something like this."

"I was worried about myself and what this meant for my family. My first thought was my kids. They are still in their teens. What will happen to them?" Nga recalls.

That, however, was not the worst part. It was the feeling of helplessness that followed that really made this so much more difficult she says. "Not knowing, that's what makes you miserable."

After Nga's first visit to Tu Du hospital, she had to wait for another two days to get a follow-up appointment.

"The whole time my mind was racing with a million thoughts and questions. I locked myself in my room and cried

the whole time. But I didn't want to let my kids see me in this state so I would make up some excuse to stay in my room."

Having two boys she feels ironically made this slightly easier. "Boys tend to be in a world of their own so they may not be as perceptive. Mine had no idea what was going on."

She rationalises this further. "As a mother and as a woman, I would rather face these difficulties than have my children or my loved ones go through this. I want to keep my sadness buried inside me and put on a brave face to protect them. I decided I wouldn't tell anyone till I met the doctor and understood the situation more clearly. This was my battle and I needed to be the one to fight it."

Nga's story is an incredible reminder of how ordinary people can show extraordinary courage in times of crisis.

The day of the appointment finally came by which time Nga says the worry and anxiety of the previous few days had reached a crescendo. She would soon find out there was a silver lining.

"The doctor told me I was lucky. The disease had been caught at an early stage and was treatable. To say I was relieved would be putting it mildly," Nga reveals. She underwent a loop electrosurgical excision procedure (LEEP), a common procedure to remove abnormal cervical cells and tissue, which uses a wire loop heated by electric current[1].

"After leaving the hospital, the first people I told were my mother and younger sister. As women, I felt, they would understand why I had chosen to keep my ordeal under wraps all this while. After that, I told my sons but kept the true nature of the diagnosis from them."

Nga's next appointment will determine the course of action and whether the current treatment has been a success.

Getting philosophical she says, "This was a reassurance from God that my time had not yet come." It gave her the much needed motivation to use her personal journey to educate other women.

"I have always been proactive about undergoing regular screenings for both breast and cervical cancers because I know women are at risk. Which is why I can confidently say that regular screenings have saved my life. If I hadn't been so diligent about my appointments maybe the doctors wouldn't have caught it at an early stage," Nga says.

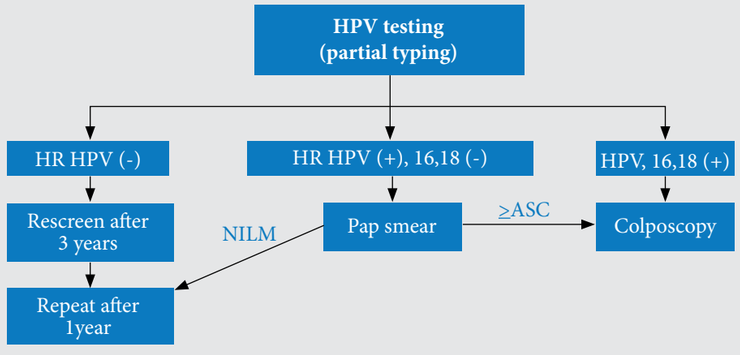
For someone who kept her situation hidden from her loved ones, Nga is now a beacon of hope for other women – willing to share her story, offer a word of encouragement and an intuitive understanding of what these women are facing. "I know so much more about cervical cancer today than I did before. I am not a medical professional but I talk to other women in a way that I know they will appreciate – as one woman to another and as someone who has been on this path before them."

"The one thing I always say is learn to prioritise your health. As women we feel that putting ourselves first makes us selfish. But taking care of your health is important so that you can take care of the people you love the most," she says smiling. A smile that has stayed with Nga on her journey.

[1] *The American Congress of Obstetricians and Gynecologists. Patient FAQs Special Procedures. Loop Electrosurgical Excision Procedure (LEEP)*

In November 2016, the Vietnam Ministry of Health launched the National Action Plan on Cervical Cancer Prevention and Control 2016-2025. The three key objectives of the Action Plan are to increase awareness for the authorities and level of understanding for the community on cervical cancer and cervical cancer prevention and control measures; strengthen the capacity in preventing, screening and treatment for cervical cancer with an aim of early detection, reduced morbidity and timely treatment for invasive cervical cancer; and strengthen capacity and improve cost-effectiveness in monitoring and administration of cervical cancer.

As part of the Action Plan, HPV testing, including HPV testing to identify genotypes 16 and 18 was highlighted for those health facilities with capacity and capability. The following flowchart highlights one of the recommended algorithms.



Ref: National Action Plan on Cervical Cancer Prevention and Control. 2016-2025. Ministry of Health, Government of Vietnam.

The power of knowing when to conceive

Helping women know where they stand with AMH

PROF. CHII-RUEY TZENG

Prof. Chii-Ruey Tzeng, President of the Asia Pacific Initiative on Reproduction (ASPIRE), was trained in endocrinology and infertility at Harvard Medical School's Brigham and Women's Hospital. He was also part of the team that produced Taiwan's first IVF baby in 1985. In this exclusive interview with **Dia:gram**, Prof. Tzeng talks about fertility trends in Taiwan and how the Anti-Müllerian Hormone (AMH) can help empower women in family planning.

Women in Taiwan, and across Asia Pacific in general, are getting married later. The average age of marriage for a Taiwanese woman is in her 30's. While falling fertility is a worldwide concern, the impact is more pronounced in Asia which is home to over half the world's population.

Falling fertility matters because it can impact economic growth, cultural stability and society as a whole. With higher standards of education, better living conditions and the social empowerment of women, the trend increasingly among women is to seek control on when, and how, to start their families. For example, Prof. Tzeng notes that over the last two or three years he has observed a marked increase in the demand for social egg freezing, which is legal in Taiwan.

While we reap the benefits of this as a society it often comes at a high personal cost for couples struggling to conceive.

At birth women have about two million eggs in their ovaries. This is the entire supply of eggs for a lifetime. As women age, the number of eggs suitable for a viable pregnancy decrease in quantity and quality. This can impact a woman's ability to get pregnant naturally.

Challenges to conception

However, there are many other roadblocks that women could potentially encounter when trying to conceive,

regardless of their age. Prof. Tzeng has observed that patients with endometriosis experience significantly greater difficulty in conceiving. Endometriosis is a common condition that occurs in approximately six to ten percent of the general female population. Among women with endometriosis, about 30 to 50 percent are infertile[1].

Polycystic ovarian syndrome (PCOS) is another concern among women looking to conceive. In fact, at Taipei Medical University (TMU), where Prof. Tzeng practices, it is the second leading cause of infertility.

Prof. Tzeng shares that patients with PCOS usually display high levels of Anti-Müllerian Hormone, or AMH.

AMH is a type of protein that belongs to the Transforming Growth Factor beta (TGF-b) family and is usually secreted from the preantral follicles, or the small antral follicles. Prof. Tzeng says that he uses AMH to help evaluate symptoms and guide treatment for PCOS patients. For patients with a history of surgery for ovarian cysts who are looking to conceive, he also uses AMH to assess their post-operative ovarian reserve.

AMH as a tool for IVF

AMH levels can help predict the number of eggs that can be obtained during IVF, according to Prof. Tzeng. He explains that since AMH levels are not linked to the patient's reproductive cycle, in other words consistent during the proliferative phase as well as the ovulation phase, he finds this indicator more reliable than other markers which provide varied results depending on the phase of the patient's reproductive cycle. The ovarian reserve test which measures AMH can give insight into the remaining quantity of eggs and therefore the remaining fertile time for a woman. This, in turn, can empower couples to make decisions about the right time to get pregnant naturally or to consider treatment. "In fact, there are some studies that show that AMH levels are associated with pregnancy outcomes – the higher the AMH levels, the higher the pregnancy rate. So, it is essential for clinicians to use AMH to evaluate the outcome of IVF," said Prof. Tzeng.

"As clinicians, we have a responsibility to raise awareness among both married and unmarried women about their fertility potential."

AMH is fast becoming the pre-eminent tool for fertility specialists around the world to determine the chances of their patients getting pregnant.

In the past, a woman would leave the decision to fate wondering how many more years she could wait to have children while fulfilling life goals whether personal, such as trying something new, or professional, related to career milestones. This would leave her with two choices: start trying to conceive and find out, or try a few years down the road and hope it isn't too late.

But AMH is revolutionary because it takes the guesswork out of trying to get pregnant by pinpointing a woman's chances of getting pregnant today, how that might change and what treatment, if needed, could maximise chances of conception.

Overall, patients in Taiwan have been showing decreased AMH levels over the last two decades according to Prof. Tzeng. He suggests that there are many factors in this decline, including environmental toxins which may adversely impact fertility.

"As clinicians, we have a responsibility to raise awareness among both married and unmarried women about their ovarian fertility potential, and that AMH is a very important marker for this. Women should have routine physical check-ups that include AMH testing," said Prof. Tzeng.

The fertility landscape, and the tools available to doctors treating patients hoping to conceive, have evolved significantly since 1985 when Prof. Tzeng participated in producing the first IVF baby in Taiwan. Back then, IVF was the conventional assisted reproduction method.

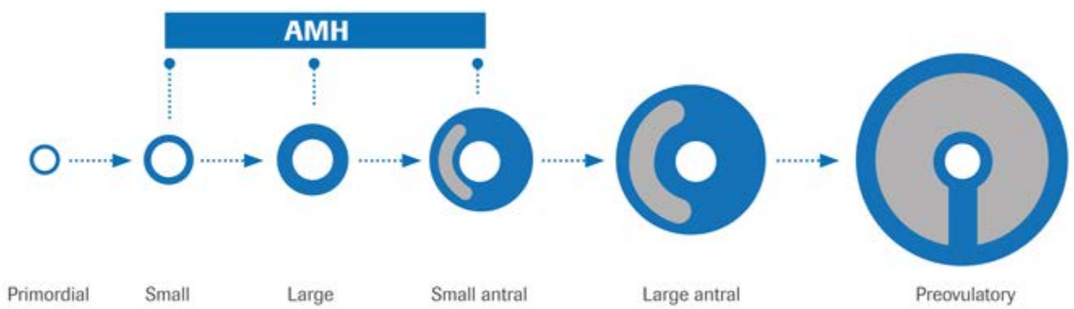
Prof. Tzeng reflects that doctors today have many different options to aid people in family planning including intracytoplasmic sperm injection (ICSI), cryo-technology to preserve the egg, embryo, and sperm, and preimplantation genetic diagnosis (PGS).

"The fertility potential in this region is tremendous," said Prof. Tzeng.

"I hope that we are able to look for better methods as well as better quality of healthcare for women."

[1]*Bulletti C, et al. (2010). Journal of Assisted Reproduction and Genetics: 27(8):441-447. Endometriosis and infertility*

Infertility and Ovarian Reserve



Breaking silos to unlock the value of diagnostics

Data shows that diagnostics guides over 70 percent of clinical decision-making but only receives around two to five percent of healthcare funding[1]. **Dia:gram** reports on a panel discussion in Taiwan which brought together experts from across the healthcare chain to explore ways to collaborate and harness the power of diagnostics for sustainable healthcare.

Diagnostics is the backbone of healthcare, yet current systems and reimbursement models fail to unlock its true value. In order to investigate this problem and facilitate solutions, Roche Diagnostics partnered with the Asia Pacific Federation of Clinical Biochemistry and Laboratory Medicine (APFCB) to organise a panel discussion on the sidelines of the 14th Asia–Pacific Clinical Biochemistry and Laboratory Medicine Congress in 2016. The one-hour discussion brought together six healthcare leaders from the laboratory, industry, insurance and clinical sectors to share their perspectives on the value of diagnostics across the healthcare chain. From addressing what value means to different stakeholders, to identifying barriers in the appropriate use of diagnostics, the panel explored a range of ideas to drive better utilisation of laboratory medicine within the health system.

Defining value

Professor Howard Morris, Professor of Medical Sciences at the University of South Australia and a Clinical Scientist in Chemical Pathology, started the discussion by asking a fundamental question: What is "value" in healthcare? In the case of in vitro diagnostics, he said, value could be defined by how much the test results influenced the pathway of the patient through the healthcare system. "Reducing the length of time that the patient needs to be in the system and consequently, healthcare costs, is where laboratories could have a significant impact," Prof. Morris said.

Take the example of chest pain, a common emergency, accounting for nearly ten percent of emergency room consultations[2]. Yet, diagnosing a heart attack is one of the most challenging problems faced by doctors in hospital emergency departments. This is because heart attack symptoms can range from chest pain that radiates into the arms, to jaw pain, sweating and nausea. Since these symptoms are not specific, they present additional challenges in the fast and accurate diagnosis of a heart attack.

Currently available blood tests look for elevated levels of certain proteins, including the troponin T protein, which is released during a heart attack. However, these proteins are typically only detectable three hours after a heart attack, when the muscles of the heart have already sustained damage. According to current guidelines, patients with symptoms suggestive of a heart attack, must remain in the hospital for at least three hours before receiving a diagnosis[3]. This means that even patients who do not have a heart attack remain in the emergency room, using already strained resources and leading to a hospital bed shortage.

Dr. Raphael Twerenbold, MD, Department of Internal Medicine, University Hospital Basel, Switzerland, said high-sensitivity troponin T testing can now speed up diagnosis of a heart attack to less than an hour instead of three to six hours. "We found that, along with ruling in a heart attack, we could also rule out a heart attack and allow patients to be discharged much earlier from the emergency department thereby saving costs and ensuring greater efficiency within the healthcare system," he said. However, new technologies or diagnostic data points are only useful if a physician can put them into context. In reality, the gap between clinical research and clinical practice can be significant, Dr. Twerenbold said.

Physicians rely on a few corner stones such as the clinical presentation of the patient and existing tests and tools. Clinicians have to be brought on board to adopt the new technology and shown how it can support their work to improve patients' outcomes. Without sufficient context, new technologies can cause confusion among clinicians. This is where the diagnostic industry has a key role to play.

Left to right: Dr. David Lu, Professor Howard Morris & Dr. Aw Tar Choon

Barriers to better use of diagnostics

One major obstacle in the better use of new diagnostic information, as in the case of troponin T, is the view of diagnostics as just a service. Dr. Maurizio Ferrari, President of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) commented that there is still some work to be done if the laboratory doesn't want to be viewed like other services within a hospital. "We need laboratorians to see themselves as collaborators and get more involved with the clinicians in the interpretation of the data," he said.

The speakers recognised that several cultural and subjective factors limited collaborative efforts. Laboratorians can be famously introverted and tend to be siloed which is why a model for collaborative work with the physician would need to be established. As some of the more repetitive functions of laboratories are automated, there is an opportunity for laboratorians to get involved in complex clinical discussions and decision-making based on the subtleties in test results. Laboratorians must understand their evolving position within the healthcare community as it grows from that of diagnostic test service provider to a central player in ensuring quality, prevention, and cost savings for populations, said Dr. Ferrari. "This changing role will call for increased collaboration between laboratory professionals and the physician community, and more sophisticated knowledge on the part of the laboratorian on how diagnostic prevention impacts health systems."

Such impact would also drive funding for tests. Dr. David Lu, Deputy Regional Chief Medical Officer & Vice President, Life & Health Products, Swiss Reinsurance Company Ltd, Hong Kong acknowledged that diagnostics is fundamental to insurance. "Without diagnostics, we have no insurance. From assessment of risk, to insurance product design as well as pricing and reimbursement, it is all dependent on diagnostics," he said.

But with a plethora of new tests and biomarkers on the market, insurers are looking to fund tests that truly affect treatment decisions and outcomes for patients. Tests that provide questionable information, false positives with insufficient specificity and sensitivity all have the potential to distort the insurance market, he said.

Prof. Morris said that generating evidence in laboratory medicine remained a difficult task. "Unlike the pharmaceutical industry where significant profits are being made and millions of dollars are spent to prove that a particular drug is effective in


Dr. Maurizio Ferrari

treating the disease, the diagnostic industry is simply not able to acquire the funding required to run such studies," he said.

However, this is starting to change. Lance Little, MD of Roche Diagnostics Asia Pacific, said the clinical efficacy requirements to bring a new test to market were on the upswing. He cited the example of the ATHENA trial – a landmark study of HPV DNA testing efficacy in 47,000 women over seven years[4]. Results from the study have had a profound influence on clinical practice guidelines for cervical cancer detection[5]. The data showed that to be clinically useful, a test system had to be validated towards the end point of picking up disease and not just an HPV infection. This is important for cervical screening programmes as HPV infections are extremely common among young women. Only assays whose clinical sensitivity and specificity for pre-cancer lesions are validated in a properly designed prospective study would yield the kind of early detection, risk stratification and appropriate treatment targets that can save lives while reducing the costs of treating disease detected at a later stage.

As healthcare models across the world shift their emphasis from volumes to value, the speakers agreed that the academic rigour involved in large trials along with the clinical validation of diagnostic tests can raise their profile. "When patient outcomes are the basis for reimbursement, laboratory medicine specialists will need to articulate the value they bring," Prof. Morris said.

Adding to this notion of value, Dr. Lu talked about the role of diagnostics experts in contextualising the value that advances in personalised medicine and companion diagnostics would bring to patient care. "The value of a data point that would help the physician choose the right treatment for the patient would definitely control downstream costs. It would also help modernise the insurance packages as they are not designed with the latest diagnostics tests in mind," he said.

Breaking silos to unlock value

The speakers then discussed strategies to realise the value of diagnostics. Dr. Aw Tar Choon, Senior Consultant, Laboratory Medicine, Changi General Hospital, Singapore, said a key but often ignored area is the removal of unnecessary or unimportant tests. "It is easy to add on tests to a panel but unusual to remove them. For instance, we reviewed the data from full cardiac panels for an entire year and realised that the older markers were not providing any additional benefit," he said.

Another key issue is the place laboratory medicine occupies within medical education curricula. Dr. Aw cited a study that showed the average amount of time spent in the curriculum on anatomy and physiology ranges from 16 to 300 hours. "But the median time spent on laboratory medicine, which includes most of the diagnostic tests that we do, is only eight hours. Of course, the students who then become doctors feel diffident interpreting a laboratory test result," he added.


Mr. Lance Little

Prof. Morris said that there were considerable gaps in the way that clinicians and laboratories communicated with each other. "It is largely subjective and often does not work very well. So it is up to professional societies to initiate and enhance clinical collaborations and relationships both at an international and national level."


Dr. Raphael Twerenbold

Dr. Twerenbold said the fastest way for new tests to gain acceptance was to leverage best practice guidelines through international societies. To get maximum acceptance it was crucial to find ways for physicians to integrate the information from the laboratory test into their clinical decision-making. He said the challenging question here was who should tell the physician how to utilise the test results.

"If the industry goes to physicians and organises a talk on how to do it, it would be harder for it to get accepted," he said. Adding, "the first step was to seek the cooperation of all parties and then channel these innovations through the physician."

Mr. Little agreed that there was a clear opportunity for the industry, scientists, physicians and laboratory medicine experts to come together to interpret diagnostic data in a way that would deliver value. If they missed this opportunity, he warned that the diagnostics industry was in danger of being disrupted by forces from outside the clinical world like Google, Apple and IBM. "There are others who can connect the dots to enable the right people to make the right decisions on behalf of the patient," he said.

From left to right: Prof. Woe-Horng Fang, Associate Professor, Department of Clinical Laboratory Sciences and Medical Biotechnology, College of Medicine, National Taiwan University; Dr. Elizabeth Frank, former Treasurer, APFCB and Founder, Bio Chem Diagnostics Laboratory; Dr. Leslie Lai, immediate past President, APFCB and Consultant Chemical Pathologist and Endocrinologist, Gleneagles Hospital, Kuala Lumpur, Malaysia; Dr. David Lu, Deputy Regional Chief Medical Officer & Vice President, Life & Health Products, Swiss Reinsurance Company Ltd, Hong Kong; Dr. Maurizio Ferrari, President of IFCC and Full Professor of Clinical Pathology, Vita-Salute San Raffaele University, Milan, Italy; Professor Howard Morris, Professor of Medical Sciences, University of South Australia and a Clinical Scientist in Chemical Pathology at SA Pathology, Adelaide, South Australia; Dr. Aw Tar Choon, Senior Consultant, Laboratory Medicine, Changi General Hospital, Singapore; Dr. Raphael Twerenbold, MD, Department of Internal Medicine, University Hospital Basel, Switzerland; Mr. Lance Little, Managing Director of Roche Diagnostics Asia Pacific; Dr. Gi-Ming Lai, Vice Superintendent, Cancer Center, Taipei Municipal Wangfang Hospital and CEO of Formosa Cancer Foundation.

"When patient outcomes are the basis for reimbursement, laboratory medicine specialists need to articulate the value they bring."

Dr. Aw said, "If laboratory medicine is not to be marginalised, we have to be more proactive in this area. To remain consultable and stay relevant, we must seize all the opportunities available."

In conclusion, the speakers agreed discussion and dialogue to bring about collaborative models of working were key to ensuring health systems saw the true value of diagnostics. Dr. Ferrari said improved communication and sharing of best practices also had a crucial part to play. He said the pathway to such global best practices would need to be generated by the collaborative efforts of each region's medical community.

"Successful rooting of such practices will be measured by the ability of its healthcare professionals to effectively articulate the new value proposition of diagnostic testing, not only among themselves but to their policy makers, payers, and patient populations," he said.

[1]European Diagnostic Manufacturers Association [2]Rubini Gimenez M, Twerenbold R, Reichlin T, et al. (2014). Eur Heart J; 35: 2303–2311. Direct comparison of high-sensitivity-cardiac troponin I vs. T for the early diagnosis of acute myocardial infarction. [3]Holli A. DeVon, Nancy Hogan, et al. (2010). Time to Treatment for Acute Coronary Syndromes: The Cost of Indecision, US National Center for Biotechnology Information [4]www.hpv16and18.com/hcp/athena-hpv-clinical-trial/background-study-design.html. Last accessed 10 October 2016 [5]The American College of Obstetricians and Gynecologists. (2012). ACOG Practice Bulletin. Clinical Management Guidelines for Obstetrician-Gynecologists: Screening for Cervical Cancer

Ten questions with Howard Morris

Prof. Howard Morris is Professor of Medical Sciences at the University of South Australia and a Clinical Scientist in Chemical Pathology at SA Pathology, South Australia. In this interview with **Dia:gram**, Prof Morris talks about the role of laboratory medicine and his vision for the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) when he takes up the role of President in January 2018.

1 *What made you enter the field of laboratory medicine?*

I started as a fundamental bio-chemist in university and was drawn to the application and usefulness of bio-chemistry for healthcare. I enjoyed the philosophy of this exact science being translated into what we can do, and taking a rational approach to make changes in healthcare to change peoples' lives.

2 *Your wife also works in the same field. Is work off limits at the dinner table?*

Not at all - we discuss issues that we encounter in our respective work environments. For many years, she worked in the private sector, and I worked in the public sector and that was a source of lively debate. We both enjoy a very fruitful relationship in terms of an exchange of ideas.

3 *You start as the President of the IFCC in January 2018. Can you talk about your journey, or your path to this position?*

I've been fortunate to work closely with clinicians over the last 20 years working in Adelaide, Australia. I would attend ward rounds in the endocrine ward and sit and discuss patients with their physicians.

I did this to ensure that there was a seamless relationship between the test result and its application to patient management.

This experience led me to be involved in the national association and later on, the IFCC, initially in the scientific division. The scientific division focused on standardisation and harmonisation of assays. Over the years, this has led to improved patient outcomes and care.

This focus has seen standard tests like cholesterol much more effective as we are now in a place where any laboratory using any major system will receive the same result for the same patient. Prior to this, there was huge variation. We have made a major contribution. This journey has led me to where I am now, taking up my new role as President of IFCC.

4 *As President of the IFCC, how will you strengthen the position of laboratory medicine?*

I hope to enhance the work for evaluating the value of individual tests to provide a sustainable and affordable service to the community. That means adopting automation and implementing point-of-care testing where that is the most cost effective way.

We need appropriate laboratory management and basic business principles so that we're not wasting our valuable resources. We need evidence-based laboratory medicine to ensure we're adopting tests that actually contribute to patient outcomes and there is evidence for that. We need to put those together, through a tool that is leveraging the value of laboratory medicine, and that could be the value proposition. If you can't measure it, you can't manage it.

5 *What was the catalyst to writing your recent manuscript?*

Well, my own personal thinking arose out of the local system in South Australia where we are in the process of transforming healthcare. There's a new 2.86 billion dollar hospital construction and many of the hospitals are becoming specialised. This is causing great anxiety amongst the medical professionals. However, within all of this, laboratory medicine is not even in the discussion. To be able to develop a healthcare system that is financially sustainable, I believe there has to be a paradigm shift. I would like to see laboratory medicine professionals being able to contribute to discussions about the healthcare system.

"Clinical laboratory professionals need to play a bigger role in initiating clinical trials in order to demonstrate their value."

6 *What do you think is the most underestimated aspect of diagnostics and how can this be addressed?*

The way in which diagnostics can change the patient pathway is underestimated. We've heard how specialist colleagues ignore a result because they don't understand where it fits in. We need to define the clinical pathway of a patient, and then evaluate the role of laboratory testing in modifying or enhancing that pathway.

We would like to see more laboratory medicine professionals providing leadership for clinical trials – thinking about the use of their tests, collaborating with their colleagues, and then conducting those trials and providing the evidence so people can make decisions based on this evidence.

Our clinical laboratory professionals need to play a bigger role in initiating clinical trials in order to demonstrate their value.

7 *Whose role is it to advocate the value of diagnostics?*

There will be opportunities for individuals in the laboratory to advocate for the value of their tests. Within the hospital, or the healthcare system, if the funding changes to one based on patient outcomes, the individual laboratory professionals will have to be there to advocate for the value of their performance. In a larger scenario, laboratory professionals and leaders could be initiating clinical trials on the usefulness of tests, and conducting those in conjunction with clinicians to be able to write academic papers. This will provide the evidence for the big payers, such as health insurance companies or governmental departments, when they make decisions for reimbursement of testing based on those data.

8 *Are you concerned about the future of laboratory medicine?*

I think the crises facing the healthcare system are there whether we like them or not. What we can do is educate and arm ourselves with processes so that we can take part as equal partners in the debate. If we were to stick to our old ways of thinking that we just provide this service, the risk is we will move further and further away from the decision-making about healthcare delivery. I'm a glass half-full kind of person. If we apply ourselves to addressing these problems and working on solutions, I believe we'll have success.

9 *What are you reading, or what have you read recently that has left an impression on you?*

I'm reading a book by Annie Proulx entitled 'Barkskins'. It's a significant book, tracing the development of Canada, from the 16th to the 20th century. It is highly thought provoking in terms of the short sightedness of humankind coming into a new environment, seeing and acting on the immediate, with no concern about the deeper implications. In the Canadian environment, it's about deforestation without considering the human as well as the environmental costs. It is profound in terms of global warming and what that all means for us now.

10 *What inspires you and keeps you going?*

Understanding the fundamental properties, particularly of life – I find life and its complexity, intriguing. I love to hear stories about the intricacies of biology. I just heard a lecture from Maurizio Ferrari on the new findings in molecular genomics, and a plenary lecture last night on lung cancer. These lectures highlighted being able to understand fundamental molecular and basic changes and their implications. For instance, now a single base change in an epidermal growth factor receptor, produces all the horrors of lung cancer in an individual. Looking at the complexity of that system, being able to identify its individual parts and tell a story is inspiring. ▪

Thailand's journey to laboratory excellence

Redesigning laboratory practice for future success

MRS. NAIYANA WATTANASRI

Mrs. Naiyana Wattanasri, the outgoing chairman and founder of the Thailand Medical Technology Council, helped develop a systems quality roadmap for laboratory accreditation for the entire country. In this exclusive interview with **Dia:gram**, she speaks about the Laboratory Benchmarking Survey and experiences improving laboratory performance in Thailand.

When Mrs. Wattanasri looks back on her experience of over 40 years in laboratory quality management, her proudest achievement is establishing the Thailand Medical Technology Standard in 1998. This accreditation pathway helped align laboratory processes to local needs.

"When we were designing the accreditation process, I questioned the suitability of importing wholesale the western standards and instead established a suitable standard that every laboratory in Thailand could use."

Mrs. Wattanasri explains that while western laboratories tend to separate administrative functions from technical ones, she saw the rationale for merging both. The goal was to create greater synergies between quality process management staff and those responsible for laboratory safety.

This approach was commended by the World Health Organisation (WHO) for helping to reduce gaps in existing laboratory standards and those stipulated by ISO. Thailand's success is now enabling other countries across Asia, as well as Africa, to adopt a similar approach.

Today, the perception of the laboratory's role has shifted significantly with laboratories firmly established at the core of an increasingly complex healthcare system, according to Mrs. Wattanasri.

"Physicians, nurses and patients all see the importance of the laboratory test results and the value we can bring," she said.

LAB LESSONS

A first for Thailand: Benchmarking to improve laboratory quality, speed and efficiency

The laboratory is crucial to the diagnostic cycle and therefore needs to have a programme in place to monitor the diagnostic process. This can help identify, address and reduce errors while boosting efficiency. Studies show that benchmarking exercises to analyse performance against other laboratories provide a scientific way of evaluating gaps and instituting continuous improvement of common laboratory tasks and functions.

The need for benchmarking is especially acute in Asia Pacific, where there is an urgency around delivering better diagnosis and treatment to vast populations. Since 2011, Roche has been conducting surveys to understand the state of laboratory medicine in the region. The idea was to introduce benchmarking of certain key quality indicators to a wide range of laboratories. The questionnaires were designed to elicit information on three key areas of quality, speed and cost with a focus on clinical chemistry and immunoassays. It has now evolved into one of the largest surveys of its kind in the Asia Pacific region, with the 2015 survey drawing 643 participants across 13 countries.

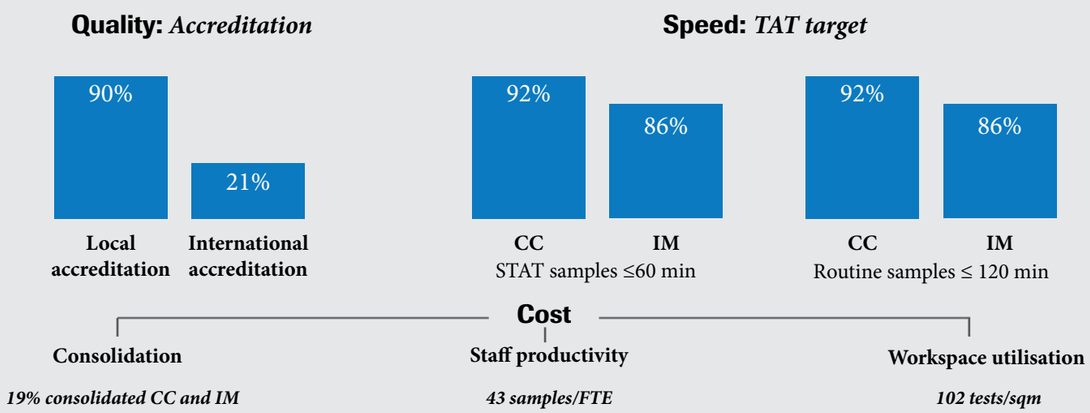
Three years ago, the Thailand Medical Technology Council partnered with Roche Diagnostics to run the National Laboratory Benchmarking survey. Mrs. Wattanasri said it was the first time the Council collaborated with a healthcare company to conduct the survey with a view to bring a new level of insight into process improvements.

"We decided to go with Roche because this is a company that also provides academic expertise to its customers. We reviewed previous surveys and saw that the results were very valuable to laboratories," she added.

In order to tailor the survey to the local context, Mrs Wattanasri said the Council added questions about the problems faced by laboratories in their daily operations, ranging from procurement systems to internal quality controls, and laboratory safety systems.

Key facts on Thai laboratories

Based on data from 155 participants



CC = *Clinical Chemistry* IM = *Immunoassay*

The Council introduced the survey during the Laboratory Accreditation Forum 2014, an annual meeting for medical laboratories in Thailand. Over 300 participants from across the country were encouraged to join and more than half of them did so voluntarily. With 155 participating hospitals, the Laboratory Benchmarking Survey provided useful insights into local practices and ways to improve performance.

According to Mrs. Wattanasri, the survey results highlighted that the participating laboratories had the expected levels of management but were facing some key challenges.

Results showed that 42 percent of laboratories had international accreditation with ISO 15189 being the most common type of accreditation. External Quality Checks (EQC) were considered important and 57 percent of the participating laboratories said they were involved in such programs.

Another aspect examined by the survey was the turn-around time (TAT). Each laboratory sets its own key performance indicators of TAT for each step of the whole testing process, including pre-analytic TAT, analytic TAT and post-analytic TAT. The survey results showed that most errors occurred during the pre-analytic phase. "Around 10 percent of participants had automated pre-analysis and more were encouraged to do so to reduce errors," Mrs. Wattanasri said. Another challenge the survey highlighted was the lack of human resources, which affected the speed with which results were released to physicians. Though many laboratories rely on their IT systems for auto validation, haematology and clinical chemistry test results require manual approval.

Mrs. Wattanasri noted that the lack of trained personnel, limited budgets and inconsistent quality standards are challenges common to laboratories across the region. For instance, only 63 percent of participants said they complete internal quality controls due to budgetary limitations.

"We shared the results with 50 laboratory networks across the country so that they could benchmark themselves according to the results," she added.

Mrs. Wattanasri said the council also shared the survey results with various stakeholders including the Ministry of Public Health and the National Health Security Office so that funding and purchasing directives could be better tailored to support laboratory needs. Recently, the Ministry of Health issued a new code guiding laboratories on how to select and use new medical equipment more efficiently.

Two years after the survey, the yearly customer satisfactory survey conducted by the laboratory networks shows positive sentiment among physicians and patients.

Some of post-survey continuous improvement activities conducted by the participants are accreditation, Lean Six Sigma, customer (physicians, patients and other healthcare personnel) satisfactory survey, continuous training for employees, and error rate monitoring.

As an industry veteran, Mrs. Wattanasri's advice to aspiring laboratory technicians is to have a patient-focused mindset.

"When you see patients you can tell they are anxious about their lab results, as it guides the physicians' decision-making. So your job as a laboratory technician is no longer relegated to the background, it is at the core of the patient's journey."

"We shared the results with 50 laboratory networks across the country so that they could benchmark themselves according to the results."

CASE STUDY

Rajvithi Hospital was one of the 155 participants in the Thailand Laboratory Benchmarking Survey in 2014. Rajvithi Hospital processes nearly 20,000 tests a day.

Mr. Ithirit Chaowalerd, who manages the Clinical Chemistry section, said that the hospital wanted to participate in the survey to measure how it compares to the peer group and identify any weaknesses that could be improved.

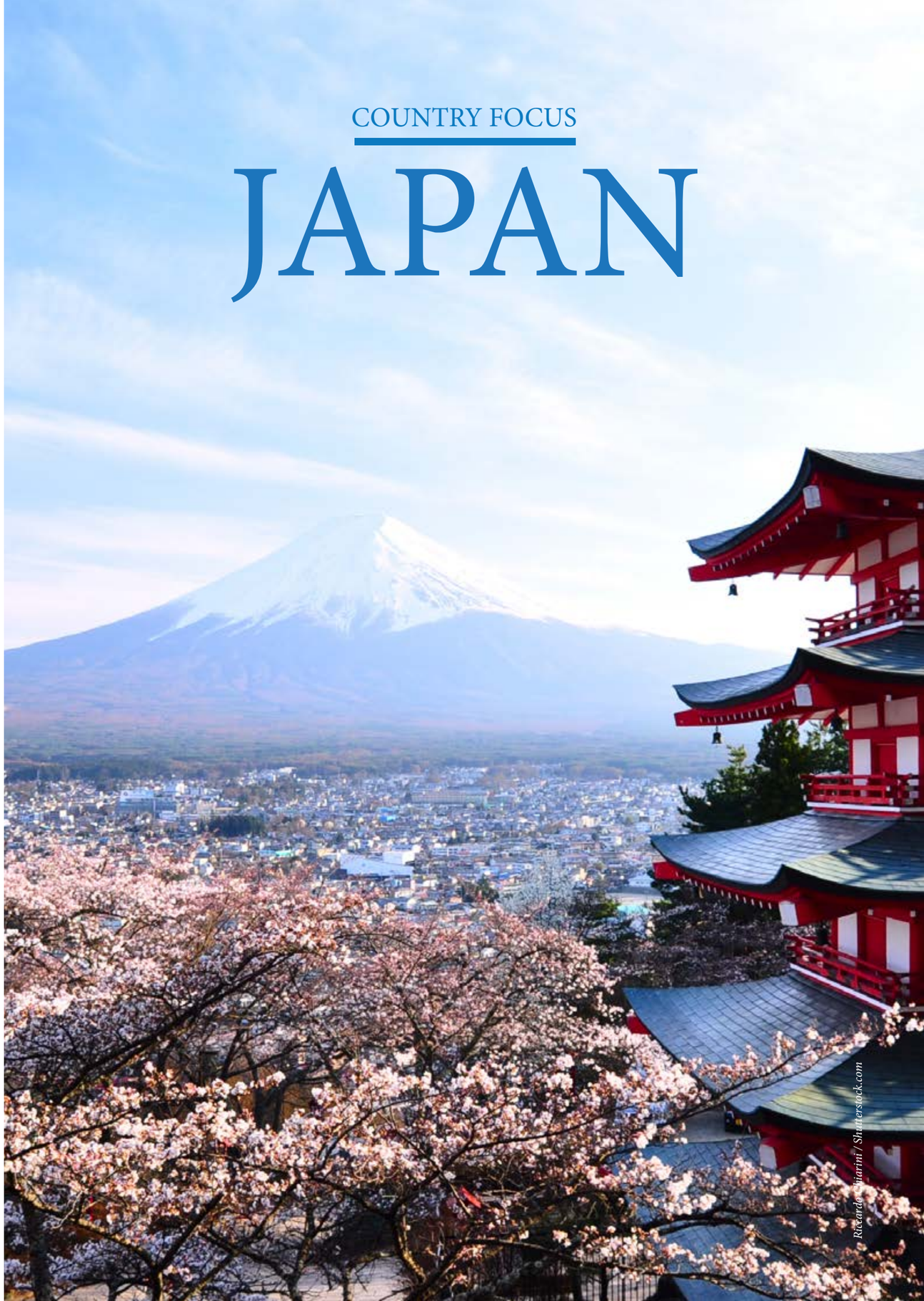
"Achieving the balance between quality, speed and cost is the art of laboratory management," said Mr. Chaowalerd. It is with this balance in mind that the hospital installed automation two years ago. After this change, the TAT achievement rate rose from 70-80 percent to almost 90 percent despite the fact that test volumes also rose by 10-15 percent every year, according to Mr. Chaowalerd.

Last year, Roche's workflow solutions team helped analyse the testing process and identified areas for improvement. The TAT for post-analytics was reduced 30-40 percent with auto validation.

Mr. Chaowalerd said that automation has freed up medical technicians to focus on academic areas and publish papers internationally, while pursuing continued improvement of processes.

COUNTRY FOCUS

JAPAN



Riccardo Mojorini / Shutterstock.com

Lung cancer in Japan

Improving lung cancer survival rates through better diagnosis and treatment

DR. TETSUYA MITSUDOMI

Lung cancer remains a leading cause of death in Japan[1]. But, improved diagnosis and treatment for lung cancer is giving hope to patients as more are living longer. **Dia:gram** caught up with ***Dr. Tetsuya Mitsudomi***, Professor at the Division of Thoracic Surgery, Department of Surgery, Kindai University Faculty of Medicine, Osaka-Sayama, Japan about developments in genomics and diagnostics that have altered how the disease is detected, treated and managed.

Japan is no exception to the global trend of non-communicable diseases, such as cancer, heart disease and stroke replacing infectious diseases, as the main causes of death. In fact, cancer has been the leading cause of death in Japan since 1981[2].

Among the various cancers, lung cancer continues to be a leading cause of death among Japanese men aged 65 to 84 years and the second-highest cause of death among women of the same age group[1]. While tobacco use is a predominant risk factor and the prevalence of smoking among Japanese men is high, in fact considerably higher than the Western male population, the lung cancer mortality rate is surprisingly lower than in Western countries. This incongruity has come to be known as the "Japanese smoking paradox"[3].

Within lung cancer types, non-small cell lung cancer is the most common responsible for 80 to 85 percent of lung cancers[4]. Among the Japanese, much like the rest of the world, this type of lung cancer is more commonly found in non-smokers, women and young adults[5].

Dr. Mitsudomi, who is also the President of the Japan Lung Cancer Society (JLCS) and President-elect of the International Association for the Study of Lung Cancer (IASLC), said lung cancer screening rates in Japan were rising and attributed it, in part, to the availability of better diagnostics. A study, based on data from the Ministry of Health, Labour and Welfare, Centre for Cancer Control and Information Services and the National Cancer Centre, showed that mortality rates in lung cancer decreased with the improvement in cancer screening rates[6].

"The diagnostic and therapeutic landscape of non-small cell lung cancer has changed dramatically. In Japan, the use of computed tomography scans for early detection is currently practiced. Our understanding of driver mutations and discovery of early stage nodules, which may or may not need treatment, have taught us that lung cancer is a very heterogenous disease," he said.

Dr. Mitsudomi has spent his career increasing awareness and educating physicians about this heterogeneity. He recalls the discovery of activating mutations in the EGFR gene, which launched the era of personalised or targeted medicine in lung cancer in 2004.

Targeted drugs work differently from standard chemotherapy drugs. They can work when chemotherapy fails, may have fewer side effects and better efficacy. Dr. Mitsudomi says he has seen some patients respond very quickly to targeted therapy with large tumors shrinking to nothing in just a month, while some patients have no response at all.

"We asked ourselves – why did this happen? All of us in the medical community wanted to know what factors led to these results," said Dr. Mitsudomi.

This quest for answers changed Dr. Mitsudomi's career and his life. "I started to examine our samples for the EGFR mutations and found that these mutations were very common in Japanese lung cancer patients."

It turned out to be a tipping point for him. "I was a surgeon. After the discovery, I became very interested in therapy too, so we ran clinical trials. We split the patients with EGFR mutation into two groups. One group had conventional chemotherapy, the other one had targeted therapy, gefitinib. And we found that, as expected, the group that had the targeted therapy had a longer progression-free survival than the group with chemotherapy. So, on the back of this, the guidelines changed, and now it is common practice to check for the EGFR mutation before treating patients with lung cancer. And we know, mutation frequency among Asians and the Japanese are different from Caucasians," he added.

Dr. Mitsudomi uses this example to emphasise the importance of testing beyond initial diagnosis. "It is crucial. You may have been able to guess that this histologic type can have a higher chance of carrying an EGFR mutation but you can only confirm that by testing tumour tissue. So the role of a specific diagnosis is very, very important in lung cancer." With researchers learning more about mutations in non-small cell lung cancer cells, the development of newer drugs to specifically target these changes and the use of new, more advanced diagnostic tools is transforming lung cancer treatment.

An example of this lies in the wave of change that occurred in 2007 with the discovery of the Anaplastic Lymphoma Kinase (ALK) gene translocation as a driver for lung cancer. Evidence shows young people and non-smokers with lung cancer frequently have mutations in the ALK[7]. Dr. Mitsudomi notes, "Today, we have the inhibitors for these driver mutations which make treatment very helpful. But after 10 months or so, we see that the tumours start to regrow because they develop resistance."

"So you see each time we take one step forward we discover something new. This is a constantly evolving area of research," he added. Dr. Mitsudomi is right on this account. In the last five years, the field of lung cancer has seen yet another advancement with the development of immunotherapy. Immunotherapy is seen as the next frontier in cancer treatment as it focuses on harnessing the body's immune system to fight cancer cells. In addition to being more effective than traditional chemotherapy drugs and radiation therapy at slowing a cancer's growth and spread, immunotherapy often has fewer side effects and minimises damage to normal, healthy cells.

"Antibodies that target either PD-1 or PD-L1 have shown good results in a subset of patients whose tumors overexpress PD-L1," Dr. Mitsudomi said. With this, the diagnostic algorithm has broadened to include new tests such as PD-L1. Patients with non-small cell lung cancer are tested for EGFR, ALK and also PD-L1. "If the patient has a driver mutation or overexpression of immune-biomarker, then we use the appropriate drug. This has completely transformed the treatment pathways and may increase patient survival," Dr. Mitsudomi added.

It is not just the changing treatment landscape that Dr. Mitsudomi is deeply interested in. He is equally passionate about imparting knowledge to the next generation of doctors and has been driving activities for the Japan Lung Cancer Society. The society publishes guidelines and runs courses for nurses and allied health professionals. Recently, it has also launched a patient advocacy programme in partnership with a local patient group. As patients are increasingly more knowledgeable and want to find out more about the new treatments and clinical trials, the society is sponsoring patient attendance at international lung cancer conferences.

Improving patient experience is at the core of Dr. Mitsudomi's mission. He finds that lung cancer research is at an exciting stage because of the ways in which it directly benefits patients. "The diagnostics industry has kept pace with developments in medicine. Immunology, molecular diagnostics, genome sequencing – all of these advances are now being translated and applied routinely in the clinic for better patient experience, which is amazing to see," he said.

[1]*Yang L, Fujimoto J, Qiu D, et al. (2010). Ann Oncol 21(2): 389-396. Trends in cancer mortality in the elderly in Japan, 1970-2007*

[2]*Cancer Registry and Statistics. Cancer Information Service, National Cancer Center, Japan*

[3]*Takahashi I, Matsuzaka M, et al. (2008). Public Health: 122(9):891-6. Differences in the influence of tobacco smoking on lung cancer between Japan and the USA: possible explanations for the 'smoking paradox' in Japan*

[4]*American Cancer Society. (2016). Lung Cancer (Non-Small Cell). Detailed Guide*

[5]*Samet JM, et al. (2009). Clin Cancer Res: 15(18): 5626–5645. Lung Cancer in never smokers: clinical epidemiology and environmental risk factors*

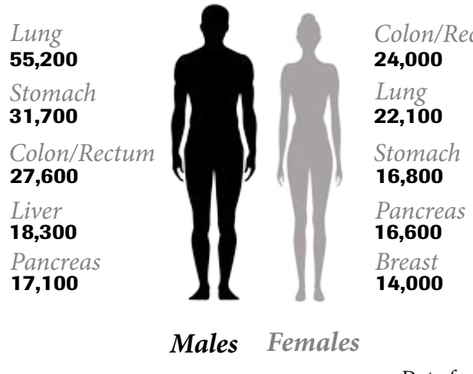
[6]*Yoshida M, Kondo K, Tada T. (2010). The Journal of Medical Investigation 57: 251-259. The relation between the cancer screening rate and the cancer mortality rate in Japan*

[7]*Barbara J. Gitlitz, et al. (2015). Journal of Thoracic Oncology Vol 10, Number 9, Supplement 2. The Genomics of Young Lung Cancer Study*

[8] *Monitoring of Cancer Incidence in Japan - Survival 2006-2008 Report (Center for Cancer Control and Information Services, National Cancer Center, 2016)*
Population-based survival of cancer patients diagnosed between 1993 and 1999 in Japan: a chronological and international comparative study. Matsuda T, Ajiki W, Marugame T, Ioka A, Tsukuma H, Sobue T; Research Group of Population-Based Cancer Registries of Japan. Japanese Journal of Clinical Oncology 2011; 41: 40-51

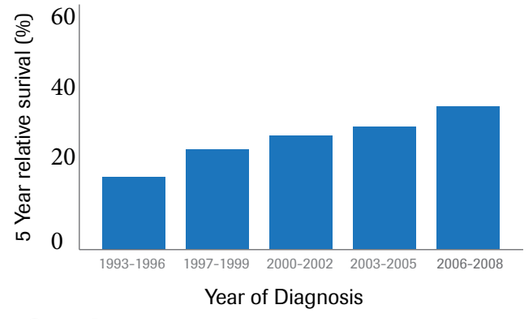
Cancer mortality in Japan[2]

Top 5 cancers by site (2016)



Trends in 5 year survival[8]

From 1993 - 2008



Data from National Cancer Center, Japan

Decoding fertility with a personalised approach

Anti- Müllerian Hormone (AMH) with automated assay shows significant benefits in study trial

A recent multicentre, international study demonstrated that assessing AMH with automated assay during in-vitro fertilization (IVF) resulted in similar efficacy and improved patient safety when compared to conventional ovarian stimulation[1].

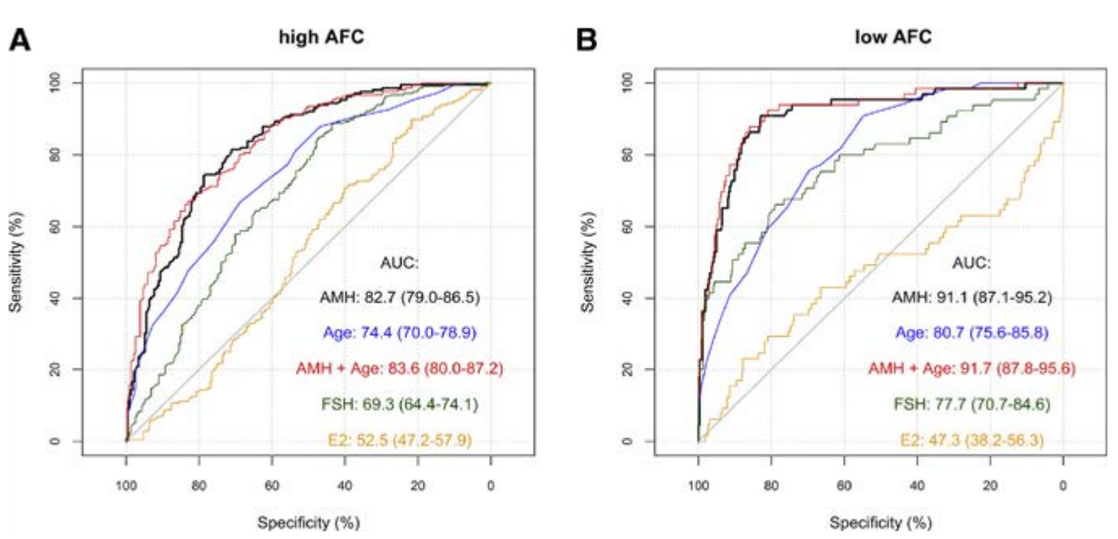
AMH is an important fertility marker used by healthcare professionals to assess ovarian reserve levels. Assessment of AMH with automated assay incorporates a formula to calculate a specific drug dosage for the patient based on their AMH levels (assessed by automated Elecsys®), in combination with age and body weight. This individualised approach has been called an important step towards personalised medicine. AMH assessment has evolved from manual method, with enzyme-linked immunosorbent assay (ELISA), performed by lab technicians into automated method performed by machine.

The manual AMH carries inconsistency and sometimes discrepancy with clinical pictures[2]. The recent automation in AMH testing has created significant improvement in accuracy and reliability, making individualised calculation of drug dose possible.

Previously, gynaecologists would determine the appropriate drug dose to stimulate egg production in approximate ranges (low, mid, high dose) based on age and only occasionally AMH levels.

AMH which was discovered a decade ago as a human sex differentiation hormone in utero is nearly absent in adult males, while it reaches peak levels in females in early adulthood (mid-20s) before progressively declining to undetectable levels at menopause. This characteristic makes AMH a unique direct parameter to assess ovulatory potential in women that is more reliable than other markers such as follicle stimulating hormone (FSH), estradiol (E2) or ultrasound assessment with antral follicle count (AFC)[3].

[1]Nyboe Andersen A, et al. (2017). Fertil Steril 107(2): 387-396.e4
[2]Nelson SM, et al. (2015). Fertil Steril 104(4): 1016-1021.e6
[3]Iliodromiti S, et al. (2015). Hum Reprod Update 21(6):698-710



ROC curves for classifications of (A) low AFC and (B) high AFC, by AMH, FSH, E_2 and age. For low AFC, n subjects AFC > 7. For high AFC, n 1/4 216 subjects with AFC > 15 versus 235 patients AFC % 15.

Anderson. 2015. Fertil Steril. Automated AMH assay in ovarian assessment

Management of high-risk HPV positive women in cervical cancer screening

Study reveals promising results for triaging HPV-positive women with p16/Ki-67 dual-stained cytology[1]

Results from a sub-study nested into the landmark ATHENA trial, showed higher sensitivity to triage HPV-positive women with dual-stained cytology p16/Ki-67 compared to conventional triage with cytology (74.9% vs 51.9%, p<0.001), whilst retaining similar specificity (74.1% vs. 75.0%; p =0.3198).

The study, published in Gynecologic Oncology, included more than 7,000 women aged 25 years and above. These women, who were referred to colposcopy, had valid cervical biopsy and HPV DNA test results from the cross-sectional phase of ATHENA.

P16/Ki-67 dual-stained cytology was retrospectively performed on residual cytologic material collected into a second liquid-based cytology vial during the ATHENA enrolment visit. The diagnostic performance of dual-stained cytology, with or without HPV16/18 genotyping, for the detection of biopsy-confirmed cervical intraepithelial neoplasia grade 3 or worse (CIN3+) and the number of colposcopies required per CIN3+ detected was compared to Pap cytology.

The results showed promise for dual-immuno-staining for p16/Ki-67, in addition to 16/18 genotyping as a triage of HPV-positive women.

[1]Wright Jr, TC, et al. (2017). Triaging HPV-positive women with p16/Ki-67 dual-stained cytology: Results from a sub-study nested into the ATHENA trial. Gynecologic Oncology 144: 51-56

Identifying the key Vitamin D in diagnosing deficiency

Vitamin D3, not D2, is the key to overcoming a deficiency[1]

Research published in July this year in the American Journal of Clinical Nutrition showed that Vitamin D3, when given at standard doses in the daily diet, is significantly more effective in raising serum biological levels of Vitamin D status when compared to Vitamin D2.

This randomised, double-blind, placebo-controlled food fortification trial was conducted in 335 healthy South Asian and white European women aged 20-64 years old. The participants were divided into five groups: placebo; juice supplemented with 15µg Vitamin D2; biscuit supplemented with 15µg Vitamin D2; juice supplemented with 15µg Vitamin D3; and biscuit supplemented with 15µg Vitamin D3.

The trial demonstrated that there was a higher association between Vitamin D3 (which is animal-based) in raising the serum biological marker of Vitamin D (25-hydroxyvitamin D [25(OH)D]) after a 12-week period than vitamin D2 (which is plant-based). The groups given juice and biscuit supplemented with Vitamin D2 saw increases in total 25(OH)D levels of 33% and 34% respectively, while the groups given juice and biscuit supplemented with Vitamin D3 saw increases of 75% and 74% respectively.

Additionally, South Asian women appeared to have a greater response to both Vitamin D2 and D3 than European women.

Serum 25(OH)D was measured by liquid chromatography-tandem mass spectrometry at baseline and at weeks 6 and 12 of the study.

The researchers concluded that the findings could hold significant implications for current Vitamin D deficiency guidelines. They may have implications for the nutritional supplements industry as they have the potential to link Vitamin D supplementation to measurable clinical outcomes.

[1]Tripkovic, L., et al. (2017). Am J Clin Nutr

Using saliva to recognise early Alzheimer's disease

Small molecules in saliva could help identify those at risk of developing the condition[1]

A pilot study published in the Journal of Alzheimer's Disease demonstrated the potential of small molecules in saliva in early identification of those at risk of developing Alzheimer's disease. Investigators from the Beaumont Research Institute of Beaumont Health, Michigan found that these saliva molecules hold promise as reliable diagnostic biomarkers.

The study involved 29 adults in three groups: mild cognitive impairment, Alzheimer's disease and a control group. Using metabolomics, the goal of the study was to find unique patterns of molecules in the saliva of the study participants that could be used to diagnose the disease in its early stages. Treatment for Alzheimer's is considered the most effective during the earliest stages.

From the saliva specimens collected, researchers positively and accurately identified significant concentration changes in 22 metabolites in the saliva of the mild cognitive impairment and Alzheimer's disease groups compared to the control group. From this data, the researchers were able to predict those most at risk of developing Alzheimer's disease.

The researchers concluded that given the ease and convenience of collecting saliva, accurate and sensitive saliva biomarkers would be ideal for screening those at greatest risk of developing Alzheimer's disease.

[1]Yilmaz, A., et al. (2017). J Alzheimers Dis 58(2): 355-359

Key Events *(July - Dec 2017)*

July

European Society of Human Reproduction and Embryology (ESHRE)
2 – 5 July
Geneva, Switzerland
www.eshre2017.eu

69th AACC Annual Scientific Meeting and Clinical Lab Expo
30 July – 3 August
San Diego, California, USA
www.aacc.org/meetings-and-events/2017-annual-meeting

August

Molecular & Cancer Biomarkers
24 – 25 August
Birmingham, UK
www.molecular-cancer-biomarkers.conferenceseries.com

European Society of Cardiology (ESC) Congress
26 – 30 August
Barcelona, Spain
www.escardio.org/Congresses-&-Events/ESC-Congress

September

13th Asia Pacific Congress of Maternal Fetal Medicine (APCMFM)
1 – 3 September
New Delhi, India
www.obg.cuhk.edu.hk/apcmfm/apcmfm-2017/

The Economist Heart Health Asia 2017
21 September
Seoul, South Korea
www.events.economist.com/events-conferences/asia/heart-health-in-asia

October

European Research Organisation on Genital Infection and Neoplasia (EUROGIN)
8 – 11 October
Amsterdam, Netherlands
www.eurogin.com/2017

7th Annual Next Generation Sequencing Congress
10 - 11 October
Singapore
www.ngsasia-congress.com

4th Annual Microbiology and Infectious Disease Congress
10 - 11 October
Singapore
www.microbiologyasia-congress.com

18th World Conference on Lung Cancer
15 – 18 October
Yokohama, Japan
www.iaslc.org/events/18th-world-conference-lung-cancer

Asia-Oceania Research Organisation in Genital Infection and Neoplasia (AOGIN) 2017
18 – 19 October
Tokyo, Japan
www.aogin2017tokyo.umin.jp

Laboratory Medicine Congress and Exhibition (LMCE) 2017 and 58th Annual Meeting
18 - 20 October
Seoul, South Korea
www.lmce-kslm.org/

November

2017 Asia Pacific MedTech Forum
7 - 8 November
Singapore
www.apacmed.org/event/asia-pacific-medtech-forum-2017

European Society for Medical Oncology (ESMO) Asia
17 – 19 November
Singapore
www.esmo.org/Conferences/ESMO-Asia-2017-Congress/Programme

Asian Conference on Emergency Medicine (ACEM)
22 – 25 November
Regnum Carya Belek, Analya, Turkey
www.acem2017.org

28th Regional Congress of International Society of Blood Transfusion (ISBT)
25 – 28 November
Guangzhou, China
www.isbtweb.org/guangzhou

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