Advancing Pharmacogenomics from the Bench to the Clinic with qPCR — Insights from Astrid Irwanto, Cofounder and COO of NalaGenetics

An in-depth conversation with this research scientist turned entrepreneur reveals how her education and research led her to generate innovative solutions and help pave a future where pharmacogenomics drives healthcare decisions.

Introduction

Astrid Irwanto is the cofounder and chief operating officer of NalaGenetics, a company taking a novel, personalized approach to understanding genetic susceptibility to drug reactions in Southeast Asian populations. Irwanto obtained a PhD in human genetics and then explored aspects of many complex human genetic diseases in her postdoctoral research, specifically how genetic variations relate to disease risks; her PhD and postdoctoral work, along with personal experiences, now fuel her pursuits at NalaGenetics. Bio-Rad's Candice Cox recently met with Astrid to ask about the history of NalaGenetics within the area of pharmacogenomics and why she decided to apply her academic research to a molecular diagnostics company using techniques such as qPCR on the CFX Opus 96 Dx Real-Time PCR System, among others.

Candice: Astrid, this company has been a great fit for your research interests. Could you speak about how NalaGenetics came to be and how it proposes to impact human health in Southeast Asia?

Astrid: During my PhD and postdoctoral work, we published a New England Journal of Medicine paper on the biomarkers used to detect an adverse drug reaction called dapsone hypersensitivity syndrome. It occurs in some individuals treated for leprosy, which is prevalent in Indonesia, ranking at number three globally. However, in countries like Singapore and the U.S., leprosy is almost nonexistent. As it turns out, dapsone hypersensitivity syndrome is caused by an *HLA* variant primarily present in Asian populations, most abundant in East Indonesians or Aboriginal groups with Melanesian ancestry. So, when we discovered this association, we decided not just to publish it but also to take action.

We first created a simple qPCR assay, and all our subsequent qPCR assays began from that one biomarker. We aimed to make this as affordable as possible and managed to have the assay done for less than $5, USD, with shipment to Indonesia. To date, this assay kit has been used to screen much of the East Indonesian population, especially in the Papua region, using the Ministry of Health budget.

For leprosy patients, before administering a drug, they are given a strip pack from Novartis and the WHO to test if they are positive for the *HLA* variant, *HLA-B˚13:01*. If positive, they are excluded from dapsone but can take the other two antibiotics. Nala is still committed to providing that test at cost.

But then we had other projects we wanted to pursue, owing to my own personal story. My father is tetraplegic, paralyzed from the chest down, due to the administration of two anticoagulants 20 years ago for a chest pain that was thought to be a cardiovascular issue.

Candice: What side effect did the anticoagulant cause?

Astrid: It caused bleeding in his gums and apparently in the C3 region of his spine that was not identified, and he lost sensation the next day, about 12 hours later. This problem occurred due to the adverse reaction to the anticoagulant. So, the question became what can be done to prevent this because at least 30% of these adverse reactions to these common drugs are linked to our genetics. We feel there are many actions we can take, especially in this part of the world, [as the adverse reaction is more common in countries] with large Asian populations. In fact, when we started looking at the *CYP2D6* gene, we realized that commercial kits don't detect or screen for a key mutation or variant for this gene, called **36*, occurring in 20–30% of people in Asia, especially [those of] Chinese descent. So, the vision for our Nala PGx Core® Assay Kit, is to be as inclusive as possible and put in all the prevalent biomarkers in Asian countries, making pharmacogenomic tests relevant and affordable for these populations. Our vision is to make this technology as accessible as possible.

Candice: With that introduction, I don't think I need to ask about the mission of your company; clearly, it came from a very personal perspective.

Astrid: Yes, we always write on our internal web page that we want to make DNA tests as ubiquitous as blood tests.

Candice: How do you accomplish the goal of understanding population variation in Southeast Asia?

Astrid: We still do a lot of research to make sure we always refer to the local population reference data if available. And we're trying to kickstart our government to do more of this work. For example, last week we signed an agreement with the government of Indonesia to begin their first human genome project. Finally!

Candice: That's a significant achievement right there.

Astrid: And we really do need that, especially in Indonesia, where we already see population diversity between people in Papua versus those in Java and Sumatra. These differences in ethnicity can impact whether we have the right biomarker for the dapsone hypersensitivity syndrome. For example, in the Javanese population, it's almost zero.

These groups are not that far from each other in terms of geographical distance, so we need to get to know this information better to target or predict disease risk. We're now focused on preventative medicine, which is challenging and not as attractive a business as treatment since people don't always have the mindset of the importance of prevention.

Candice: How does that affect the delivery of healthcare?

Astrid: The community is still very reactive because they have financial resources available for treatment of disease but not for preventative care. Also, the ability to obtain health insurance varies. It could be established in one area, but elsewhere, it can be just beginning to be offered. In our case, the genetic testing that we're offering is linked to the insurance format available in some settings, as it is preemptive testing.

Candice: Your recent application note with us discusses how you validated your Nala PGx Core® Assay on Bio-Rad's new CFX Opus Real-Time PCR System. Why did you choose to validate the compatibility of your pharmacogenomics assay with this thermal cycler?

Astrid: Initially for the CFX96 [Touch Real-Time PCR Detection System], we already had experience with your reagents; we obviously want to make sure that an assay we make is compatible with your instrument. We chose it because we know your real-time thermal cycler is ubiquitous in this part of the world and affordable too. We also found that most of our clients actually have your real-time PCR systems, which further confirmed our decision.

Then, when we saw that the CFX Opus System was replacing the CFX Touch System, we decided to validate it on the new platform. We also found that a few of our clients planned to switch from the Bio-Rad CFX96 System to CFX Opus 96 System, so we needed to support them in that transition. The CFX Opus fits our premise of making an offering that is accessible and affordable. In diagnostics, it's a question of cost per test, right?

If customers don't have the CFX platform, we provide suggestions for other instruments as well. We have optimized the thresholds to make sure that the outputs are compatible with other real-time PCR systems [not from Bio-Rad].

Candice: In terms of your assay development, were there any specific features of the hardware or software that made the CFX Opus Real-Time PCR System more useful to you?

Astrid: We liked the fact that it is a standard qPCR machine with five-channel detection, which was important because our Nala PGx Core® Kit requires three detection channels. For a particular variant in the *CYP2D6* gene, it has three different types of nucleotides in the population. It makes a difference whether you carry a T or an A in this position because it actually determines whether you're going to have a decreased or a loss-of-function enzyme that will impact your recommendation to take the drug.

Candice: So, your assay requirements and the widespread availability of the CFX platform drove your decision to use this instrument. Is Nala promoting preemptive testing in hospitals so that clinicians know patients' genetic risk of an ADR [adverse drug reaction] before their hospital visit? And why is preemptive testing safer for patients compared to testing just at the time of a new prescription?

Astrid: Pharmacogenomics is most beneficial when used at the right time. You want physicians to make the right recommendations for products and doses. Testing someone's genetics three days after a heart attack isn't practical. The issue today is that this information isn't readily available, which can lead to trial and error if a patient needs immediate medication. Having this information available in advance, during a patient's healthy state, can save time and enhance medical checkups. It also offers incentives for patients and payers. Some insurance companies now reimburse for these tests in the U.S. In our region, we have three insurance companies covering it for their clients. For example, if a client has a critical-illness policy, they're asked to take our test. Our test can save costs for insurers by reducing hospitalization for adverse reactions and the trial and error of different drugs.

Candice: How do you ensure data privacy and security for patients' genetic information with preemptive genetic testing?

Astrid: We're very cautious about how we store data. While HIPAA isn't enforced in Southeast Asia, we follow its principles. HIPAA keeps genetic and personal information separate so that even if hacked, it can't be linked directly to personal data. We don't have HIPAA certification here, but we do have an ISO 27001 certification related to information security. We also comply with government regulations, such as Singapore's PDPA [Personal Data Protection Act] and Indonesia's policy prohibiting health data from leaving the country. We keep data on local servers and use a secure API to relay it to healthcare providers. Yearly audits ensure compliance.

Candice: What is the advantage of a clinical customer using the Nala PGx Core® Kit to determine the genetic risk of ADRs compared to running a large NGS screen?

Astrid: Nala PGx Core® focuses on the most impactful genes related to pharmacogenomics, making it cost-effective and

efficient for clinical customers. You don't need all the world's genes for a pharmacogenomics test. You can target a smaller subset with the most significant impact on your population; it fits well into qPCR settings. It allows for quick results with fewer samples and is cost-effective compared to large NGS screens. As pharmacogenomics gains acceptance and becomes a national screening program, NalaGenetics is ready to scale up with more high-throughput platforms.

Candice: Do you use other molecular techniques besides qPCR in your product development?

Astrid: Yes, we offer a user interface for clinical decision support that enables laboratory technicians, physicians, and clinics to access a knowledge base with curated information, drug recommendations, and bioinformatics pipelines. Besides qPCR, we can analyze pharmacogenomics results from microarray and short-read NGS, and are moving towards long-read NGS technology to support a wider range of platforms.

Candice: How do you integrate these different technologies with qPCR?

Astrid: Each technology has its strengths and limitations. qPCR excels in cost-effectiveness and fast turnaround, making it suitable for preemptive testing. While NGS offers more comprehensive data, it's not as cost-effective. To promote pharmacogenomics, we need to change the mindset of the medical community. Education and outreach efforts are essential to drive the adoption of these technologies.

Candice: Thank you for sharing this great example of a successful collaboration using the Nala PGx Core® on Bio-Rad's CFX Opus 96 Dx System for in vitro diagnostics and CFX Opus 96 System for research use applications. It truly showcases the positive impact of the pilot study approach and highlighting the significance of preemptive testing for these individuals.

Your journey from academic researcher to creator of NalaGenetics shows your commitment to revolutionizing healthcare in Southeast Asia. We hope that NalaGenetics, under your leadership as the cofounder and COO, can achieve its mission to provide affordable and accessible genetic testing solutions and shift the medical community's mindset about the ability to enhance patient outcomes.

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Bio-Rad Laboratories, Inc.

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Website *bio-rad.com* ***USA*** *1 800 424 6723* ***Australia*** *61 2 9914 2800* ***Austria*** *00 800 00 24 67 23* ***Belgium*** *00 800 00 24 67 23* ***Brazil*** *4003 0399*
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