
# Primary Care and Precision Medicine

*An interview with* **Latha Palaniappan, MD, MS**

LATHA PALANIAPPAN MD, MS, is a professor of Primary Care and Population Health in the Department of Medicine at Stanford. She is an internist and clinical researcher focused on the study of diverse populations, chronic disease and prevention. Dr. Palaniappan addresses the health knowledge gap in Asian subgroups and other understudied racial/ethnic minorities. During her time as the Medical Director of Clinical Research at Palo Alto Medical Foundation (PAMF), she led the organization-wide initiative to collect patient race/ethnicity and language information. Her current work examines the clinical effectiveness of structured physical activity programs for diabetes management, as well as best exercise regimens for normal-weight diabetics. She is currently working on implementation of evidence-based genetic and pharmacogenetic testing in Primary Care Clinics as the Scientific Director of Precision Genomics and Pharmacogenomics in Primary Care.

Dr Palaniappan agreed to address a few questions with us.

**Q1. On the 'Strength Training Regimen for Normal Weight Diabetics' (STRONG-D[1]) Study and the 'Initiate and Maintain Physical Activity in Clinics' (IMPACT[2]) Diabetes Study:**

**a.** Could you please briefly summarize the results of the STRONG and IMPACT studies?

**A. STRONG-D study**

While it is known that strength and aerobic training are beneficial in obese diabetics, there is currently insufficient evidence to recommend this regimen in normal-weight diabetics (NWD).[1a] "Strength Training Regimen in Normal Weight Diabetes" (STRONG-D) looked to examine the effectiveness of different exercise regimen types in controlling diabetes within the normal weight type 2 diabetes population. Participants were randomly assigned to either strength training, aerobic training or combined strength and aerobic training months while investigators measured changes in the Hemoglobin A1C over the 9-month study period. TThrough doing this, our primary goal was to determine whether strength training aided glycemic control better than aerobic training for normal weight diabetics..[1a]

In our preliminary results, we saw that strength training and a combined strength training + aerobic approach have comparable benefits that were greater than the benefits of only aerobic exercise.[1a]

**IMPACT Study**

The Initiate and Maintain Physical Activity in Clinics (IMPACT) Study aims to compare structured group exercise within the clinic to usual care in T2DM patients. The main purpose of the study is to determine the optimal and feasible level and weekly frequency of structured contact in a clinical setting needed to initiate and maintain physical activity recommendations long-term. We began this project because we were seeing that although structured exercise interventions have been proven effective for reducing hemoglobin A1C levels in patients, around 38% of patients with T2DM did not exercise under recommended levels and 31% did not exercise at all. Within this, participants were randomized into three different exercise regimens: instructor-led exercise once a week, instructor-led exercise training sessions three times a week, and no instructor-led sessions. Findings will enable the clinical implementation of a structured exercise regimen designed to specifically address the aerobic and resistance training recommendations for patients with T2DM.[2a]

Final reports, conclusions, and papers for these studies are in preparation.

**b.** Have you also performed gene profiling, gene expression, or clinical biomarker analysis for studies through the DISCOVeR Lab? How can these markers be used to track patients on their road to better health?

**A.** The DISCOVeR Lab was created specifically to focus on the differences in patient-centered outcomes and racial/ethnic disparities present in cardiometabolic diseases. In working with collaborators in instutitions all over the globe, DISCOVer Lab has played a large role in translating findings from patient care into new treatments.

We have recently been working with pharmacogenomic testing in order to see the impacts that commonly prescribed medications have on Asian subpopulations and also looking at characteristics associated with colorectal, breast and cervical cancer screening. These screenings are able to uncover information about a patient's risk for certain conditions and provide healthcare teams more information on how to approach treatment options. For example, through preemptive screening programs at Stanford we were able to determine that a woman had a significant risk for breast and ovarian cancer and were able to set her up on a health care program that involved regular detection and monitoring. Without the screening, her health care team would not be able to put these procedures in place and the care she got wouldn't have been personalized to her conditions.

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**c.** What is the role and function of the DISCOVeR Lab in highlighting racial/ethnic health disparities in cardiometabolic disease risk, burden, screening, treatment and outcomes in multiethnic populations? Have you been able to identify healthcare deserts through your work in this area?

**A.** A big emphasis of my research with DISCOVeR Lab has been to address the gap in the knowledge of health in Asian subgroups and other understudied racial and ethnic minorities. As we do more research across different ethnic and racial groups, we are determining that most guidelines used in the United States do not account for different populations and are therefore not usable for certain conditions. This is a huge healthcare desert that not only impacts the care that our patients are receiving in our hospitals but also global understandings of diseases.

Our work shows that Asian Indian men and woman and Filipino men have a greater proportionate mortality burden from cardiovascular diseases and that the mortality burden of hypertensive heart disease is higher in every Asian-American subgroup than in Non-Hispanic Whites. This pattern calls attention to the need for more research to help directs more specific treatment and prevention efforts and overall reduce health disparities in this population.

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**d.** How do you foresee results from the STRONG-D and IMPACT Studies informing the health of the targeted populations at large?

**A.** Both STRONG-D and IMPACT dealt with looking at patients with Type 2 Diabetes and seeing how different interventions impacted their overall quality of life and also the management of their conditions. Through understanding how life changes such as adding strength training and aerobic changes can impact an individual's experience with Diabetes, we can directly work to create larger guidelines of management.

**Q2. On the Humanwide Pilot Project[3] – Objective data for health assessment:**

**a.** Humanwide was a precision health project embedded in primary care aiming to leverage high-tech and high-touch medicine to promote wellness, predict and prevent illness, and tailor treatment to individual medical and psychosocial needs. Can you please briefly summarize the outcomes from the perspective of the healthcare professionals who participated in the Project?

**A.** The Stanford vision of Precision Health is to predict, prevent and cure and Humanwide sought to implement that vision within our clinical settings. Our early experience with Humanwide showed that the interventions that we took were

successful in improving patient health and that the creation of this model with patient-centered data is feasible for both patients and providers.

As a provider, I was excited that we were able to get a better understanding of a patient's health and take appropriate interventions that are not always possible in traditional care. For example, we were able to determine that a patient complaining of leg cramps was a slow metabolizer of statins and were able to adjust his dosage to resolve his cramps. This intervention is one of many unique to Humanwide and allowed for higher rates of satisfaction for both the patients and providers. I am looking forward to continuing to work on implementing the findings of Humanwide to our primary care model.

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**b.** What types of technology were employed in this Project?

**A.** What makes Humanwide such an important study was the incorporation of medical research, biomedicine, technology, and data science into the existing primary care model. Each patient received genetic screenings and pharmacogenomic testing and were given four digital health devices – a digital scale, a blood pressure cuff, a glucometer and a pedometer- to measure and track their health. On top of this, data that was accessible to physicians through patients' electronic health records, allowing the team to document factors such as stress levels, environmental exposures, and sleep habits in order to get a full-picture view of a patient's condition.

*"These results were only possible because of the technology used as well as the in-care coordination between the primary care provider, medical assistant, certified health coach, a clinical pharmacist, a behavioral health practitioner, nutritionist registered nurse, and genetic counselor that worked to interpret these results."*

The clinical difference that this technology made is that these connected devices were providing information to both the patient and the healthcare team that helped better manage, or even prevent, chronic diseases. One out of four patients had a clinically significant finding that affected the drugs or dosages that were used to treat their conditions through pharmacogenomics testing. Additionally, patients were able to determine risks for breast cancer (a risk that otherwise would have gone undiagnosed in traditional screenings) and have monitoring as a part of their healthcare. These results were only possible because of the technology used as well as the in-care coordination between the primary care provider, medical assistant, certified health coach, a clinical pharmacist, a behavioral health practitioner, nutritionist registered nurse, and genetic counselor that worked to interpret these results.

**c.** Over half of the participants were obese and 58% had one or more major cardiovascular risk factor: dyslipidemia, hypertension, diabetes. How effective was this project in addressing these risk factors for this population?

**A.** The Humanwide pilot was designed in order to identify high risk patients in cancer previvor* and pre- and early cardiovascular disease states, and then provide individualized and effective treatments. Since we encouraged the use of wearable devices in a healthy population, we were not only able to identify patients with early diabetes and hypertension, but also were able to provide a greater level of intervention for patients that had already been identified high risk factors. In working with the technology as well as a closely knit care team, we were able to address the individualized problems that patients had and set them up with proper lifestyle and medication changes to enhance their quality of life.

(* A **previvor** is someone who has an elevated predisposition to being diagnosed with cancer due to a risk running through their family.)

**d.** As in Q1, how do you foresee results from this study informing the health of the targeted populations at large?

**A.** Our hope is that medical institutions worldwide are able to take the findings from Humanwide and apply them to create more patient-centered data environments. Through our preliminary work, we were able to create a comprehensive picture of patients' behaviors, genetics, and physical attributes. We hope to expand our work further to include more patient-specific factors along with more data to understand trends to enhance care for different populations of patients including across different racial and ethnic groups.

**Q3. Among the many of the topics you tackle are institutionalized healthcare deserts or long-standing individual habits that are exacerbated by, e.g., environment or individual choices.**

**a.** What have you learned from your studies to affect the institutionalization of healthcare facilities, for example, by technologies – mobile units, personal devices, telehealth follow up and coaching?

**A.** Through Humanwide we were able to see how patient-centered, data-driven health care works in practice and how the integration of technology can lead to a whole new level of health care. With that said, the difficulties of bringing the benefits of Precision Health to patients around the country are evident. Right now, doctors across the country need to engage in discourse to shift towards a system that focuses on preventative care and precision health. The system that we used is so unique and heavily reliant on technology, so we acknowledge that it's going to be difficult for this model to be adopted completely in hospitals in the country, however we hope that parts of the model can begin to be implemented.

**b.** Likewise, what have you learned to prevent the adoption of individual habits?

**A.** A good deal of my research has looked at how individual habits impact a person's health overall – whether it be their exercise regiments or their dietary preferences. The choices we made are directly reflected in our health and overall making small, yet conscious decisions can also help prevent and manage conditions. Therefore, it's important that health care teams are involved in looking at these factors that we know are influencing health and working with patients in order to determine ways to create better living systems.

**c.** What have you learned from precision diagnostics (gene or biomarker panels) to aid in treating patients?

**A.** I think the biggest takeaway is that the usage of precision diagnostics is able to drastically impact our patient's satisfaction and overall care. In Humanwide alone, we saw that the usage of pharmacogenemic testing had a significant impact on the care we were able to provide for patients.

As both genetic testing and pharmacogenomic testing become more available, we hope to take advantage of it in clinical settings to learn more about risks our patients may have. In medicine in general, we still have work to do in exploring these different technologies and understanding how they can be applied within our clinical practices. It has become clear that the future of medicine relies on this integration.

**Q4. In the 'Variant Interpretation in Current Pharmacogenetic Testing' paper,[4] you and your co-authors note that "the discordant phenotype analysis provided by two pharmacogenetic testing companies … [induced an] … uncertainty and unnecessary distress experienced by the patient" that "highlights the need for consensus in phenotype reporting within the industry."**

**a.** Furthermore, it seems that this unnecessary distress could be mitigated by a healthcare provider alerting a patient that, e.g., these tests "were not reviewed by the U.S. Food and Drug Administration (FDA)" and that, in general, "the FDA warned the public regarding genetic tests with claims to predict response to specific medications and that changing treatment based on interpretations made by individual companies could lead to inappropriate treatment decisions and potentially have serious health consequences for patients."

What is the role of the primary care provider in counseling the patient on such discordant analysis?

**A.** Currently, we see genetic testing companies designating their phenotype assignments and treatment recommendations based on their own interpretations of tests rather than adhering to universal guidelines, such as CPIC. Therefore, clinicians who are approached by patients with the results from these companies have to carefully analyze the data in order to explain exactly what the information means. Since companies may not be completely transparent in their interpretations of their tests, it is harder to determine what exactly the test results are indicative of. The burden of understanding and confirming these test results, along with translating the data to patient treatments and interventions, lies with the clinician.

**b.** You cite an example in "Variant Interpretation …" on the confusion caused by specific discrepancies for a patient genetic data from two companies. How should the full variant picture be provided to all in the healthcare chain – e.g., pharmacists, genetic counselors, and others?

**A.** There are two scenarios that can be used in order to provide genetic testing information from genetic testing companies to providers. As highlighted in the paper, shifting genetic companies to adhere to universal CPIC guidelines would allow for medical providers to view the data with confidence and allow for a direct connection between companies and providers. By creating a system in which the results would be directly provided to the clinicians, it would allow for all parts of a healthcare team to have direct access to the data and also be able to understand the results quickly.

**c.** What role do you look for the FDA to play in this scenario – e.g., informing providers through some formal mechanism?

**A.** The U.S. Food and Drug Administration has not reviewed companies creating these genetic tests but has instead recommended that providers make their own individual assessment of genetic test results and how these results impact a patient's treatments. As we move towards more evidence-based pharmacogenomics in clinical settings, it calls for more universal guidelines and a greater deal of attention on how these tests are conducted and analyzed. The FDA has announced a collaborative review of scientific evidence to support associations between genetic information and specific medications in February 2020, so hopefully in the near future we will be seeing greater guidelines and standards set in place for these genetic testing companies.

**d.** What are your thoughts on how to reconcile such cases in general?

**A.** Based on the example that we highlight in this paper, it's clear that the current process has distinct flaws. As of right now, if consumers are concerned about a specific test result from a direct-to-consumer test company, it is best to consult with a genetic counselor or equivalent health care provider to better understand the results. Tests are not 100% accurate – they might be wrong due to errors in the test and also could be incorrectly interpreted, so having a professional opinion is always best.

Thank you, Latha! JPM


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