REVIEW ARTICLE

Non-invasive Diagnostic Tools: Cardiometabolic Risk Assessment and Prediction

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ABSTRACT

Cardiometabolic risks (CMRs) have rapidly increased to epidemic proportions worldwide in the past three decades. Cardiovascular disease (CVD) remains the number one killer. No country has reduced, reversed, or prevented the increase in the incidence or prevalence of chronic metabolic diseases. Framingham Heart Study group described the modifiable risk factors that promote the development of CVD. They also developed risk calculators, for the prediction of acute vascular events such as heart attacks and stroke. The risk predictor algorithms were fine-tuned, as and when additional risk factors were discovered. However, at the time of this writing, there is no such calculator for assessment, stratification, and management of CMRs. On the other hand, numbers of non-invasive diagnostic devices have been developed for continuous monitoring of blood pressure and glucose profiles. We have described in our earlier articles, non-invasive diagnostic platform developed by LD-Technologies, Miami, Florida, capable of monitoring CMRs, cluster of risks, and computing risk scores for various dysfunctions, such as autonomous/sympathetic neuronal, and micro- and macro-vascular systems. In a one of a kind study, that has been described as the "largest," –Scripps Research Institute, La Jolla, California (www.scripps.edu), is following over a million individual's activities with a simple activity tracker, Fitbit. In an earlier article, we described a novel non-invasive diagnostic approach to monitor the development of early CMRs in a healthy population. The same diagnostic platform is also capable of providing information on risk assessment, risk stratification, and risk management strategies. We will discuss in this overview, some of the non-invasive diagnostic tools available, for monitoring biomarker assays, for the assessment of CMRs. In addition, we advocate the development of apps or health-portals that can collect, analyze the data from multiple devices or sources, and develop a seamless integration of data for risk stratification and risk prediction. In view of the anticipated variety, and volume of the available data, the analysis, and use of such data from multiple diagnostic devices, will be increasingly dependent on the ability to appropriately collect, curate, and integrate data from different devices and sources. Currently, several data integration tools are available. We have just briefly discussed a novel approach in this overview, to collect information at the level of individuals, as well as at the population level, CMR assessment, risk management, risk prediction, and risk prevention.

Key words: Cardiometabolic diseases, Diabetes, Non-invasive diagnostics, Obesity

INTRODUCTION

Metabolic diseases such as hypertension, excess weight, obesity, and type-2 diabetes have increased in the incidence and prevalence, to epidemic proportions worldwide in the past three decades.[1-15] The chronic metabolic diseases contribute significantly, to the morbidity and mortality associated with cardiovascular diseases (CVD). CVD is still the number one killer worldwide and has remained in this position for over 100 years.[4] All the metabolic diseases are basically lifestyle diseases; as such they can be delayed or prevented by early interventions, including healthy diet, increased physical activities or by minimal medications. The United States Preventive Services

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Task Force (USPSTF) recommends, that physicians screen patients for dyslipidemia (prediabetes or type-2 diabetes), when they are 40–70 years old and are overweight or obese. According to a recent article in the Journal of General Medicine, by the researchers at the Northwestern University School of Medicine, 53% of patients who had prediabetes or type-2 diabetes would not be screened.[9] For instance, African-American, Latino, and South Asians develop type-2 diabetes, at a much younger age than the average Caucasian. Current prevention screening recommendations, if followed, would leave 70% of Asians, with prediabetes or undiagnosed diabetes, until their next screening. In an earlier article, we articulated how a novel approach of screening the young adults with emerging technologies will provide us the capabilities for early diagnosis and better management of the risks, as well as for the reduction and prevention of cardiometabolic diseases.

According to a recent article by the researchers at the Centers for Disease Control (USA), after an almost 20-year increase in the national prevalence and incidence of diabetes, an 8-year period of stable prevalence and a decrease in the incidence has been observed.[16] This decrease in the incidence seems to be driven by non-Hispanic individuals, suggesting possible causes for this observation to be ethnic-specific, as well as due to other demographic disparities. The increasing burden of diabetes seems to be the result of increases in obesity and prediabetes. More than 100 million individuals in the USA have diabetes or prediabetes.[17] The number of prediabetics is four-fold higher than that of diabetics in the USA. Furthermore, a new first of a kind study, by the researchers at the Imperial College London and the World Health Organization reports that from 1975 to 2016, the number of girls with obesity increased from 5 million to 50 million, and boys from 6 million to 74 million. In other words, childhood obesity increased 10-fold worldwide since 1975.[18] If we look at the global picture, India was considered "diabetes capital" a few years ago, now China has outranked India but there are speculations based on trend measurements that India may take over China again in the near future. Noncommunicable risk factor collaborator group used data from 751 studies from 146 counties for their estimate of trends. Based on their study, they predict, if the post 2000 trends in the increase in the incidence of diabetes continue, the probability of meeting the global target of halting the rise in diabetes by 2020 to the 2015 level is <1%.

National Health Service (NHS) of the UK has shifted its focus on preventive health care. To achieve the set goals, long-term plan of NHS features digital health prominently. According to their latest "News Item," – within the next 5 years, all patients in England, will be entitled to online digital consultations with a general practitioner, and women will be able to access their maternity notes, with their smartphone or other connected devices. The long-term plan, mentions of digital tools in connection with all kinds of conditions, includes non-communicable diseases, such as excess weight, hypertension, obesity, diabetes, vascular diseases, and cancer. This month (July 1, 2019) marks a milestone in the journey of digitization; its scheduled completion date for the roll-out of the "NHS App," described as the "digital front door" to the NHS services. The app itself is unlikely to expand any further. Instead, the intention seems to be to plug in additional digital products, through open application programming interfaces.[19] Maurice Smith, a member of the governing body of NHS concludes, "what it does is, to demonstrate the direction of the digital travel. Society, in general, is moving toward digitally-enabled ways of working and interacting with services, and this inevitable transition to 'digital health' has to be reflected in all aspects of healthcare.

What we are proposing through a series of articles on the topic of our interest, "integration of emerging diagnostic technologies for better health care," is to describe a similar direction of travel. Currently, there is a great interest, and tremendous efforts to develop simple, cost effective, non-invasive diagnostic tools and technologies. All of these technologies, use simple, sophisticated sensors, to elicit expected physiological responses from human body, gather the data, compute, use proprietary software and trained algorithms, to provide expected results, interpretations, and conclusions. Because they do not directly measure any biomarkers as the blood chemistry does, the values expressed are not "real values" but algorithm-based derivatives. In view of this fact, they need to be thoroughly validated by independent clinical studies, and appropriate corrections made in their interpretations. Furthermore, all of the devices on the market although are capable of developing diagnostic data on a variety of biomarkers, do not have the capability of integrating such data to develop a meaningful interpretation. We will use time-tested cardiovascular risk calculator as an example, describe some non-invasive diagnostic tools and platforms to illustrate our concept of "integration of things" for better diagnosis, risk assessment, risk prediction, and risk management.

As mentioned in our introduction, metabolic diseases have increased in the incidence and prevalence worldwide, to epidemic proportions. All of these metabolic diseases contribute significantly, to the cardiovascular (CVD) and cerebrovascular disease morbidity and mortality. Framingham Heart Studies (FHS) initiated by the National Institutes of Health (NIH), USA some seven decades ago, developed the concept of "risk factors" for coronary artery disease (CAD) and published its findings in 1957.[20] FHS demonstrated the epidemiological relations of cigarette smoking, blood pressure, and cholesterol, to the incidence of CAD. FHS researchers have developed a general CAD risk profile for use in primary care settings for calculating 10-year risk for developing CVD.[21] Several studies have explored currently

available and widely used CVD risk assessment models, to examine the evidence available on new biomarkers and the nonclinical measures in improving the risk prediction in the population level. Adding C-reactive protein, lipoprotein little-A (Lpa) levels, and to conventional cardiovascular risk models, have been shown to improve risk prediction for cardiovascular events.[22-24]

Similarly, there are suggestions that adding Lpa to the known cluster of risks will improve risk prediction for certain ethnic populations (South Asians). Risk stratification for CVD remains suboptimal, even after the introduction of global risk assessment by various scores. Researchers from the University Medical Center, Germany, have emphasized potential use of biomarkers for risk stratification, in initially healthy subjects and patients, with manifest chronic atherosclerosis, particularly focusing on the integrated value of the combination of these markers. In an earlier article on this topic, we proposed using healthy cohorts from a pool of fitness and wellness enthusiasts, to follow early risk assessment, risk stratification, and robust management of the diagnosed risks. In this overview, we will describe the use of non-invasive diagnostic tools; discuss how some of the diagnostic platforms have achieved computing, integration, analysis, and interpretation capabilities. In addition, we advocate the development of a modular portal that can take such diagnostic data, which are relevant for risk assessment and stratification of cardiometabolic risks (CMRs) from multiple devices, and fine-tune the risk prediction for CVD development and acute events associated with this disease.

DISCUSSION

Of the three metabolic diseases, detection of hypertension and excess weight or obesity is easy. Blood pressure monitors are in use for over 100 years. Having said that, we would like to see the use of 24-h ambulatory blood pressure monitoring for the management of hypertension. These devices can be programmed and continuously used for over a 24-h period. They can also monitor heart rate, compute average readings, and help in predicting the likelihood of cardiovascular and cerebrovascular disease-linked hypertension. If need be, these devices could be improved to detect endothelial dysfunction, the earliest manifestation of vascular disease. As far as the excess weight, and obesity, measurements, height/weight, as well as waist/hip ratio, will provide the needed measurements. When it comes to diabetes, current guidelines prefer the use of fasting glucose and hemoglobin A1c (HBA1c) measurements from the same sample, preferably.[25]

In our efforts to develop and promote the use of non-invasive diagnostic devices, senior author of this article, Dr. Rao secured a grant from the Indian Council of Medical Research, India, and developed a prototype, of a non-invasive glucometer using near infrared (IR) sensors.[26] The IR emitter was a 940 nm IR-light-emitting diode, and the detector was a photodiode chip, with 1100 nm wavelength. The idea was to develop a device that will compute both blood glucose values and HBA1c values from the same reading. We also have validated the use of Abbott FreeStyle Libre [Figure 1] for its usefulness in continuous glucose profiling in the interstitial tissues. As shown in Figure 1, the glucose profile provides data on median glucose level, expected goal to achieve, and calculates HBA1c values. Figure 2 shows a glucose profile of a diabetic patient, who is on medication for over 20 years. In addition to the median glucose level (154), and low threshold (70), the data also provide color-coded indexing of low (green), moderate (yellow), and high (orange) values. Ability to monitor glucose every 15 min noninvasively empowers the patient to self-monitor the effect of medication, diet, and physical activity on glucose levels at the touch of a button.

Figure 3 shows average glucose values computed for the 24-h reading. Having such data accessible make the patient aware of the daily variations in the glucose level and provide a unique opportunity, to contemplate on the effect of daily diet and physical activity on the glucose levels. Again, this kind of information empowers the patient, to make adjustments in lifestyle so that elevated mean level of glucose can be brought down to expected levels. The data analysis shown in Figure 4 also provide information on average glucose for the 24-h period, percent of time the glucose was in target level (20%), percent of time below target (2%), percent of time above target (78%). Having such information, helps the

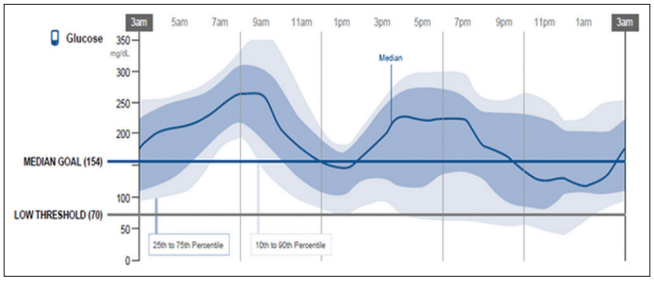

Figure 1: Glucose profile of a diabetic not under any medication (hemoglobin A1c – 9.8%) (Courtesy: Abbott Diabetes Care; Bengaluru, India)

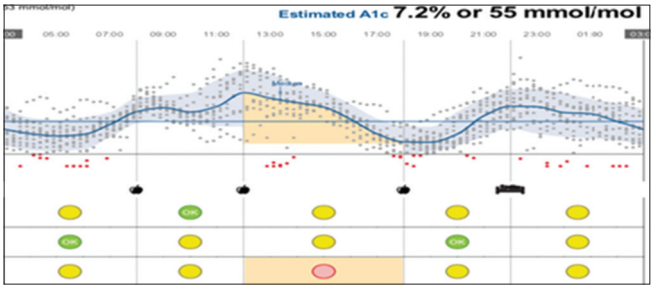

Figure 2: Glucose profile of a diabetic under medication (hemoglobin A1c – 7.2%) (Personal data: Karnataka Institute of Endocrinology and Research, Bengaluru, India)

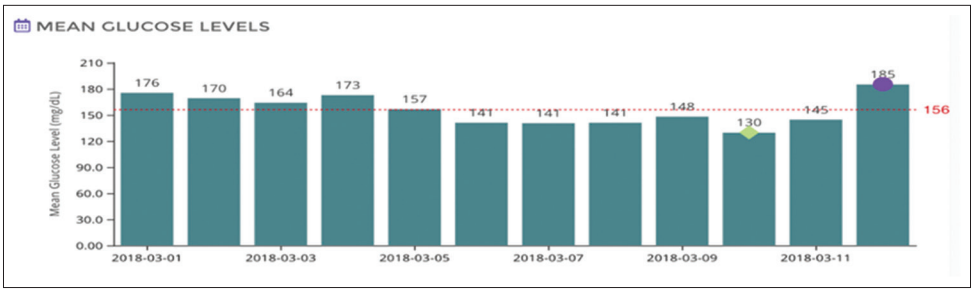

Figure 3: Daily mean glucose values, computed from approximately 96 data points per day (Personal data: Karnataka Institute of Endocrinology, Bengaluru, India)

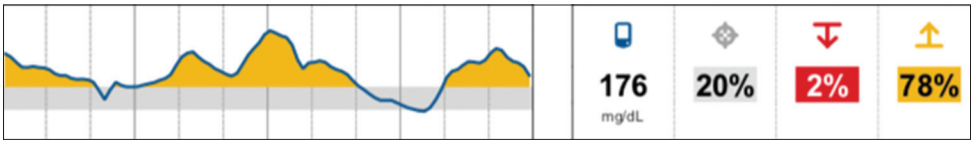

Figure 4: Daily glucose summary (average, time in target, below target, above target) (Personal data: Karnataka Institute of Endocrinology, Bengaluru, India)

patient to pay attention to the time the level of glucose was higher than the target level and thus provides an opportunity to the patient to try various interventions to lower the glucose level to the targeted goal. This is the closest to personalized/precision medicine at the time of this writing.

In addition to our efforts toward the development of diagnostic devices, we also work with inventors, innovators, and entrepreneurs, to validate various diagnostic tools and platforms. We work closely with Dr. Albert Maarek of Miami, Florida, who is the innovator of LD-products, a unique non-invasive diagnostic platform, for diagnosis of CMRs. Figure 5 shows the three basic devices used to do various diagnostic tests. The FDA approved devices used are oximeter, blood pressure monitor, and a galvanic skin response monitor. The combination of these devices on a single platform is described by the innovator as "data systems," with different names, as indicated in Figure 5. The Sudo Path System is used to monitor early stages of peripheral neuropathy and changes in microcirculation. TM-Oxi System is used for monitoring diabetic autonomic neuropathy and endothelial function. EX-Complex TSS is used for monitoring diabetes-related clinical complications and management of risk factors. Gandhi and Rao have validated TM-Oxi and Sudo Path systems.[27-29] In their collaborative studies, using plethysmography to compute the risks, CVD risk score had a sensitivity of 82.5% and specificity of 96.8% for detecting CAD. In a separate study, we compared two different groups of diabetes patients and found their Sudo-motor score had a sensitivity of 91.4% and a specificity of 79.1% to detect diabetes-mediated peripheral neuropathy.[29]

As mentioned earlier, ES complex data system focuses on diabetes treatment management and early detection of clinical complications. Figure 6 shows bar graphs for relative

Figure 5: (Courtesy: Dr Albert Maarek, LD-Technologies, Miami, Florida)

risk, for various biomarkers. Risks are color-coded from green (low-risk), yellow (medium risk), orange (moderate risk), and red (high risk). In this patient profile, body mass as represented as fat mass, impaired glucose tolerance, and blood pressure are colored red and in view of this finding their CMR score is 15 and their autonomous nervous system score (ANR) is 8. We have used this system to evaluate treatment success. Figure 7 shows data from studies where we followed the effect of treatment on various risk factors. These patients were prediabetics, or they were in the early stages of diabetes. Most of their risk could be managed by simple lifestyle changes, including diet, physical activity, and antiglycemic treatment. In collaboration with Dr. Pratiksha Gandhi, Chairwoman, IPC Heart Care, Mumbai, India, we have validated, early diagnosis of CMRs, and management of success or otherwise, of various complementary therapies using the three "test systems" of LD-technologies.[27-29]

In 2018, LD-Technologies developed their revised version of LD products [Figure 8], ANS-1/TM flow, peripheral arterial disease (PAD) series, and life probes, a "health kiosk." They improved their earlier concept of testing and eliciting biological/physiological responses from human body, fine-tuned their proprietary software, and trained their algorithms to

provide a host of functional responses and biomarkers. In this newly developed system, technologies used are: SWEATC, galvanic skin response monitor capable of monitoring small fiber neuropathy; ES-BC, a bioimpedance analyzer to monitor body composition; LD-Oxy, a photoplethysmography (PTG) monitor to measure endothelial dysfunction, fitness, cardiac autonomic dysfunction, and cardiac autonomic neuropathy; and TBL-ABI, a volume plethysmography monitor to measure PAD and blood pressure analysis (CASP). These various tests seem to help in the diagnosis of clinical symptoms and causes that underlie such dysfunctions.

Some examples include ANS dysfunction, indicative of exercise intolerance, mental stress, fatigue, and weakness; baroreceptor dysfunction, indicative of headache, excessive sweating, and high blood pressure; cardiac autonomic neuropathy, indicative of dizziness and fainting, urinary problems, sexual difficulties, altered digestion, and inability to recognize low blood sugar; sinus node dysfunction, indicative of fatigue, dizziness, chest pain, confusion, and palpitations; endothelial dysfunction, pain in leg, shortness of breath, and muscle weakness; high blood pressure, headache, fatigue, vision problems, chest pain, difficulty in breathing, and irregular heartbeat; peripheral artery disease, lower extremity pain, muscle cramping of thighs or calves when walking, and climbing stairs or exercising; small fiber neuropathy, chronic pain, pins and needles, pricks, and tingling numbness. In spite of the fact that the developers claim the capabilities of these tests to diagnose a variety of symptoms and causes associated with the development of CMRs, these systems need a robust independent clinical validation to establish the specificity and efficiency of their ability to diagnose these symptoms and relate it to one or more of the related causes.

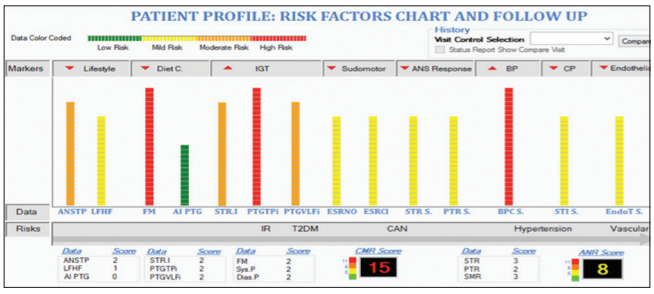

Figure 6: Risk factors for cardiometabolic diseases (Courtesy: Dr. Albert Maarek, LD-Technologies, Miami, Florida)

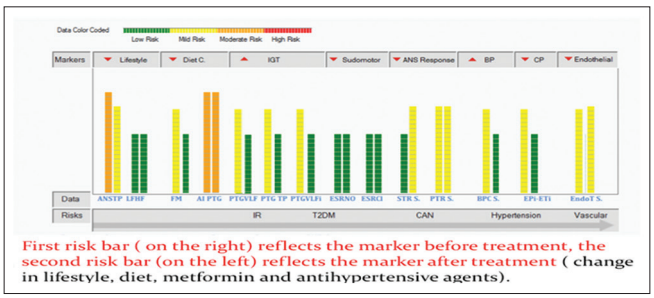

Figure 7: Risk factors for cardiometabolic diseases: Before and after treatment (Courtesy: LD-Technologies, Miami, Florida)

Similar to our earlier collaborative studies on the various data systems (TM-Oxi, Sudo Path), we have started validating the new version of LD-products. We have briefly discussed some cases and flow charts, to explain the importance of such tests in fitness management, risk assessment, risk stratification, and treatment management. Figure 9 shows clinical symptoms of a patient. Clinical symptoms of a patient Male 80 years old, height 168 cm. weight 67 kg. Not under any medication. Symptoms: Dizziness, weakness, numbness (legs), tremors, mood swings, anxiety, short of breath. The data presented summarizes biomarker tests for each of the visits, color-coded to indicate low, moderate, and high risk. Some risks have remained unchanged whereas; others have either improved or progressed to a higher risk. Just a glance at such a finding, baffles the scientist or clinicians in turns of making sense out of results of such elaborate tests. However, proprietary software and algorithms are used to collect such results, compute, analyze, and develop scores for a cluster of risks. Figure 10 shows Wellness Index, which is derived from the collective data from three test scores, vascular risk score, autonomic risk score, and lifestyle risk score. Test results for

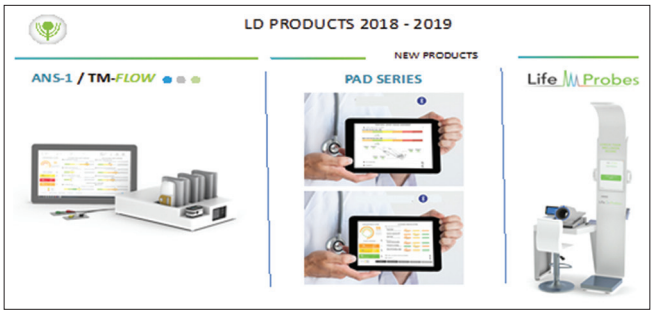

Figure 8: LD-products for TM-flow data systems (Courtesy: Dr. Albert Maarek, LD-Technologies, Miami, Florida)

Biomarkers	maj-18	sep-18	feb-19	apr-19	maj-19	jun-19	jun-19
Wellness/Index	66%	64%	68%	65%	86%	68%	67%
Lifestyle	28%	28%	26%	28%	37%	29%	28%
Autonomic Score	19%	18%	24%	22%	27%	20%	24%
Cardiovascular Score	19%	18%	18%	15%	22%	19%	15%
Parasymp standing up							
Parasymp breathing							
Sympathetic failure							
Ortostatic hypotension							
POTS							
Inflammation	253	253	253	253	87	253	253
HRV	450	450	450	450	1266	450	450
Recovery exercise	19	17	21	20	41	24	20
Parasympathtic	9	10	7	14	20	20	13
Mental stress	2,5	2,8	2,5	2,8	2,6	2,5	2,5
Digestive system	563	819	896	653	742	640	627
Serotonin	922	717	218	691	563	320	435
Dopamine	640	448	154	397	320	128	282
pH regulation	44	64	70	51	59	51	49
Oxygen saturation	96%	96	97	96	96	96	97
Microcirculation	640	794	717	512	640	576	730
Oxidative stress	742	1037	883	602	883	640	883
Thyroid	518	851	986	800	742	685	493
Minute volume	7,7	9,1	6,7	10	5,3	5,9	8,3
Stroke volume	142	150	120	176	95,2	112	148
Heart rate in rest	54	61	56	57	56	53	56
Blood pressure	147/76	152/77	137/77	159/71	132/84	124/68	145/71
Coagulation	50	58	55	84	62	60	53
Lipid profile	0,41	0,41	0,41	0,45	0,48	0,41	0,64

Figure 9: Risk profiling using LD-flow data systems (Personal data: Wellness Screening Concept and Health Knowledge AB, Sweden)

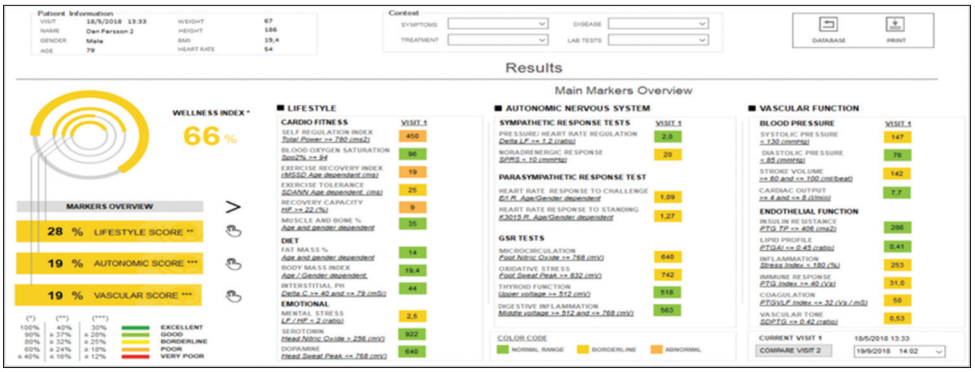

Figure 10: Computing wellness index based on biomarkers (Personal data: Wellness Screening Concept and Health Knowledge AB, Sweden)

each of these risk scores, vascular, autonomic, and lifestyle, are color-coded, as shown in Figure 10. Overall, wellness of this patient as computed by the collective data is 66%. The goal of the trainer/clinician is to correct the observed risks under each category and demonstrate the improvements in fitness, wellness index, and post-intervention.

In the case of this patient, there is a lot of room for intervention and improvement of risk scores as the vascular score (19%), autonomic score (19%), and lifestyle score (28%) are relatively low. By appropriate interventions of biomarkers responsible for these low scores, one can improve the overall Wellness Index. Results of such studies, demonstrating how one can develop interventions, and improve various risk scores, will be the subject of our next article in this series.

Figure 11 shows the summary data from another patient, with excellent Wellness Index [Figure 11, left side]. However, what one can appreciate from this study is that even in a case where the Wellness Index is 92%, there is still room to improve [Figure 11, right side] the Wellness Index from 92 to 97%. The optimal value for Wellness Index is 100%, for lifestyle score is 40%, autonomic score 30%, and for vascular score 30%, together these scores add up to 100%. CMR score includes biomarkers such as insulin resistance, hypertension, lipid profile, diabetes-neuropathy, endothelial dysfunction, and other symptoms of CVDs; whereas vascular risk score includes inflammation, immune responses, lipid profile, vascular tone, blood pressure, CASP, coagulation, and arterial brachial index; autonomic score, on the other hand, provides information on microcirculation, C-fiber activity, cardiac innervation, adrenergic response, nor-adrenergic response, parasympathetic responses, and baroreceptor function associated data, as shown in Figure 12.

The purpose of this overview was not to describe all the available noninvasive tools for monitoring metabolic risks, but to explain the future directions; we want to pursue in the field of clinical and diagnostic cardiology, for early detection, risk assessment, risk prediction, and therapeutic management

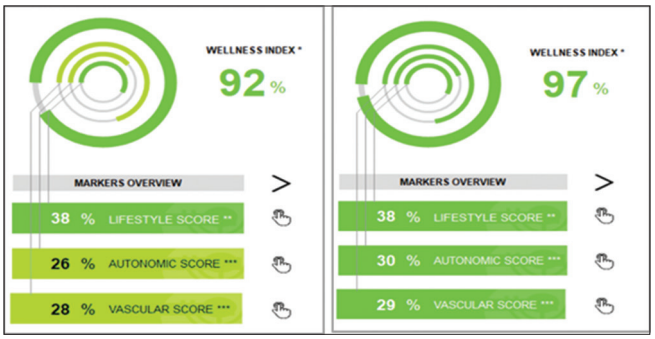

Figure 11: Computing wellness index based on biomarkers (Personal data: Wellness Screening Concept and Health Knowledge AB, Sweden)

of CMRs. Having said that, we want to inform the readers that the future of clinical diagnosis and management of diseases will heavily depend on the integration of available emerging technologies. Therefore, we will have to start thinking as to how, we can use this wealth of information coming from a variety of independent tools, to develop a state-of-the-art health-portal or an app that can capture these data and generate appropriate risk assessment, and data interpretation charts for empowering the patients. Such an app or a portal should have the built-in capability, to share the information with the clinicians as well as health-care professional. For instance, the new Apple watch-4 can share the data with clinicians, if they have already set-up patient health portals. If we just take cardiometabolic disease as cluster of metabolic disease; currently, we have the ability to diagnose all the major metabolic risks, including oxidative stress, chronic inflammation, excess weight, visceral obesity, body-mass index, altered micro- and macro-circulation, endothelial dysfunction, hardening of the arteries, clinical complications associated with obesity, diabetes, and cardiovascular and cerebrovascular diseases. The system may not be perfect, but it is a good start, and there is plenty of room for improvement, based on clinical validation.

Researchers have come a long way at the LD-technologies, in improving their products for non-invasive diagnosis

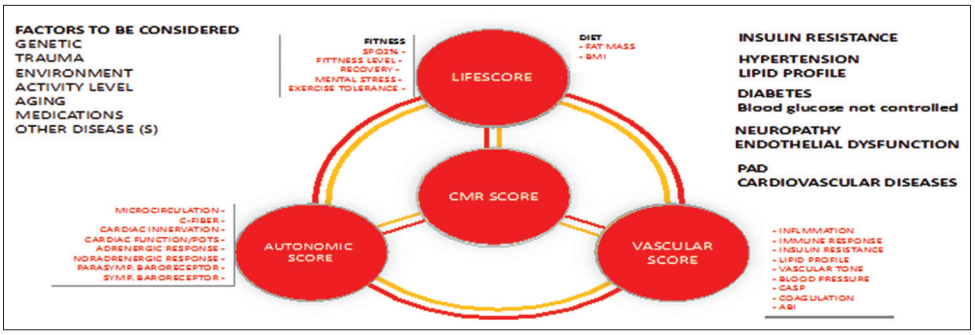

Figure 12: Factors used for computing risk scores and wellness index (Personal data: Wellness Screening Concept and Health Knowledge AB, Sweden)

of CMRs and cluster of risks. In addition, by developing proprietary software, analytics, and algorithms, they have been able to generate information on a variety of risks, cluster of risks and risk scores for vascular dysfunctions, and autonomic dysfunctions. It is worth discussing how these researchers have been able to take individual test results (as electrical outputs) obtained by a variety of sensors, using well-tested devices such as oximeter, blood pressure monitor, and galvanic skin monitor, compute values for biomarkers and train their algorithms to provide information on symptoms and causes. If you just carefully examine the results presented in Figure 12, you will realize the power of sensors, computing software analytics, and algorithms. In view of the fact that majority of these biomarkers are not assayed directly, we feel the need to validate these results with appropriate clinical studies. One other indirect way to validate, the data are using appropriate interventions to see if such interventions change the risk scores. We are currently in the process of developing such investigational studies in Sweden, India, and the USA.

Another area that we are very much interested is, how we can improve this diagnostic platform further. Since these are patented technologies, we will not be able to directly alter the functioning of any of the components of this platform. However, we can use this information as well as data from other sources on a separate "smart platform" to compute, integrate, and fine-tune the risk prediction, and risk management capabilities. Let us briefly discuss a novel approach to build such a health portal or an app. We will limit here to those devices that will provide complementary information for improving early diagnosis and better management of cardiometabolic diseases. Diabetes is a major contributor to the morbidity and mortality of CVDs. In view of this fact, the addition of values for glucose or HBA1c in computing early risk for diabetes will add value for risk prediction. We can import the data on glucose profile of a patient directly onto our "health portal" from devices such as Abbott FreeStyle Libre or Dexcom-G6 continuous glucose monitor (CGM). If we want to make these emerging tools popular and useful, we will have to make them user-friendly for patients, clinicians, as well as health-care providers. Currently, available diagnostic tools generate useful data, compute, and generate a wealth of information on their findings (charts, graphs, alerts, etc.). However, what we are suggesting in our novel approach for integration is that these individual values obtained on biomarkers from various diagnostic devices, be collected on a smart app, and appropriate software analysis and algorithm be developed, to process this information along with any other biomarker or risk associated with the CMRs, to fine-tune the risk prediction equations or scores.

Scripps Translational Science Institute funded by the NIH has been working with Fitbit, an activity tracker to deploy one million participants in the "All of Us," research program. According to the researchers, "the goal of this research is to gain insight into how wearable devices might impact compliance and engagement in a large national cohort study of this scale." In this large study, they will be collecting a variety of data with this tracking device, such as physical activity, exercise, sleep data, heart rate, and cardiorespiratory fitness. Such data are very useful to monitor the development of metabolic diseases. All of Us project, envisages to build one of the world's largest data sets, with the specific goal of improving the ability to prevent and treat disease, based on individual differences in lifestyles. In a press release on January 2019, NIH launched the "Fitbit Bring-Your-Own-Device (BYOD)" project, the First Digital Health Technology Initiative' in the USA. Researchers of this one of a kind project, express that data sharing is a high priority to both researchers and participants. In an earlier article, we articulated the use of "fitness and wellness" participants to build a dataset for developing early diagnosis and effective management of metabolic risks. In building such a platform for population-based studies, one can create programs that can take into account all the known risk factors so that data analysis and risk prediction for the development of disease-specific risks could be fine-tuned. For instance, tracking devices could add additional features to the analytical capabilities of the existing devices to meet such requirements.

We have already described the capabilities of LD-technology products, to measure various risks associated with CMRs,

including diabetes-related clinical complications such as endothelial dysfunction, peripheral neuropathy, and PAD. Greatest potential to reduce the burden of stroke, for instance, is by primary prevention of the first-ever stroke.[30] Researchers at AUT University Auckland, New Zealand, have developed a new app, the "stroke riskometer." They used data from 752 stroke outcomes from a sample of 9501 individuals, across three countries (New Zealand, Russia, and Netherlands), to investigate the performance of a novel stroke risk prediction tool algorithm, compared to a standard stroke risk prediction algorithm (Framingham stroke risk score [FSRS]). The stroke riskometer performed well against the FSRS. Other related complications including, diabetes retinopathy (DR) and diabetic maculopathy, are the leading causes of blindness worldwide. Changes in tiny blood vessels of the eye may predict a higher risk of later narrowing in the large blood vessels in the legs, according to a study presented at the American Heart Association's epidemiology and prevention/Lifestyle and Cardiometabolic Health 2017 Scientific Sessions. Mobile fundus cameras are available, for routine screening of eyes at the population level. In addition, automated screening algorithms have begun to be incorporated into the national DR screening programs in Scotland and the UK.[31] LD-technology devices measure altered flow dynamics in micro as well as macrocirculation and have been shown to predict diabetic neuropathy as well as diabetes-mediated peripheral artery disease. We are interested in developing wearables capable of "pulse waveform" analysis, at various pulse points so that one can monitor altered flow velocity of regional vascular beds.[32] In a short overview on such an important topic, it is rather difficult to discuss all aspects of this novel approach. Readers are urged to refer to articles, comprehensive reviews, and monographs on this subject.[33-41]

CONCLUSIONS

Metabolic diseases such as hypertension, excess weight, obesity, type-2 diabetes, and vascular disease have increased rapidly to epidemic proportions worldwide. These chronic diseases contribute significantly, to the increased morbidity and mortality related to vascular disease. FHS group has defined the modifiable risk factors that promote the development of CVDs. Vascular disease has remained the number one killer, for over a century. FHS group based on their findings developed Framingham Risk Score calculator for both CVD and Stroke events. As and when additional biomarkers were discovered, the risk prediction has been fine-tuned by adding the newly discovered biomarkers and retraining the risk prediction algorithms. Several studies have demonstrated that robust management of modifiable risk factors, significantly reduces premature mortality due to ischemic heart disease. In spite of these observations, the trends in the increased incidence of metabolic diseases have not slowed down. Modern medicine has failed to reduce, or prevent, these chronic metabolic diseases. In an earlier article, we articulated some novel approaches to diagnose early risks and effectively manage the observed risks. In our efforts to develop novel preventive strategies, we are working on the development of cost-effective non-invasive diagnostic platforms as well as validating the existing devices and platforms. Advances in medical device technologies, availability of inexpensive sensors, and the newer applications of software analytics and improved algorithms have accelerated the integration of emerging diagnostic technologies, for the development of improved platforms for monitoring biomarkers, computing the risk assessment, risk stratification, and risk management.

In this overview, we have described some of the diagnostic tools and platforms available with special emphasis on biomarkers, related to cardiometabolic diseases. We have emphasized, the importance of integration of emerging diagnostic technologies, to fine-tune risk assessment, risk stratification, and risk management. When we review the available emerging technologies, it becomes evident that unlike classical blood chemistry, the newer diagnostic tests rely heavily on software analytics and proprietary algorithms. We have discussed how LD-technology products, obtain their data for biological and physiological functions with a variety non-invasive technologies, compute, integrate and interpret these data, to match the clinical symptoms and possible causes, that underlie these clinical conditions. Using such non-invasive technology largest population-based studies are under progress to track physical activities, biological and physiological functions, to validate cardiorespiratory fitness. The road ahead will bring in a host of diagnostic tools, big data computing, artificial intelligence, and machine learning algorithms, to improve risk assessment, risk stratification, and risk prediction. What we have documented in this article is the immediate need to validate all the new non-invasive diagnostic tools in terms of specificity, accuracy, and improved prediction capabilities. We also have stressed the need, to develop an app or a health portal that can collect data from a variety of non-invasive diagnostic tools, integrate seamlessly to any existing dataset, and provide improved prediction capabilities. We have used Abbott CGM and LD-technology products as examples for integration of technologies for monitoring CMR, cluster of risks, and interpretation of such integrated data.

We have just discussed two major non-invasive devices in this overview, CGM, and LD technology products, for monitoring CMR. The two commercially available CGMs are measure of interstitial glucose instead of blood glucose. The HBA1c values are obtained using software analytics and specific algorithms. Similarly, the LD-products obtain most of their test data using three devices, oximetry, blood pressure monitor, and skin response monitor. Much of the data reported as clinical symptoms and causes or derived

using proprietary software and algorithms. Even from big data users such as IBM-Watson, algorithm-based results, and interpretation present some limitations. Developers of these emerging technologies do not provide any information as to how various biomarkers are estimated. In view of this fact, it is difficult to completely rely on these interpretations, when working with large cohorts, or patients. The solution we have suggested in our overview is to use these techniques and develop extensive clinical data, suggest appropriate interventions for the observed risks and see if the suggested interventions improve individual risk scores or collective risk scores. As mentioned earlier in this overview, we are trying to validate noninvasive diagnostic tools and platforms in the USA, Sweden, and India. We will report our findings as and when we have sufficient data.

ACKNOWLEDGMENTS

Senior author, Gundu H.R. Rao, Emeritus Professor, University of Minnesota, thanks, Mr. Aneel J. Antony for his collaboration on the Noninvasive Glucometer Development Studies. He thanks Indian Council of Medical Research (ICMR), for funding glucometer-related studies. He also thanks, Dr Pratiksha Gandhi, Chairwoman, IPC Heartcare, Mumbai, India, Dr Albert Maarek of LD Technologies, Miami, Florida and Ms. Elena Malmefeldt, Wellness Concepts, Sweden, for their collaboration in device development and clinical validation studies. He thanks, National Design Research Forum (NDRF) of Defence Research and Development Organization (DRDO), Government of India, for sponsoring our research proposal to the ICMR, as well as honoring Dr. Rao with membership on the Board of advisors, Medical Device Development, NDRF. Finally, he expresses his appreciation to the Institutions of Engineers, Bengaluru, India, for electing him as their first Fellow of Institutions of Engineers.

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How to cite this article: Malmefeldt E, Rao GHR. Noninvasive Diagnostic Tools: Cardiometabolic Risk Assessment and Prediction. J Clin Cardiol Diagn 2019;2(1):1-10.