deNovo Medica

Leader in digital CPD for Southern African healthcare professionals

Earn up to 3 free CEUs

Best future practice

Better options for best clinical practice

Role of technology, disrupters and genomics in modern medicine*

Faculty

Dr R Motara
Cardiologist
Johannesburg

Prof J Ker (Snr)
Deputy-Dean (retired)
University of Pretoria
Pretoria

Prof P Rheeder
Physician
Pretoria

Prof G Tintinger
Pulmonologist
Pretoria

Dr C Kapnias
Panorama Healthcare Centre
Cape Town

Prof de Wet Swanepoel
Audiology
Pretoria

Dr E Venter
Dietitian
Cape Town

Dr S Sharma
Abbott Laboratories
India

Dr J Trusher
Clinical pathologist
Johannesburg

Prof M Pepper
Molecular research
Pretoria

Dr J Knezovich
Specialist pathologist
Johannesburg

Prof M Chetty
Managed care, University of KwaZulu Natal
Durban
KwaZulu-Natal

This report was made possible by an unrestricted educational grant from **Cipla**. *The content of the report is independent of the sponsor.*

Cipla

Introduction

In a rapidly changing healthcare environment characterised by disruption and volatility, technology and data are key to a future of holistic care that will move away from treatment to prevention, from prescribing medicine to promoting wellness, from hospitalisation to home-based care.

But while technology transforms the world, healthcare professionals also need to transcend it, harnessing artificial intelligence to enable better care and empower patients. The future of health is the health of the future.

KEY MESSAGES

- Healthcare in the information age requires a paradigm shift away from working in silos
- The 'lone doctor' model of primary care needs to give way to one based on teamwork and collaboration
- Telehealth, electronic medicine and innovative home management are the future of chronic disease treatment
- All non-communicable diseases (NCDs) share two common pathogenic features, namely inflammation and atherosclerosis
- There may be considerable benefit to targeting residual inflammatory risk to reduce the risk of cardiovascular events
- Point of Care tests play an important role in reducing the disease burden of NCDs while new technologies allow for laboratory testing to be more personalised
- Pharmacogenomics, the study of how genotype affects response to medication, facilitates choosing the most appropriate drug and dose and may reduce overall healthcare costs
- Genomic medicine involves genotyping and, where feasible, gene manipulation to prevent, diagnose and treat disease.

*A report based on a symposium focussed on improving clinical practice held in Johannesburg, 24-25 August 2019

Dr Riaz Motara
Cardiologist
CEO of Brandmed

Family practice reimagined with better care of chronic NCDs

Healthcare is a continuum and a new healthcare system needs to deliver on that continuum. This will require a move away from the current industrial age of medicine that has lasted the last 100 years. The change is not only about digital solutions. Critical to a health system of the information age will be to move away from working in silos.

"Everyone works in their own silo and there is little or no sharing of data, to the detriment of the patient. Diseases too are treated in silos, even though many NCDs exist together and should therefore not be treated in isolation."

Critical to a health system of the 'information age' will be to move away from working in silos

The view persists that doctors are responsible for everything. The 'lone doctor' model of primary care is currently in crisis. Burnout is common and many leave practice within two years of starting.[1] The burden of disease is growing and resources become fewer and fewer, including the number of doctors.

The lone doctor model has a broad negative impact on patients. Aspects affected include access (e.g. getting a prompt appointment) and care co-ordination (a high proportion of referrals to specialists are not accompanied by any supporting information from the primary care practitioner). In 25% of visits, the doctor does not ask the patient about their concerns. Despite well-designed guidelines, many NCD patients are poorly managed/controlled. So a future healthcare system will need a focus on outcomes-based care.

As patient volumes increase, value is still expected despite the same amount of time and resources. Cost drivers that require attention include worsening epidemiology, unnecessary hospitalisation, over-servicing, fraud and doctor-hopping because of patient mistrust. These and others need to be addressed when designing a new system.

There are exciting technological developments in progress, including biotechnological advances targeting the microbiome to create new drug classes, gene replacement therapy and 3-D organs that mimic actual living organs. The latter means that in a lung transplant the patient will in effect get their own lungs back. "But one cannot simply design new technologies and deploy them in an existing system. Practice itself needs to be reimagined."

Central to this paradigm shift is the move from *I* to *We,* from *He*/*She* to *They* and from *My Patients* to *Our Patients*. "You cannot do it alone. Everything going forward is about collaboration. Teamwork is essential and the formerly lone doctor needs to become a team leader." The team doesn't necessarily need to be large one and can grow as needed. Teams will allow practices to become multidisciplinary 'patient care medical homes' that are patient-centred and emphasise lifestyle/wellness. They will embrace functional medicine, viewing the body as a human whole and not as separate organs or body parts.

"So embrace change, transcend your fears and transform your practice and yourself"

Practices such as this would be able effectively to address the entire spectrum of chronic NCDs making use of technology to support the process. For example, distance telehealth consultations can obviate the need for face-to-face consultations, without sacrificing empathy and the doctor/patient relationship. While the future of practice may be data-driven, the patient needs to remain at the centre of the healthcare pathway. "So embrace the change, transcend your fears and transform your practice and yourself."

Professor James Ker
Specialist Physician
Pretoria

Home monitoring for NCDs – past, present and future

Chronic NCDs carry a considerable burden. Self-management and home monitoring are becoming central to delivering high-value healthcare and represent a paradigm shift in the management of these conditions.

Home monitoring improves self-management and perceived benefits thereof include reduced use of hospitals and other resources, reduced complications, better outcomes and positive effects on costs. However, better research is required to confirm these impressions as there are no randomised controlled trials to get rid of bias and confounders. However, numerous quantitative and qualitative studies have shown that it has positive outcomes, whereby a formerly passive patient being treated by a paternalistic doctor is empowered to participate actively in their own healthcare. Self-management was shown to be associated with better adherence to prescribed medication and treatment plans, better clinical outcomes, better patient-orientated outcomes, e.g. quality of life, and an improved doctor/patient relationship. These positive effects can be ensured with patient-centred training, using nurses to assist and the use of a structured self-management plan for the patient and treatment plan for the practitioner. Importantly too, doctors need to trust and accept the patient's self-management, allow them to express their own ideas in this regard and ensure that there is no discrepancy between their view of the disease and the patient's.

Taking hypertension as an example, the issues are as follows: adherence to drugs and lifestyle measures, reaching target blood pressure, control of blood pressure and, crucially, understanding blood pressure variability. In the latter instance, 24-hour ambulatory monitoring and home monitoring play an important role. "Home-based monitoring is now in international guidelines, having been shown to provide a more precise assessment of cardiovascular prognosis. It identifies masked and white-coat hypertension, which are often missed by clinic readings. Empowering the patient in the management of their condition improves control and adherence."

Collective data on self-management of hypertension, including home-based blood pressure monitoring, have shown that it helps to address poor understanding of the condition, improving treatment adherence. It allows for individualised targeted treatment fostering a better therapeutic alliance between doctor and patient characterised by congruent beliefs and perceptions and better communication, as home-based monitoring with feedback promotes better adherence to medication. Providing information alone is not effective. "Better self-management leads to better blood pressure reduction and thus to better outcomes."

Hypertension management is in need of transformation. The digital revolution is making a meaningful contribution to this change, and home-based monitoring is at the heart of it.[2] "Telehealth, electronic medicine and innovative home management are the future."

"Home-based monitoring is now in international guidelines, having been shown to provide a more precise assessment of cardiovascular prognosis"

Professor Paul Rheeder
Faculty of Health Sciences
University of Pretoria

Diabetes care – the old, the new and the future

The public sector in South Africa still follows the traditional paradigm for treating type 2 diabetes, one that requires revision given new data available in 2019. This traditional paradigm means that after diagnosis step one is metformin, step two is to add a sulphonylurea and step three is insulin therapy.

The new paradigm is patient-centric, recognising that all patients are unique and require thorough individualised assessment before treatment is prescribed. Decision-making should be shared and a treatment plan agreed upon. Once implemented, ongoing monitoring and support need to be offered.

The development of novel diabetes drugs has explored the mechanisms implicated in the development of diabetes (such as insulin resistance or lack of insulin secretion).[3] Metformin is the classic diabetes drug, improving insulin resistance, and has additional useful effects in respect of being anti-inflammatory and anti-cancer. New treatments include the incretin-based therapies, the GLP-1 agonists and DPP-4 inhibitors. Their advantages include a low risk of hypoglycaemia.

The former promote weight loss, but have a number of concerning side-effects. Cost is also a factor. The latter are weight neutral, but not especially potent drugs. All new medications for diabetes now require evidence of cardiovascular safety/benefit and in this regard the GLP-1 agonists, liraglutide and semaglutide, were shown to reduce deaths from cardiovascular causes.[4]

Both GLP-1 agonists and SGLT-2 inhibitors reduce combined cardiovascular outcomes in patients with established atherosclerotic disease, but depending on dose, have different effects on glucose, blood pressure and weight.

SGLT-2s are not especially potent as antidiabetic agents and may not be game-changers in glucose control. But all agents in this class have weight and blood pressure benefits and offer clinically significant risk reduction across composite cardiovascular endpoints. Across the board, they also reduce the progression of kidney disease. While they do carry a risk of urinary tract infections, these are relatively infrequent and the risk low.

Current US guidelines recommend individualising targets and considering two drugs at baseline if HbA_{1c} is >9%. It is now recommended that insulin be delayed as long as possible, but should be used from baseline when HbA_{1c} is >10%.

Once a patient is on metformin, what should come next? If there is established disease (CVD), either a GLP-1 or SGLT-2 is recommended. Both of these as well as DPP-4s are options if avoiding hypoglycaemia is a priority, while GLP-1s have the most benefit on weight loss. "Where cost is a factor, as in the public sector, we're still limited to sulphonylureas."

Technology will also become increasingly important, e.g. in the form of continuous glucose monitoring which may completely replace capillary glucose testing in future. This, together with insulin pumps, already plays a role, especially in type 1 diabetes. Harnessing data also adds value when used consistently and interpreted accurately and can be used to improve patient compliance. In future, subcutaneous GLP-1s will be taken weekly, rather than daily; they may even be taken orally. There is also the possibility of combining long-acting insulin with the GLP-1 agonist lixisenatide. "We are moving into an exciting future of personalised diabetes care."

Current US guidelines recommend individualising targets and considering two drugs at baseline if HbA_{1c} is >9%

Professor Greg Tintinger
Pulmonologist
Pretoria

Clinical opportunities to target Inflammation and anti-inflammation in NCDs

'Non-communicable diseases' is a broad term for a group of diseases that are, for the most part, not associated with infectious organisms.

There are four main NCDs, namely, namely CVDs, cancers, diabetes and chronic lung diseases, which account for 80% of NCD deaths, and they share in common four behavioural risk factors – tobacco use, excessive alcohol consumption, poor diet and lack of physical activity.[5,6] Atherosclerotic CVD is responsible for the greatest morbidity and mortality. The leading risk factors and diseases accounting for global deaths and disability-adjusted life years are hypertension (approximately 18% and 7%), ischaemic heart disease (approximately 14% and 5%), tobacco smoking (approximately 12% and 6%) and cerebrovascular disease (approximately 11% and 4%).[7]

In South Africa, the age-standardised death rates for NCDs are now higher than those from HIV/AIDS and tuberculosis combined, and, as in other parts of the world, CVD is the most common NCD.[8] More than two-thirds of South African women and almost one-third of men are overweight or obese and a recent cross-sectional study of adults presenting for elective surgery during a one-week period in the Western Cape showed that 52% had hypertension.[8,9]

In addition to the high prevalence, morbidity and mortality associated with NCDs, they share two common pathogenic features, namely inflammation and atherosclerosis.

Two specific cell types, the endothelial cell and the monocyte/macrophage, play a crucial role in the development of atherosclerosis. Vascular endothelial cells help to regulate perfusion and blood pressure by producing a variety of chemical messengers that control vascular tone, blood flow, immune cell and platelet activity/adhesion. Normal endothelial function supports vasodilatation; inhibition of cell growth and maintenance of normal vascular wall structure; and inhibition of thrombosis, inflammation and angiogenesis. Conversely, endothelial dysfunction is associated with vasoconstriction, inflammation, reduced anticoagulant properties, expression of adhesion molecules and release of chemokines and other cytokines, as well as production of reactive oxygen species from the endothelium. Classic CVD risk factors (Table 1) are all associated with impairment of endothelial cell function, and endothelial dysfunction occurs early in the development of atherosclerosis. It is an early predictor of subsequent cardiovascular events and mortality.

Table 1. Pathophysiological stimuli of endothelial cell dysfunction in atherosclerosis[10-12]

• Genetic susceptibility
• Hypercholesterolaemia (e.g. oxidatively modified lipoproteins)
• Obesity, physical inactivity, smoking
• Diabetes, metabolic syndrome (e.g. advanced glycation end-products, reactive oxygen species, adipokines)
• Hypertension (e.g. angiotensin-II, reactive oxygen species)
• Sex hormonal imbalance (e.g. oestrogen deficiency, menopause)
• Aging (e.g. advanced glycation end-products, cell senescence)
• Oxidative stress (multifactorial)
• Proinflammatory cytokines (e.g. interleukin-1, tumour necrosis factor)
• Infectious agents (e.g. bacterial endotoxins, viruses)
• Environmental toxins (e.g. cigarette smoke, air pollutants)
• Haemodynamic forces (e.g. disturbed blood flow)

Table 2. Factors that contribute to the pro-inflammatory substrate within the arterial wall (intima)	
1.	Cholesterol crystals, reactive oxidants, matrix metalloproteinases, cytokines, cellular debris
2.	Dysfunctional endothelial cells, activated macrophages, modified smooth muscle cells, T-cells and neutrophils
3.	NLRP3 inflammasome complex inside macrophages

In addition to endothelial dysfunction and in contrast to the robust inflammatory response due to exogenous mediators (e.g. infectious agents), endogenous mediators of inflammation, such as those associated with the tissue stress caused by smoking, obesity and hypertension, generate a low-grade inflammatory response (called para-inflammation), in which fever is absent, white cell count is normal and C-reactive protein (CRP) is only mildly raised. Para-inflammation is present in all NCDs and contributes to the initiation and progression of atherosclerosis.

Detection of inflammation may be helpful to estimate future cardiovascular risk and to determine who may benefit from anti-inflammatory therapies

An early event in the pathogenesis of atherosclerosis is development of a fatty streak, due to selective recruitment of circulating monocytes into the intima where they differentiate into macrophages and internalise modified lipoproteins to become foam cells. This is followed by migration and proliferation of vascular smooth muscle cells inside the vessel wall, and synthesis of extracellular matrix components within the intima, thereby generating a fibromuscular plaque. With progressive structural modelling, a fibrous cap develops, which overlies a lipid-rich necrotic core consisting of oxidised lipoproteins, cholesterol crystals, cellular debris and varying degrees of calcification (Figure 1). Macrophage-mediated removal of cellular debris and dead cells is impaired inside the atherosclerotic plaque and the plaque contents are pro-inflammatory. Damaged tissue and cholesterol crystals activate the immune response and, because anti-inflammatory mechanisms and resolution of inflammation are impaired, vascular inflammation becomes chronic and persistent (Table 2).

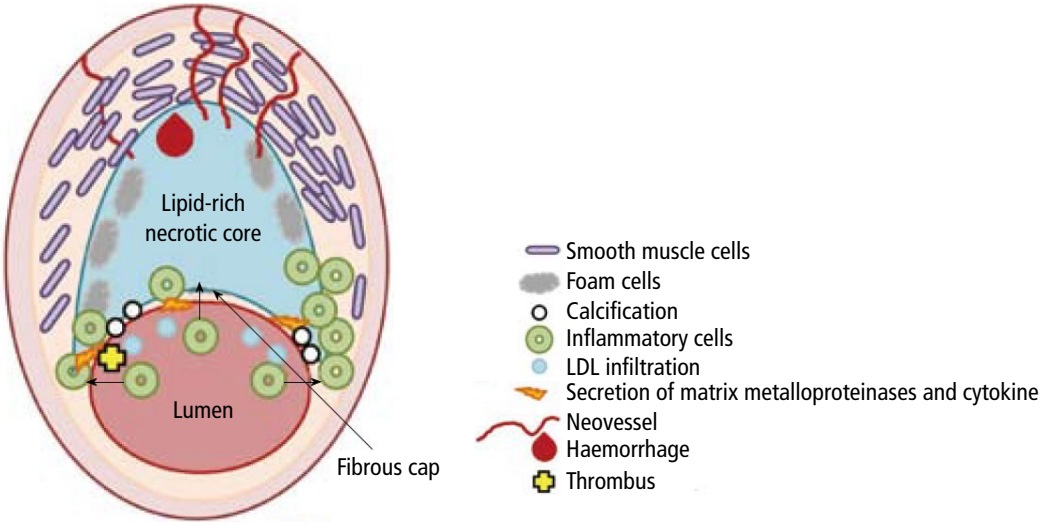

Figure 1. Diagram of a thin fibrous cap atheroma
World J Radiol 2012 August 28; **4**(8): 353-371

The inflammasome is a multiprotein molecule inside macrophages that induces and amplifies inflammation. It is primed and activated by oxidised LDL and cholesterol crystals and it is the key mediator of interleukin (IL)-1 family cytokine production, which are important vascular and systemic inflammatory mediators that contribute to atherosclerosis (Figure 2). IL-1β causes activation of secondary inflammatory mediators, including IL-6, which is pro-inflammatory and acts systemically to elicit the acute phase response, with hepatic production of acute phase proteins including CRP, fibrinogen and plasminogen activator inhibitor (PAI).[13,14]

The lateral edges of the atherosclerotic plaque contain high concentrations of

inflammatory cells, including activated macrophages and T cells, natural killer T cells and dendritic cells, which render the plaque structurally unstable and increase the risk of plaque rupture. When the plaque ruptures the highly atherogenic contents are released into the vessel lumen, triggering thrombosis, which occludes the vessel, resulting in tissue ischaemia. [7, 10-12]

It can be seen therefore that inflammation plays a key role in the occurrence of cardiovascular events and other NCDs. It precedes the development of the atherosclerosis and leads to the development, progression and destabilisation of atherosclerotic plaques, and to the rupture of vulnerable plaques. Consequently, detection of inflammation may be helpful to estimate future cardiovascular risk and to determine who may benefit from anti-inflammatory therapies. Localised inflammation (in the plaque) can be detected using scanning techniques, including positron emission tomography scanning, magnetic resonance imaging and intravascular ultrasound. There are numerous biomarkers of systemic inflammation (Table 3). Currently, high-sensitivity CRP (hsCRP) is most useful to monitor systemic inflammation and detect ongoing low-grade inflammation. Levels ≥2-3 mg/l indicate para-inflammation associated with increased cardiovascular risk, whereas >10mg/l suggests presence of infection.

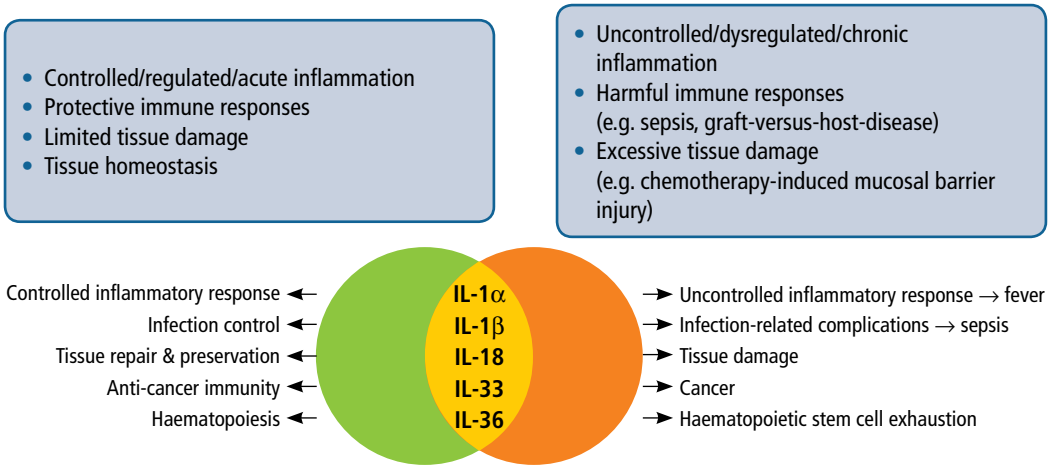

Figure 2. Effects of IL-1 family of cytokines
de Mooij CEM, *et al*. *Blood* 2017;**129**(24):3155-3164.

Table 3. Biomarkers of systemic inflammation[15]

• hsCRP (≥2mg/l indicates cardiovascular risk; >10mg/l suggests infection)
• Neutrophil:lymphocyte ratio (>4.5 predicts future cardiovascular events)
• Serum amyloid A
• Cytokines – IL-6 – IL-18 – Monocyte chemoattractant protein-1 (MCP-1) – Tumour necrosis factor (TNF)-α
• Adhesion molecules – Vascular cell adhesion molecule-1 (VCAM-1) – Intercellular adhesion molecule-1 (ICAM-1) – E-selection – P-selection
• Pentraxin-3 (acute phase reactant)
• Fibrinogen
• Apolipoprotein-associated phospholipase A2
• Soluble CD40 ligand

Several studies indicate that the cardiovascular risk associated with para-inflammation is comparable to that associated with systolic hypertension and hypercholesterolaemia, and that there may be considerable benefit to targeting residual inflammatory risk to reduce the risk of CVD events. In the Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS), treatment with canakinumab (150mg), a monoclonal antibody targeting IL-1β, in patients with previous myocardial infarction (MI) and CRP >2mg/l, was associated with a reduction in hsCRP levels and a statistically significant 15% reduction of the composite primary endpoint of nonfatal MI, stroke or cardiovascular death.[12] Other medications that have been shown to reduce CRP include ezetimibe and statins (rosuvastatin 20 mg daily reduced CRP by almost 40%). Both are associated with reduced LDL levels and a reduction in cardiovascular events. Colchicine can reduce CRP by 60%, and in the LoDoCo randomised study, in comparison with placebo, treatment with colchicine 0.5mg daily reduced the primary outcome of acute coronary syndromes, out-of-hospital cardiac arrest and non-cardioembolic ischaemic stroke by 67%.[13]

In the secondary prevention setting, patients with high hsCRP should be managed by addressing all modifiable risk factors (e.g. hypertension, smoking, diabetes, obesity), by treating with statins according to guidelines,[18] and where hsCRP remains ≥2mg/l, considering targeted therapy to reduce para-inflammation. In the primary prevention setting, in addition to Framingham cardiovascular risk assessment, measuring hsCRP can be helpful in deciding who should receive treatment with a statin.[18] Regular exercise reduces low grade systemic inflammation and, at least for most people, is likely to be an important strategy for prevention of CVD.[19]

Medications that have been shown to reduce CRP include ezetimibe and statins (rosuvastatin 20mg daily reduced CRP by almost 40%)… Colchicine can reduce CRP by 60%

Current technological disrupters in healthcare

Balancing sympathetic and parasympathetic function

Dr Costa Kapnias
Panorama Healthcare Centre
Cape Town

Lifestyle diseases are a major public health problem worldwide. Importantly, chronic stress is known to have a significant impact on health. It has a complex interaction with the immune system, suppressing immune function under some conditions and enhancing it under others. This dysregulation of immune function is associated with increased susceptibility to infections and cancer; exacerbations of asthma and allergic, autoimmune and inflammatory diseases; and long-term elevations in local and/or systemic inflammatory mediators that are thought to contribute to various disorders including CVD, obesity and depression.[20] Therefore, there exists a significant challenge to manage lifestyle efficiently in a way that produces positive and useful outcomes, while avoiding negative effects. A new paradigm in lifestyle management is to combine human and artificial intelligence to provide an individualised comprehensive analysis of all components of the patient's lifestyle, including physiological feedback, to design a lifestyle intervention programme that will improve health, quality of life and productivity. Regular monitoring of progress, in terms of autonomic, cardiac and metabolic state, enables timeous adaptations of the management programme to optimise outcomes.

There are three stages in the stress response. The initial stage, when the stressor is first perceived (and it may be real or imagined), acts at the level of the brain. The hypothalamus co-ordinates a cascade of events including activation of the autonomic nervous system, release of corticotrophin-releasing hormone (CRH) and stimulation of the hypothalamic pituitary adrenal axis, and secretion of arginine vasopressin (antidiuretic hormone

The Omegawave system is a novel, noninvasive tool that measures physiological responses to psychological stress

(ADH)). The autonomic response to perceived stress is to activate sympathetic activity, causing release of adrenaline and noradrenaline at various neural synapses preparing the body for flight or fight. Physiological responses include increased heart rate and force of myocardial contraction, vasodilation of arteries in working muscle and vasoconstriction in nonworking muscles, dilation of the pupils and bronchi, and reduced activity of the digestive system. Under normal circumstances these effects only last a short time. The second and intermediate-acting phase of the stress response occurs due to release of corticoids (glucocorticoids [cortisol] and mineralocorticoids [aldosterone]) from the adrenal cortex in response to CRH-induced stimulation of adrenocorticotropic hormone release. The primary function of glucocorticoids is to release energy by glycogenolysis and lipolysis. However, glucocorticoids also have other effects that can be detrimental in the longer term, including appetite suppression, immune dysregulation, exacerbation of gastric irritation, and feelings of depression and loss of control. Mineralocorticoids promote sodium retention and secretion of adrenalin from the adrenal medulla, both of which may contribute to a sustained increase in blood pressure. ADH secretion also contributes to changes in blood pressure. When the stressful situation remains unresolved, the body adapts to chronic stress with a continuous maintenance of the aroused state and release of stress hormones. This maladaptive stress response may result in a number of physiological and psychological problems (Table 4).[21,22] Due to the gradual decline in immune function that occurs with age (immunosenescence), chronic stress may be particularly problematic for older people.[22]

If the stressor is sufficiently dealt with or removed, the body will recover. However, with sustained exposure to stress, exhaustion may result when the body is unable to maintain normal function.

Table 4. Symptoms of sympathetic overdrive and chronic exposure to perceived stress[21-24]

• Tachycardia, hypertension, vascular and left ventricular hypertrophy
• Flushing
• General tiredness, fatigue and chronic fatigue syndromes, myalgia
• Hyperhidrosis
• Anxiety, depression, burn-out, irritability, panic
• Sleep disturbances
• Impairments of concentration and short-term memory
• Diarrhoea, indigestion, symptoms of irritable bowel syndrome
• Dysregulation of immune system, slower wound healing and recovery from trauma/surgery, allergies, increased susceptibility to infection
• Changes at the cellular level, e.g. inflammation, oxidative damage to mitochondria and DNA
• Increased use of alcohol and drugs
• Poor interpersonal relationships

It is estimated that up to 40% of South Africans suffer from high stress.[23] Many individuals in the corporate environment, which is characterised by long working hours, travel, erratic or infrequent physical activity, psychological stress and impaired work/life balance, are particularly prone to the effects of chronic stress and its associated health risks.[24] Frequently these remain undiagnosed and unmanaged. In one study, 31% of corporate executives belonging to a specialist health and fitness company in South Africa met the criteria for diagnosis of metabolic syndrome.[25] In another, more than 70% of corporate executives had pre-hypertension or hypertension, and among these individuals more than 50% reported having a sedentary lifestyle, were obese and/or had a total cholesterol ≥5.18mmol/l.[26]

These figures highlight the necessity for personalised intervention to assist

individuals in recognising stress levels and risk factors and to guide a biopsychosocial management plan for a healthier lifestyle.

The Omegawave system is a novel, noninvasive tool that measures physiological responses to psychological stress. The assessment takes four minutes and is undertaken while the individual is at rest. It measures functional states (i.e. level of sympathetic overdrive and ability of the body to adapt and recover), including the brain (EEG), heart (amplitude-frequency analysis of ECG and 20 different parameters of heart rate variability), metabolic (metabolic reaction index) and autonomic nervous systems, which form the basis of general well-being. Originally developed for use in athletes to identify optimal real-time adjustments to training loads and thereby improve athletic performance, the Omegawave has proved to be an invaluable tool to assess and monitor health and well-being among corporate executives. Results can be tracked over time, allowing assessment of functional state on a continual basis to monitor response to lifestyle and, if necessary, medical interventions, and guide timeous modifications of lifestyle and medical management. An important benefit of the Omegawave is that the results of each parameter are presented graphically, providing a simple visual representation of health risk and the benefits of intervention, enabling the individual to focus on behavioural changes and techniques that work for them to reduce stress responses from day to day and whenever they feel they need to.

Omegawave forms part of a comprehensive corporate wellness assessment, which includes a full medical examination, relevant blood tests, cardiovascular assessment and lung function. Clients are trained in stress management techniques and lifestyle modification and, where necessary are referred for appropriate further medical management.

More information may be found at: https://readyroom.info.

HearScreen is the world's first clinically validated hearing screening solution and can easily be used even by people with minimal training

Digital hearing solutions

Professor De Wet Swanepoel
Department of Speech-Language Pathology and Audiology
University of Pretoria

Hearing loss is a devastating condition because it takes away a person's connection to the world. It is associated with social isolation, depression, cognitive decline and a reduced quality of life. It's a global problem that costs $750 billion per year. Treatment is inaccessible and unaffordable for many. Digital solutions now offer a way to make a scalable impact on the problem.

Research at the University of Pretoria has produced a number of innovative solutions that are being commercialised and developed by the hearX group. They are cost-effective, time-efficient and reliable. HearScreen is the world's first clinically validated hearing screening solution and can easily be used even by people with minimal training. HearTest is the diagnostic version of HearScreen. It operates via a smartphone linked to calibrated headphones and a cloud-based management platform. HearScope is the world's first smartphone-based otoscope that also offers a forthcoming artificial intelligence system for supported diagnoses.

Digital solutions such as these are already changing service delivery models. A programme is under way in Khayelitsha that is on par with those in high-income countries but facilitated in communities by community members. Digital solutions offer accessible and affordable care and advanced data tracking, analysis and reporting; they can enable long-term quality of life gains and cost-savings.

Dr Evette Venter
Dietitian
Founder of Cell Restore
Cape Town

Personalised nutritional assessments

Personalised medicine harnessing the use of new technologies is the future. Nutrition is no exception and personalised supplementation is an innovative way of addressing nutritional imbalances at cellular level.

There is a growing epidemic of diseases of lifestyle, and current outcomes are often not good. Customising nutrition in the same way we customise drug treatments with pharmacogenomics has a role to play in this regard.

A major problem in medicine is treating only what is visible. Rather, nutrition should be viewed at cellular level. Cells are the building blocks of life, protecting DNA from damage, providing energy, enabling cell-to cell communication and responding to both internal and external signals. Nutritional strategies therefore need to focus on cellular health and protecting cells from damage.

Nutritional strategies need to focus on cellular health and protecting cells from damage

The two main problems of current nutrition are malabsorption of nutrients and the often degraded quality of nutrients today. The former can have multiple causes, including infection/inflammation, prolonged use of antibiotics and stress. The latter can be the result of toxins such as dyes and pesticides. Cows that are grain-fed rather than grass-fed produce less nutritious meat and dairy products, for example.

Supplementation is therefore a modern-day necessity, but it needs to be targeted. Patients need to be thoroughly assessed, further to which a customised supplement, personalised to a specific patient, can be developed taking into account age, weight, gender, blood test results and overall health status. The use of mindfully formulated supplements will have positive impacts on a patient's health further down the line.

Dr Shikha Sharma
Scientific Affairs Manager
Abbot Laboratories, India

The future of Point of Care in family practice

Point of Care tests (POCTs) are already widely available and used in family medicine to facilitate risk assessment, diagnosis, staging and prognosis, therapy selection, and referral decisions for a variety of conditions. Much of this technology, although relatively new to South Africa, has been around for several decades and is believed to have tremendous potential in reducing delays in diagnosing and initiating treatment for several diseases such as HIV, tuberculosis and malaria. Results can be obtained within minutes at the patient's site of care, so there are considerable benefits in respect of speed, convenience and portability. The ability of POCTs to provide drastic improvement in the turnaround time of test results has led to improved clinical outcomes and increased patient and doctor satisfaction.

Also, POCTs have an important role in reducing the disease burden of NCDs, such as CVDs (like heart attacks and stroke), cancers, chronic respiratory diseases (such as chronic obstructive pulmonary disease and asthma), chronic kidney disease and diabetes.

The ability of POCTs to provide drastic improvement in the turnaround time of test results has led to improved clinical outcomes and increased patient and doctor satisfaction

Dr Jessica Trusler
Clinical Pathologist
Ampath Laboratories
Johannesburg

New solutions in laboratory and pathology services

Technology is also transforming the laboratory and pathology sector and advances as recent as 2016 can be seen as a 'black swan event' – the availability of unprecedented computer speed and power, and the ability to transmit large data files. This has greatly increased laboratories' ability to give doctors the tools to treat NCD patients most effectively, using baseline tests to compare individual change. "While Point of Care has its place in the acute and outpatient setting, there are still tests that even now can only be done in laboratories."

For example, many more genetic tests can now be done for conditions such as hypercholesterolaemia, to look for cancers, to assist in diagnosis of syndromes and even when looking at the microbiome and its relevance to health. New technologies allow for this testing to be more personalised, and it is important to use laboratory personnel to help make greater sense of all the information, given how vast a subject genetics is. 'We are now better equipped to look at cause and effect, in order to detect 'real' problems. Connectivity has changed the playing field, allowing better access to data formerly in silos and enabling us to get results back more quickly. Continued automation of even routine processes ensures more meaningful experiences and interactions. It's not just artificial intelligence, it's augmented intelligence."

"While Point of Care has its place in the acute and outpatient setting, there are still tests that even now can only be done in laboratories."

Professor Michael Pepper
Institute for Cellular and Molecular Medicine
University of Pretoria

Genomic medicine will improve therapeutic outcomes

The human genome consists of six billion base pairs that need to be replicated, packaged and segregated with precision and fidelity each time a cell divides. There are 20 000 genes, comprising approximately 1.5% of the genome, which code for structural and regulatory proteins. Most human characteristics are polygenic, with the expression of many genes contributing to a specific and particular phenotype, and even small variants (polymorphisms) in these genes can account for differences between individuals. However, gene expression is not fixed. It can be profoundly affected by events (errors) that occur during cell division, and especially by environmental influences (epigenetic variation). These include childhood experiences, psychological stress, food and chemical exposures, which lead to suppression or expression of genes, the effect of which may be neutral, beneficial or deleterious to the individual.

Genomic medicine involves genotyping (i.e. identification of specific genetic variants) and, where feasible, gene manipulation to prevent, diagnose and treat disease (Table 5).

Table 5. Potential benefits of genomic medicine

Disease prevention	Genomic data and data on lifestyle (risk prediction and recommendations for preventative measures, e.g. lifestyle)
Diagnosis	New diagnostics, earlier detection, improved sensitivity and specificity; Therapeutic stratification
Treatment	Rational drug design (population-specific; pharmacogenomics); Gene therapy

Dr Jaysen Knezovich
Principal Scientist at Ampath Laboratories Johannesburg

Professor Morgan Chetty
Chairman of the IPA Foundation. Associate Professor and head of Managed Care and Health Services Management at the University of KwaZulu Natal, Nelson Mandela – School of Medicine

Pharmacogenetics in clinical practice

Because they reveal generalised results of drug therapy across a population, clinical drug trials do not take into consideration individual genetic influences that might affect outcomes of treatment. Nevertheless, a person's genotype will affect how they respond to a specific drug, both in terms of efficacy and the emergence of adverse side effects. The potential for different responses between individuals can be determined by specifically examining the genetic make-up of each individual.

Genes coding for structural or regulatory proteins (e.g. enzymes) may differ between individuals in a number of ways. Differences in single nucleotides (nucleotide polymorphisms), and insertion or deletion of bases can profoundly affect gene expression and protein structure, making each individual genetically unique. Likewise, duplication or deletion of genes will affect the amount of protein that is expressed, which may alter their phenotype (Figure 3). The opposite effects to those shown in Figure 3 would occur with pro-drugs (i.e. those that need to be activated to achieve their effects).

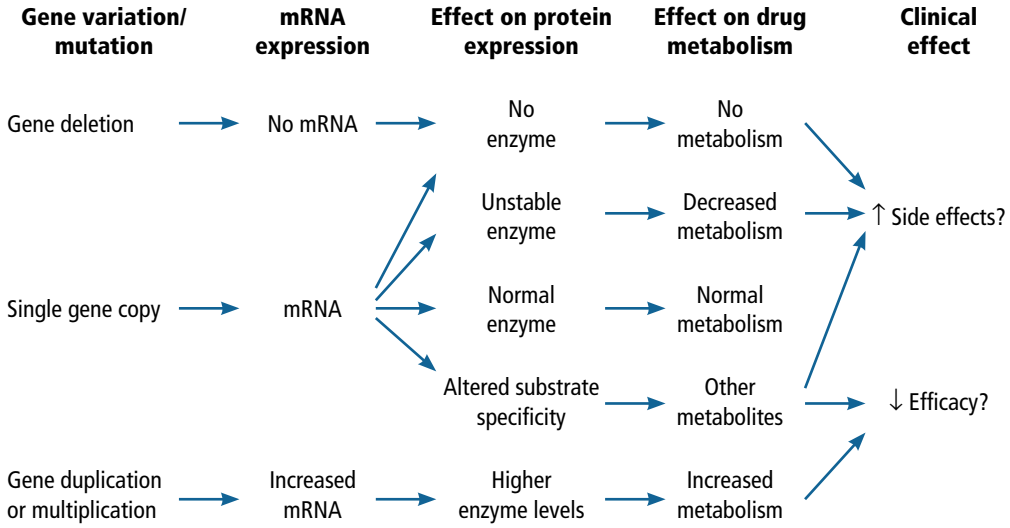

Figure 3. Potential effects of genotype on expression of proteins affecting drug metabolism

Pharmacogenomics is the study of how genotype affects response to medication and the potential risk of drug-related adverse effects. It is a step towards personalised medicine, because it facilitates choosing the most appropriate drug and dose for an individual to maximise efficacy and safety and to help ensure better adherence and therefore better outcomes. Pharmacogenomics may reduce overall healthcare costs by reducing the number of adverse drug reactions, the number of failed drug trials, the time it takes to get a drug approved, the length of time a patient needs to be on a medication, the number of medications a patient must take to find an effective therapy, and, by facilitating early detection and treatment of disease, it may reduce the effects of the disease on the body.[27]

One application of pharmacogenomics is to identify polymorphisms in the genes coding for enzymes involved in drug metabolism. With this technique patients may be classified into subgroups according to how quickly and completely they would be expected to metabolise a drug (Table 6). Depending on whether the drug is an active moiety or pro-drug and whether the metabolites themselves are pharmacologically active or inactive, the correct drug at the most appropriate dose may be selected for that individual to minimise the risk of adverse events and maximise efficacy.

Table 6. Phenotypes of drug metabolism

Phenotype	Metabolism of active component	Therapeutic implications[27]
Extensive metaboliser (normal)	Drug metabolism is normal, but there are large variations in drug metabolism in this group. There will be normal amounts of drug at usual doses	Usual dosing schedule is appropriate, but the high or low end may need dose adjustment for acceptable safety and efficacy
Ultra-rapid metaboliser	Rapid drug metabolism. May not get enough drug at normal doses	Higher than normal doses are required for efficacy and risk of side effects if metabolites are toxic. Alternative medication may be more appropriate
Intermediate metaboliser	Metabolism is slow. May have too much medication at normal doses	Lower drug clearance and higher plasma levels, with the possibility of exaggerated pharmacodynamic outcome and increased risk of concentration-dependent side effects May respond to a lower dose than normal, or an alternative medication may be more appropriate
Poor metaboliser	Metabolism is very slow. May experience side effects with normal dosing	

GeneMD is a screening test that includes 13 genes coding for proteins that are important in drug metabolism (nine genes) and for risk management (four genes). The results can be applied to guide recommendations about prescription of 140 drugs from 16 clinical categories (Table 7), i.e. to use with standard precautions, to use with caution, or to consider alternatives for current or future prescribed medication.

Table 7. Gene polymorphisms included in the GeneMD screen

Gene-drug interaction	COMT, CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, SLCO1B1, VKORC1
Risk management	Apolipoprotein E (ApoE), Factor II, Factor V Leiden, methylenetetrahydrofolate reductase (MTHFR)
Clinical categories	Cancer, cardiovascular, diabetes, gastrointestinal, Gaucher disease, gynaecology, haematology, infectious disease, multiple sclerosis, neurology, pain, psychiatry and addiction medicine, rheumatology, Sjogren's syndrome, transplantation, urologicals

Gene therapy

Gene therapy involves modification of gene expression in an individual, by replacing a gene, correcting an abnormal gene or addition of a therapeutic gene. This can be achieved by administration of specific DNA or RNA, or by genome editing, either in the germ line or in somatic cells of the affected individual. Some common indications relevant to Africa include haemoglobinopathies (e.g. sickle cell disease, thalassaemia) and HIV infection.

Ethical issues related to predictive genetic testing

Genomic medicine has ethical and social implications that need to be carefully considered. Importantly, these include issues of distributive justice (who will have access to testing and therapy, interventions are expensive) and moral controversies over who should be tested and how they should be managed in terms of pre- and post-test counselling, and what should be done with the results (Table 8). In comparison to situations where testing provides definitive results (e.g. risk of Down's syndrome), ethical issues are most likely to arise when testing merely reveals a risk and when how to proceed is uncertain. The Academy of Science of South

Africa (ASSAf) has published a guidance document that aims to address some of the ethical, legal and social implications of genetics and genomic work in South Africa[28] and this document may be downloaded free of charge at: http://research.assaf.org.za/handle/20.500.11911/106.

Table 8. Some ethical considerations for genetic testing

1.	Informed consent
2.	Privacy and confidentiality of genetic information (e.g. ownership and control of data, who should have access, how will the information be interpreted and used?)
3.	Psychosocial impact of 'at-risk' status
4.	Autonomy and conflict between views of patient and physician (e.g. patient's understanding and perception of the condition; cultural and societal perspectives vs medical professional's definition of disease, prevention and management)
5.	Familial implications (who should be told; fear of altered relationships; feelings of guilt; how to accurately communicate information to children and other family members; risk of ostracism and stigmatisation; duty of physician to disclose results to family members when the patient chooses not to)
6.	Risk (of disease and disability) communication (e.g. patient understanding, implications to family planning, fatalism)
7.	Confidentiality (e.g. potential for discrimination and misuse by employers and medical insurance companies; balance between individual privacy and best interests of family members)
8.	Direct to consumer testing (e.g. inappropriate testing, misinterpretation and misapplication of results)
9.	Justice (how to allocate resources)

References

Click on reference to access the scientific article

1. Linzer M, Manwell LB, Williams ES, *et al*. Working conditions in primary care: physician reactions and care quality. *Ann Intern Med* 2009; **151**: 28-36.
2. Dzau VJ, Balatbat CA. Future of hypertension: the need for transformation. *Hypertension* 2019; **74**: 450-457.
3. Bailey CJ. The current drug treatment landscape for diabetes and perspectives from the future. *Clin Pharmacol Ther* 2015; **98**: 170-184.
4. Marso SP, Daniels GH, Brown-Frandsen K, *et al*. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016; **375**: 311-322.
5. World Health Organization (WHO). Global Health Observatory (GHO) Data: NCD mortality and morbidity. https://www.who.int/gho/ncd/mortality_morbidity/en/. Accessed 3 September 2019.
6. Hunter DJ, Reddy KS. Noncommunicable diseases. *N Engl J Med* 2013; **369**: 1336-1343.
7. Daiber A, Steven S, Weber A, *et al*. Targeting vascular (endothelial) dysfunction. *Br J Pharm* 2017; **174**: 1591-1619.
8. Schutte AE. Urgency of South Africa to prioritise cardiovascular disease management. *Lancet.* Published Online December 6, 2018. http://dx.doi.org/10.1016/S2214-109X(18)30476-5.
9. Van der Spuy K, Crowther M, Nejthardt M, *et al*. A multicentre, cross-sectional study investigating the prevalence of hypertensive disease in patients presenting for elective surgery in the Western Cape Province, South Africa. *S Afr Med J* 2018; **108**(7): 590-595.
10. Gimbrone MA, García-Cardeña G. Endothelial cell dysfunction and the pathobiology of atherosclerosis. *Circ Res* 2016; **118(**4): 620-636.
11. Cahill PA, Redmond EM. Vascular endothelium – Gatekeeper of vessel health. *Atherosclerosis* 2016; **248**: 97-109.
12. Yamaoka-Tojo M. Endothelial function for cardiovascular disease prevention and management. *Int J Clin Cardiol* 2017; **4**: 103. Published online. DOI: 10.23937/2378-2951/1410103.
13. Grebe A, Hos F, Latz E. NLRP3 inflammasome and the IL-1 pathway in atherosclerosis. *Circ Res* 2018; **122**: 1722-1740.
14. Libby P, Rocha VZ. All roads lead to IL-6: A central hub of cardiometabolic signalling. *Int J Cardiol* 2018; **259**: 213-215.
15. Tibaut M, Caprnda M, Kubatka P, *et al.* Markers of atherosclerosis: Part 1 – Serological markers. *Heart Lung Circ* 2019; **28**(5): 667-677.
16. Ridker PM, Thuren ET, MacFadyen JG, *et al.* Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 2017; **377**(12): 1119-1131.
17. Aday AW, Ridker PM. Targeting residual inflammatory risk: A shifting paradigm for atherosclerotic disease.

This CPD accredited programme was written for *deNovo Medica* by
Dr David Webb
BSc (Hons) MBBCh
National Certificate in Exercise Science (HFPA)
and Peter Wagenaar
MA, H Dip Ed

Front Cardiovasc Med 2019; **6**: 16. Published online. DOI: 10.3389/fcvm.2019.00016.

18. Klug EQ, Raal FJ, Marais AD, *et al*. South African Dyslipidaemia Guideline Consensus Statement. A joint statement from the South African Heart Association (SA Heart) and the Lipid and Atherosclerosis Society of South Africa (LASSA). *S Afr Med J* 2018; **108**(Part2): 973-1000.
19. Mathur N, Pedersen BK. Exercise as a mean to control low-grade systemic inflammation. *Mediators of Inflammation* 2008: 109502. Published online. DOI: 10.1155/2008/109502.
20. Dhabhar FS. Enhancing versus suppressive effects of stress on immune function: implications for immunoprotection and immunopathology. *Neuroimmunomodulation* 2009; **16**: 300-317.
21. Sharma DK. Physiology of stress and its management. *J Med Stud Res* 2018; **1**: 001.
22. Schneiderman N, Ironson G, Siegel SD. Stress and health: psychological, behavioural, and biological determinants. *Ann Rev Clin Psychol* 2005; **1**: 607-628.
23. The measurement of work stress within South African companies: A luxury or necessity. *S Afr J Industrial Psychology* 2002; **28**(3): 26-31.
24. https://readyroom.info/readylife. Accessed 3 September 2019.
25. Ker JA, Rheeder P, Van Tonder R. Frequency of the metabolic syndrome in screened South African corporate executives. *Cardiovasc J South Afr* 2007; **18**: 30-33.
26. Grace J, Semple S. The prevalence of cardiovascular disease risk factors in normotensive, pre-hypertensive and hypertensive South African colliery executives. *Int J Occupat Med Env Health* 2012; **25(**4): 375-382.
27. Lu AYH. Drug-metabolism research challenges in the new millennium. Individual variability in drug therapy and safety. *Drug Metab Disposit* 1998; **26**(12): 1217-1222.
28. Academy of Science of South Africa (ASSAf), (2018). *Human Genetics and Genomics in South Africa: Ethical, Legal and Social Implications.* [Online] Available at: DOI http://dx.doi.org/10.17159/assaf.2018/0033

Published by
© 2019 deNovo Medica
Reg: 2012/216456/07
70 Arlington Street, Everglen, Cape Town, 7550
Tel: (021) 976 0485 | info@denovomedica.com