SCIENCE FOR SOUTH AFRICA

Quest

VOLUME 14 | NUMBER 3 | 2018
ISSN 1729-830X

Getting personal about psychiatry: pharmacogenetics in Africa

BASICS FOR PRECISION MEDICINE *FROM DNA TO DOCTOR*

PRECISION MEDICINE MOVING AWAY FROM ONE-SIZE-FITS-ALL

THE SCIENCE OF EVERYTHING

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CONTENTS

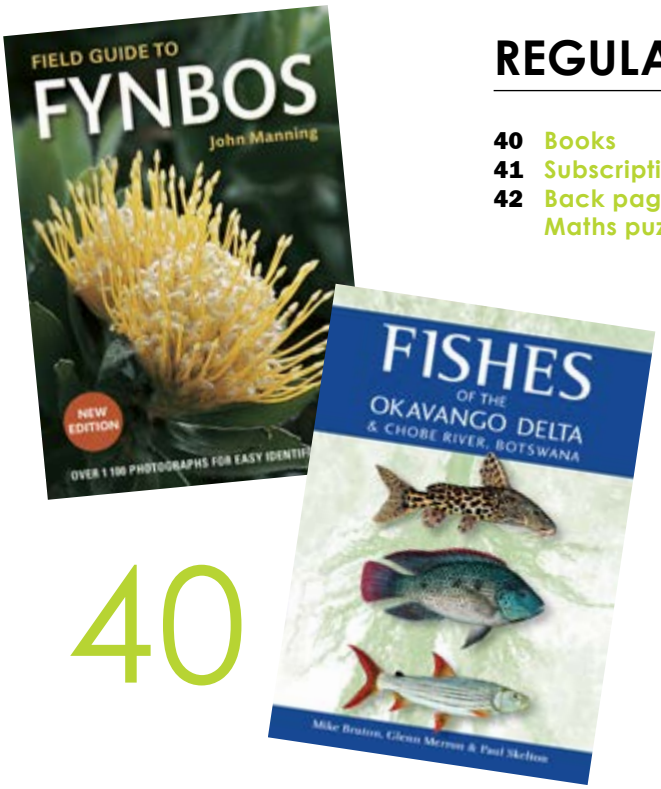
VOLUME **14** | NUMBER **3** | 2018

COVER STORIES

FEATURES

NEWS

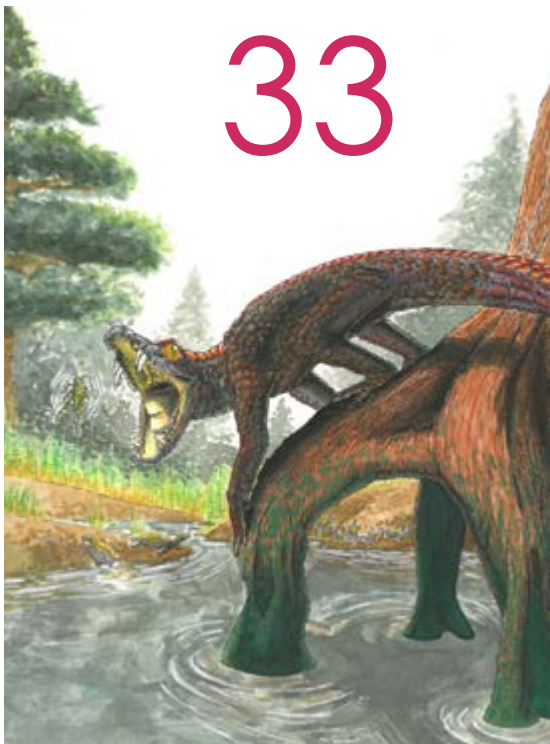
REGULARS



40

25

5



33

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Academy of Science of South Africa (ASSAf)
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(4 issues and postage)
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Design and layout
SUN MeDIA Bloemfontein

Printing
Red-Pencil Group

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Genome technologies, precision medicine and innovative therapies

We all share a common ancestry, and nowhere is this more apparent than in our genomes. Despite our differences, most of the information contained in our genomes is highly similar, if not identical. Yet it is the differences that make each of us unique. It is also these differences that have allowed for the delineation of a relatively new concept in modern medicine, namely that of 'precision medicine'. In contrast to 'personalised medicine', precision medicine aims to identify differences at a population level, thereby guiding the application of genome technologies to populations in a manner that results in improved outcomes. This is true in the three domains of prevention, diagnosis and treatment. The notion of personalised medicine on the other hand refers to the individualisation of care, which describes an ideal in which highly specific individual differences are taken into account. Given the cost, both monetary and in terms of skills required, this granularity is not technologically achievable at present across an entire population, but forms the basis for the manner in which medicine is, as far as is possible, currently practiced.

The notion that 'one-size-fits-all' in the management of human disease is not only incorrect but may in fact be dangerous. Therapies that work in one population at a given dose may not achieve the same result in another population in whom population dynamics may, over time, have resulted in the clustering of genotypic and ultimately phenotypic differences that render a given treatment either inefficacious or even frankly toxic. Likewise, diagnostic tools, configured for a given population, may not detect variants that are more prevalent in another population, thereby resulting in false negatives and therefore missed opportunities for appropriate therapies.

An exciting development in cancer immunotherapy relates to the use of cells (lymphocytes) that have been genetically engineered *ex vivo* to target and destroy patient-specific tumor cells. Positive outcomes, never before seen with blood cancers such as leukaemia and lymphoma, are now being achieved using these new therapies which have recently been approved for use in the general population, i.e. are no longer part of clinical trials. The basis for these therapies relies on the identification of a unique 'address' for each tumour to which the engineered lymphocytes are directed. Cost and the labour-intensive nature of these procedures preclude them from being applied to the entire population at present, but this situation is likely to improve, particularly as economies of scale come to bear.

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The science of everything

Reinhard Hiller explains how our understanding of DNA and the human genome can improve medical care.

Precision medicine is based on the idea that diagnosis and treatment of diseases can be boosted through the effective generation and utilisation of molecular, clinical and complementary data. In essence, precision medicine is medical care that will use genetic or molecular profiling to provide the best possible benefit for particular groups of patients. The field has largely been driven by the advent of powerful new molecular applications, notably in the form of DNA sequencing technologies that developed in the wake of the initial Human Genome Project.

Africa has been lagging in efforts to develop precision medicine solutions. Reasons, among others, include a lack of funding, adequate infrastructure, and well-trained human resources. While many African countries have had a focus on dealing with the high burden of infectious diseases, improved health provision, increased life expectancy and changes in lifestyle are causing an increase in non-communicable diseases. This, along with Africa's distinct genetic heritage, lays the foundation for creating dedicated precision medicine solutions on the continent, to the potential benefit of its own populations as well as patients across the globe.

This article provides a high-level summary of what precision medicine is, its origins, and its role in changing modern healthcare systems.

THE SCIENCE OF EVERYTHING

Deoxyribonucleic acid (DNA) is the molecule that captures the blueprint of life for all higher organisms, including humans. It contains a genetic code that:

- uses a 4-letter alphabet in the form of four distinct nucleotides, going by the name of Guanosine, Adenosine, Thymidine, and Cytosine. Or, in short, GATC
- is made up of of 3.2 billion letters
- fills a stack of paperback books 61 m high
- is 3 000 km long if printed 1mm wide
- is 100 Gbyte in size
- is organized into 22+1 chromosome pairs (XX, XY = female, male) (Figure 1), 'shelves in a library', each densely packed with human genetic information.

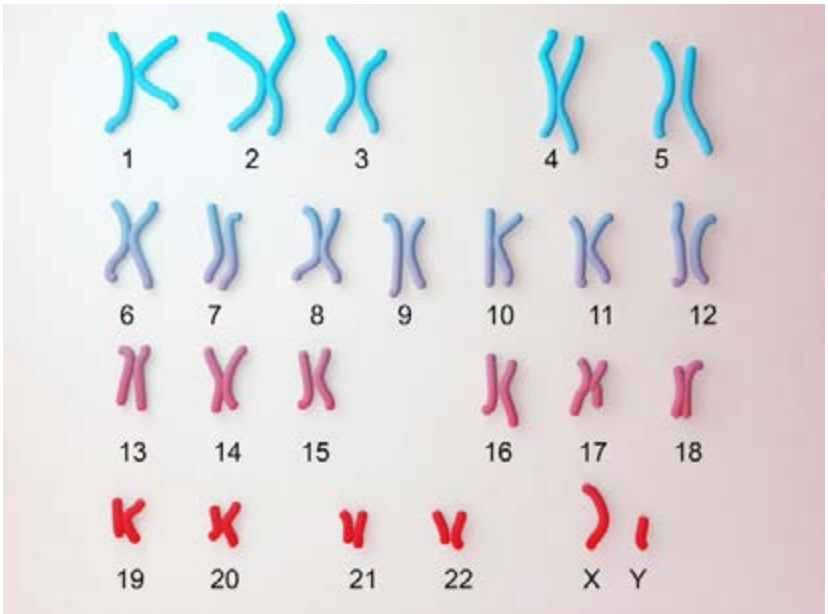

Figure 1: The human genetic code is stored in 23 pairs of chromosomes. *Getty Images*

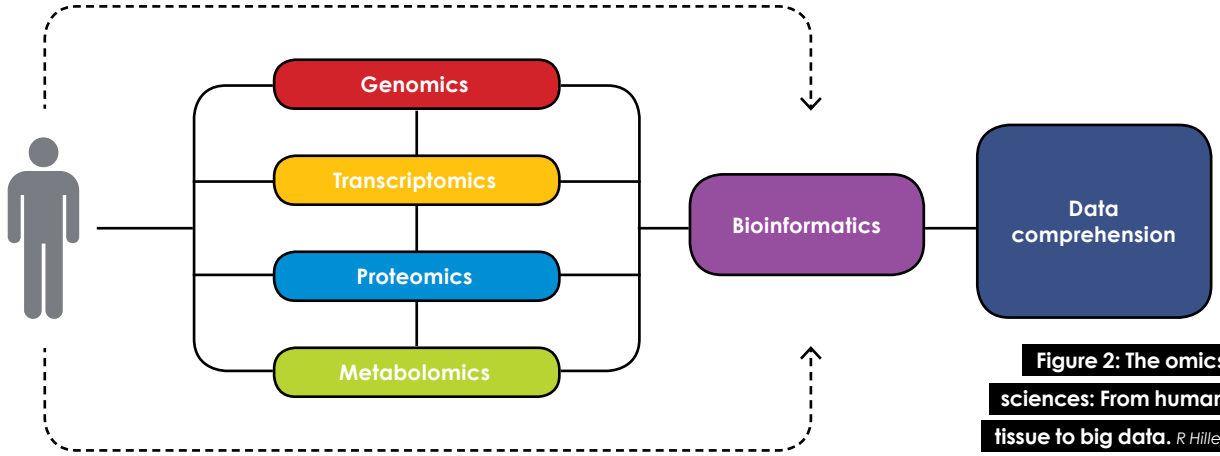

Figure 2: The omics sciences: From human tissue to big data. *R Hiller*

DNA is organised into discrete storage blocks, called genes. Humans have in the order of 22-25 000 genes. Genes are transcribed into the building blocks of cells, organs and bodies, through a sequential process of DNA conversion into ribonucleic acid (RNA), and proteins (central dogma of biology). Remarkably, only 1.5% of the genetic code comprises genes, the remainder is – to date – without clear or known function.

Although humans share the same genetic code, everyone can have a slightly different version of a gene. These gene versions are called alleles. The diversity is generated by 100s of 1000s of subtle differences in the 'GATC' letter code. Most of these sequence variations, like typos in the transcript of a written text, do not alter the meaning of a protein; they are biologically neutral and medically harmless. However, some changes may lead to an increased risk of having a specific trait or for developing a disease and are therefore the intensive focus of genetic research.

The complete complement of genes in a cell, or body, is called genome ('*ome*' is a suffix derived from Greek, for 'everything'). The study of all genes is called genomics; similar 'omics' terms have been coined for the study of all RNA, protein, or metabolite molecules (Figure 2).

As evident from the increase in scientific publications generated annually (Figure 3), the omics disciplines took off in the early 2000s and are set to shape life and biomedical sciences in the 21st century.

The rise of these disciplines has contributed to the explosion and increasing availability in computational capacity, needed to convert large-scale data sets into meaning. This occurs through the application of statistical analysis that correlate molecular omics data with other biological or patient data. This discipline is known as bioinformatics (Figure 2).

For example, the Million Veterans Project (MVP), in the US, is using questionnaires, electronic health records, and blood samples for genomic and other testing, to generate one of the biggest aggregate data repositories in the world. The increase in scope and scale of molecular and related (patient) data has exacerbated the need for even more sophisticated means of data analysis. This is leading researchers increasingly to look for help in the field of artificial intelligence, using deep or machine learning approaches to search for patterns, and meaning, in data sets.

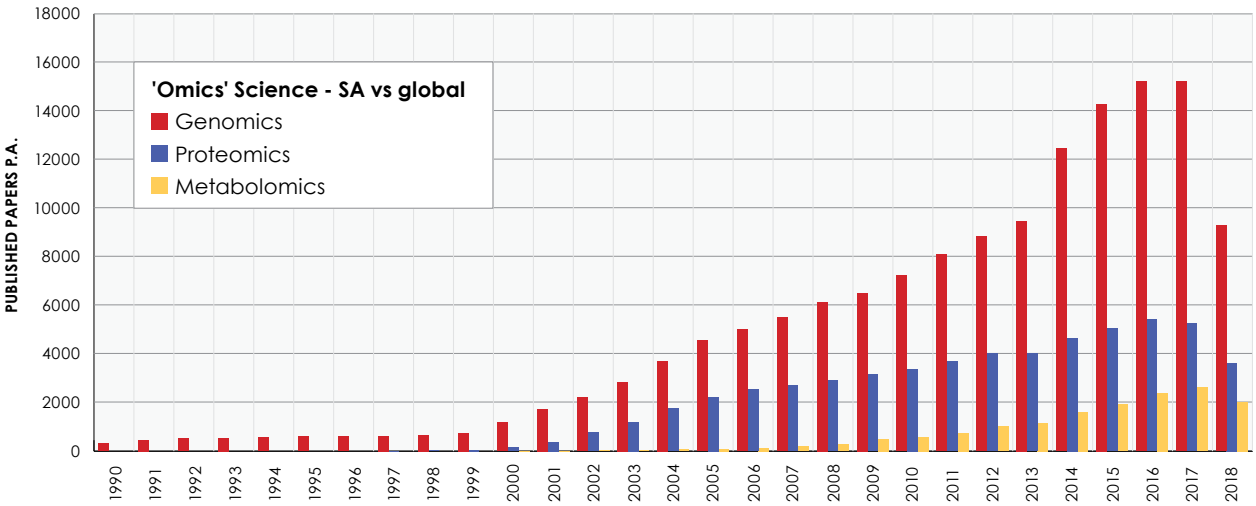

Figure 3: Omics publications over time. *Data sourced fromhttps://www.ncbi.nlm.nih.gov/pubmed/*

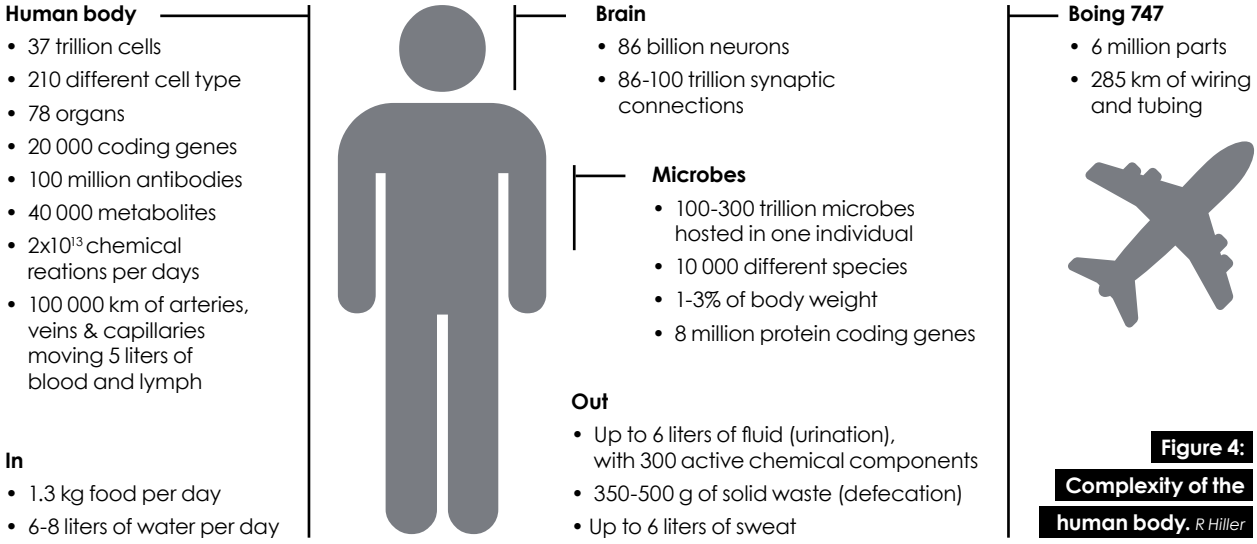

Figure 4: Complexity of the human body. *R Hiller*

A DATA-INTENSIVE APPROACH TO GRAPPLING WITH THE COMPLEXITY OF HUMAN BIOLOGY

The omics approach has shaped modern life and biomedical sciences. It evolved from a 'single-gene' to 'complete-gene' approach, to better understand the biological complexities inherent in cells, organs, and entire bodies. It aims at creating a 'systems view' in order to better clarify causes of disease development and the way in which these diseases progress.

The omics field was initially boosted by technical advancements in DNA sequencing, the process used to convert the genetic code, contained in DNA molecules, into digital information, at a rapid speed and on a very large scale. To put the extent of technological innovation into perspective, the cost of DNA sequencing an entire human genome has dropped by more than four orders of magnitude since the beginning of this century. It took five years for a one-order of magnitude drop in costs. From 2005 onwards, there has been a one-order of magnitude drop every three years. This trend continues and the current cost of the routine sequencing of entire human genomes is US$ 3 000. This is a massive drop from the original US$ 3 billion, which was the cost to sequence the very first human genome (completed in 2001).

The reason why these technologies play such a vital role in studying the biology of disease and developing novel medical solutions is the enormous complexity of the human body (Figure 4). For example, the human body has trillions of cells, billions of neurons, and hosts trillions of microbes. It is exposed to large numbers of stressors, internally and externally. A body's genetic makeup, in conjunction with lifestyle and environmental factors, plays a contributing role in if, when, and how complex medical conditions, such as diabetes, cancer, or HIV/AIDS, develop.

Tackling this biological complexity requires the extraction of large amounts of data from human tissue (e.g. blood) in unprecedented amounts, level of detail, and speed. Advanced new omics technologies, such as high-throughput DNA sequencing, allow for the generation of data, explanation of patterns, and identification of 'signatures' that correlate molecular information with clinical data and scientific literature, leading to better diagnosis and/or treatment of patients (Figure 5).

This technology-based innovation led to personalised medicine emerging as a new paradigm as early as the 1990s, with a view to individualising the treatment of patients based on their genetic traits.

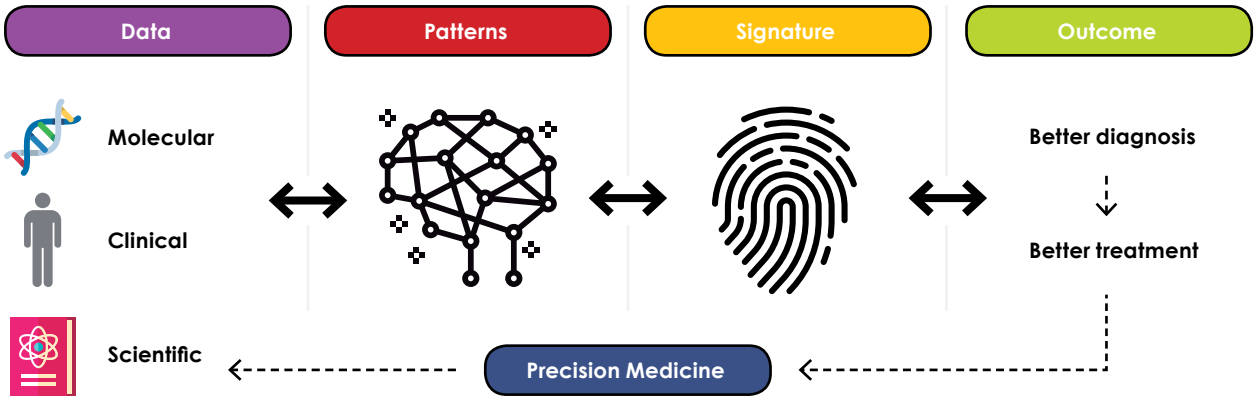

Figure 5: From data to meaning. *R Hiller*

In contrast, precision medicine today refers to the customising of medical treatments to the individual characteristics of each patient. It does not literally mean the design and development of treatments that are unique to a patient, but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a disease, in the biology and/or prognosis of those diseases that they may develop, or in that subpopulation's response to a specific treatment or therapy.

Precision medicine applications can be grouped into the following areas: (i) applications that allow for deep molecular profiling of biological conditions and therefore enable better diagnosis and more effective treatment; (ii) applications that allow the classification of patients into groups of responders to treatment or therapy; (iii) applications that predict disease risk or treatment outcomes.

Precision medicine solutions may affect health provision through innovations that occur over a long time in distinct areas (Figure 6). In the short term, patients may benefit from the rationalisation of laboratory tests, and other medical processes, to save time and money. This may occur through novel molecular applications in a laboratory, the generation of electronic health records, or the implementation of smart self-help applications that reduce pressure on constrained healthcare systems. In the medium term, data obtained from a variety of sources (hospitals, laboratories and public research) will be aggregated and analysed to work out correlative and causative patterns of disease development. Understanding of the information will be aided by artificial intelligence and lead to novel preventative, diagnostic and therapeutic solutions. In the long term, precision medicine will move to integrate the internet of medical things (IoMT), by using data obtained from, for example, contact lens glucose sensors, heart rate monitors, and sole temperature sensors. This latter phase will have a strong focus on patient autonomy and empowerment when it comes to generating and using data, as well as on disease prevention.

PRECISION MEDICINE IS MORE THAN 'OMICS' TESTING

While precision medicine is, to a large extent, based on technological progress over the last 20 years, it is fundamentally aimed at bettering the lives of patients. Precision medicine unfolds along a complex chain, including a diverse set of elements.

Why is this important for Africa?

According to the Personalized Medicine Coalition, on average 50% of existing commonly used drugs are ineffective in their target patient population. The consequence of this is that healthcare expenditure, by individuals or the state, can be ineffective or wasteful. Precision medicine aims to tackle this problem by stratifying patients according to disease risk or response to treatment.

Healthcare challenges are exacerbated in South Africa owing to (i) a lack of resources and (ii) the poorly researched effect of genetic diversity on disease susceptibility and progression in South Africa, and on the rest of the African continent. Since most existing population-based genetic studies were done on people with European ancestry, members of other ethnic groups may lose out on the benefits of precision medicine entirely. These shortcomings complicate the development, implementation and provision of precision medicine solutions in low- and middle-income economic settings, such as South Africa.

Nevertheless, Africa has some unique advantages when entering the precision medicine arena: (i) it can learn from successes and failures that other nations have made in implementing precision medicine programmes, thereby using (scarce) resources more effectively; (ii) by investing strategically, it can tackle health-related challenges in Africa in a fit-for-purpose manner rather than being dependent on solutions created elsewhere; (iii) and, it can leverage the potential embedded in the genetic and lifestyle diversity of African populations to lead discovery and innovation efforts that improve population health outcomes.

PRECISION MEDICINE IN PRACTICE: TACKLING A REAL PROBLEM IN AFRICA

Blood disorders, such as leukaemia and sickle cell disease (SCD), affect hundreds of thousands of individuals in Africa every year. Often, the only curative intervention is a stem cell transplant, which requires the matching of a suitable donor to a patient.

Owing to the complexity of the human body's immune system, finding a stem cell donor is not an easy task. If a child is affected, there is a 25% chance of finding a match in another sibling. Finding a matching donor outside the immediate family decreases the odds of success dramatically.

The molecular profiling carried out on donors, as well as patients, is based on determining the DNA sequence of a series of so-called HLA genes, a part of the immune system that is essential in telling 'friend from foe'. The system has evolved to fend off pathogens and is extremely diverse, in an interest to keep evolving pathogens at bay. However, the mechanism also means that stem cells provided from a healthy donor

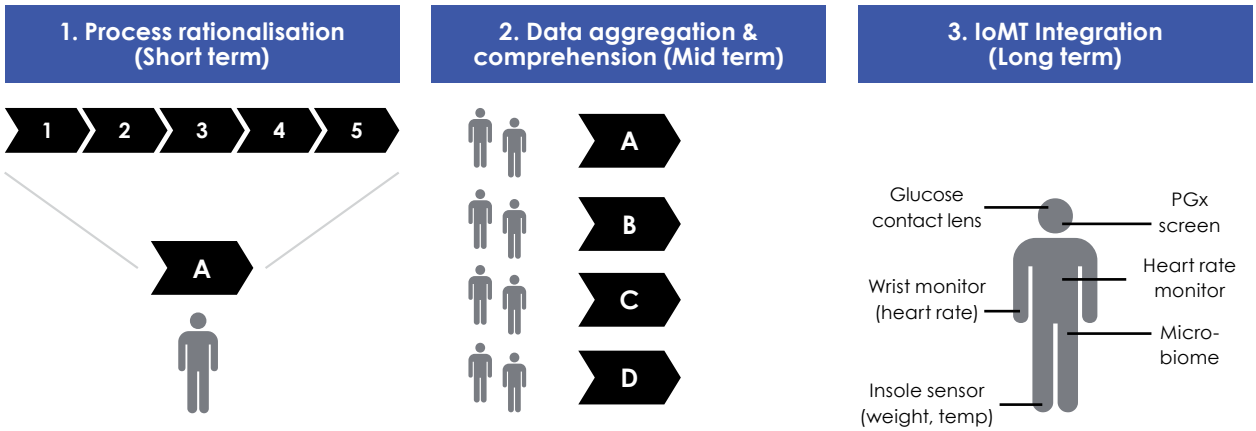

Figure 6: Precision medicine effects on patient diagnosis and treatment. *R Hiller*

may be rejected if they don't match genetically in a perfect manner.

The match making process can be likened to finding a twin by means of photography. Patients of European descent have access to large donor pools (for example, for a population of 80 million, Germany has 8 million registered donors). Finding a stem cell match requires access to a large pool of suitably characterised donors, owing to the underlying probabilities (about 1/100 000). This is facilitated by a process of 'molecular fingerprinting' where a donor's genetic information is mapped and compared with that of a patient's. It is therefore 'relatively' easier to find a stem cell donor for European-based populations than for a person of African descent. To expand the analogy above, a European searching for a twin has access to a vast library of high-resolution images of possible matches. The only option for Africans, in contrast, is to search in small libraries stocked with low-quality images, diminishing the chance of success from the beginning.

The HLA gene cluster plays a vital role in this match making process. It influences transplant success, the development of infectious diseases, autoimmune disorders, and the effectiveness of cancer immunotherapies.

This problem can be addressed by (i) recruiting many (healthy) African stem cell donors; (ii) creating adequate molecular profiles of these donors; (iii) and, facilitating donor-match-making through a proper African registry framework. In addition, genetic profiling of the immune system will enhance the success rate of cutting-edge new immunotherapies that are being tested or developed right now.

Modern DNA sequencing technology facilitates the HLA-typing of African individuals at large scale, high resolution, and low cost. We can therefore generate large libraries of 'high-resolution images' of potential stem cell donors, for people in Africa and anywhere in the world.

In 2017, the CPGR, in partnership with The Sunflower Fund, moved to implement the most advanced solution for high-resolution HLA typing in Africa. With new technology, data generated from both donors and patients, facilitate match making at unprecedented levels of efficiency. Furthermore, these data will stimulate novel research into the role and relevance of the HLA gene cluster for development of blood disorders and stimulate the generation of novel therapeutic treatments.

Therefore, high-resolution stem cell donor typing is an early example of precision medicine in Africa.

CONCLUSION

In summary, precision medicine can be characterised in the following way.

Firstly, precision medicine is, at its core, highly data-driven and analytical. It requires the systematic and comprehensive (systemic) collection and aggregation of data. To achieve this, it requires scalable and standardised processes, for data collection and comprehension. The latter is strongly supported by the emergence and adaptation of artificial intelligence to derive meaning from complex datasets.

Secondly, precision medicine is, in its approach, both comprehensive and integrative. While the integrative approach does apply to the way in which data are used, it also refers to how emergent innovations in the healthcare system (e.g. wearable technology, such as smart watches, or AI-driven self-help apps) are combined into more effective healthcare management and delivery chains. Importantly, precision medicine is a multi-disciplinary endeavor, requiring and benefitting from contributions from an array of expertise areas.

Thirdly, precision medicine aims to empower patients by providing access to increasingly sophisticated self-help tools as well as quality access to data. It realises that the role of patients should change to ensure that healthcare systems are more effective in the future. This is in consideration of the increasing incidence of non-communicable diseases in the developing world, the parallel pressure on healthcare systems, and the need for a lifestyle management approach to prevent or delay the development of disease in an aging human population.

Precision medicine is feasible in (South) Africa by using customised technical solutions in a clearly defined and solution-centred manner that tackles health problems so that cost/benefit ratios are maximised in resource-scarce settings.

FURTHER READING

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(Don't) Mind the Gap: Manufacturing Costs and Drug Prices. Scientific American. 2014. https://blogs.scientificamerican.com/the-curious-wavefunction/dont-mind-the-gap-manufacutring-costs-and-drug-prices/

Born and raised in Austria, Reinhard Hiller completed a PhD in Genetics at the University of Vienna, investigating the properties of autocatalytic ribozymes. After graduating in 2000, he joined a team of scientists to launch a start-up company (VBC GENOMICS) aimed at developing novel diagnostic applications. In 2003, he turned the patented technological solution into the first CE-marked microarray-based test for allergic diseases in Europe. A successful launch was followed by rapid market growth, leading to the acquisition of the company by the global market leader in allergy diagnostics.

In 2005, he moved to South Africa to create the Centre for Proteomic and Genomic Research (CPGR). Set up with government funding to support omics-based innovation, the CPGR has been involved in more than 1 000 projects since its inception. From an initial enabler of academic research, the company has since diversified its model to actively stimulate entrepreneurship and to develop dedicated solutions in fields such as precision medicine and food testing.

In 2015, the CPGR started an accelerator programme to stimulate 'omics' start-ups in (South) Africa. The programme has since matured its first venture, Tokeid Biotech. In 2016, the CPGR formed Artisan Biomed (Pty Ltd) to consolidate its activities in the biomedical arena. It entered into a joint venture with Lancet Laboratories, a partnership that aims at developing and providing Genomic Medicine solutions in (South) Africa. In 2017, the organisation entered into a partnership with the Sunflower Fund to launch a new stem-cell typing initiative, aming to significantly increase the number registered donors and to enhance transplant medicine in Africa. In 2018, the CPGR launched a new collaborative life science incubator, with upstart company, OneBio, to focus on nurturing entrepreneurs and scaling new start-up development.

In addition to his PhD, Reinhard has a NLP Master Practitioner degree, and he is a Member of the South African Charter of the Institute of Directors. In 2013, he completed an Executive MBA programme at the Graduate School of Business (GSB) at the University of Cape Town (UCT). His spare time is dedicated to his family and his children, Isak Themba and Sara Thandiwe.

Bridging the digital divide with photonoics

Africa has 20% of the world's population but only 4% of its internet data access. This 'digital divide', with low internet connectivity reach, particularly in rural areas, is both economic and geographic in nature. A team of international researchers, coordinated by Professor Andrew Forbes from the School of Physics at the University of the Witwatersrand in Johannesburg (Wits), South Africa, and Professor Ling Cheng of the School of Electrical and Information gathered in South Africa recently to address this problem. Their solutions were published in *Nature Photonics* in May this year.

The 'divide' can be broken down into two parts: an affordability gap due to low disposable income and a geographical gap, due to lack of infrastructure. If South Africa's gap was to be addressed by state-of-the-art optical fibre then an additional 160 000 km of fibre would be needed. This is possible but very expensive. But getting people connected is a priority, particularly for South Africa, where Broadband has been estimated to raise GDP by R130 billion and create 400 000 jobs. The Wits team are concentrating on bridging the divide by connecting communities with free-space optical (FSO) links – a network of communication channels through air, much like wifi but much faster and with a longer reach.

'Light holds tremendous promise for fast connections across medium distances,' explains Professor Andrew Forbes, team leader of the collaboration and Distinguished Professor in the School of Physics where he heads up the Wits Structured Light Laboratory. 'Even Google, Facebook and SpaceX have exotic proposals for Africa that include drones and other aerial vehicles delivering connections in a blanket manner. We are working on point to point solutions with sustainable photonics that are home-grown.'

'Internet is not a luxury but a right,' says Mitchell Cox, PhD engineering student working on the project. Existing FSO systems are able to comfortably sustain gigabit connection speeds over multi-kilometre distances. 'With further research and development into advanced digital signal processing and coding schemes, this may be increased dramatically with relatively little expense,' says Professor Ling Cheng, from the School of Electrical and Information Engineering.

The team are working towards a multi-hop FSO link that will cover tens of kilometres across the digital divide. Forbes points out that working with this team of scientists and engineers has allowed some of the most recent scientific findings to be rapidly and efficiently deployed to tackle this challenge.

A recent report by the UN has highlighted that over 4 billion people in the world are 'not connected', with Africa having the lowest penetration (22%) and the highest gender divide (25%). 'What is tragic is that economic upliftment is hindered by these divides, yet they are widening not shrinking with time,' says Forbes The UN estimates that $400 million (just under R5 billion) allotted to bridging the gender digital divide remains unspent. The Wits team has already made several technical advances to address these issues and is about to embark on a commercialisation programme with a local listed company.

A prototype of the device that could connect remote places to fast, reliable internet is tested by the team at Wits University. *Wits University*

Issue by: Schalk Mouton, Senior Communications Officer, Wits Unversity

A team of Wits physicists and engineers teamed up to build a prototype device that could solve Africa's digital divide. *Wits University*

Precision medicine – moving away from one-size-fits-all

Stefan Kohler discusses how precision health principles apply to various areas of healthcare, ranging from personalised drug treatment to precision population health interventions

More and more tools and technologies from genomics to big data can be used to help deliver the right health intervention, at the right time, to the right person or population. Step by step, better targeted care for individuals as well as populations may therefore be attainable in many areas of health.

FROM ONE-SIZE-FITS-ALL TO PRECISION MEDICINE

'Delivering the right treatments, at the right time, every time to the right person' [1] has been described as the promise of precision medicine (Figure 1). This promise has long been a goal of medicine, but the means available are changing. Hence, recent precision health approaches, including personalised medicine, represent no paradigm shift, but rather an evolution of healthcare.

The Greek physician Hippocrates (460–370 BC) is frequently named as the father of Western medicine in recognition of his contributions to medicine and for founding the Hippocratic School of Medicine. Already Hippocrates, supposedly, advised 'give different ones [liquid medicines] to different patients, for the sweet ones do not benefit everyone, nor do the astringent ones, nor are all the patients able to drink the same things' [2]. At the time, Hippocrates suggested evaluating factors like a person's age, physical appearance and the time of the year when prescribing medicines [3] to better target drug prescription to individual patients.

'While Hippocrates used a person's physique and the seasons to personalise treatments, modern science and industry hope to use your DNA [3].'

The use of genetic and molecular diagnostics, in addition to other methods of differential diagnosis, for improved targeting of drug treatments is now often referred to as personalised medicine. There is no universal definition of personalised medicine. Personalised medicine in a broader sense strives to consider all differences between people that affect health outcomes to provide better targeted healthcare. However, in contrast, personalised medicine in a narrower sense, mostly refers to the use of genetic information about people and diseases for better targeted drug therapies. The terms personalised medicine, individualised medicine, stratified medicine and precision medicine overlap and are frequently used interchangeably. Sometimes the terms precision medicine and stratified medicine are preferred to the terms personalised medicine and individualised medicine to emphasise that so-called personalised approaches usually are neither designed for specific individuals nor take into account personal factors, such as individuals' preferences, health resources or experience of disease.

After the Human Genome Project demonstrated the feasibility of decoding human DNA, there were high hopes that precision medicine would rapidly evolve (see Box 1). Similar hopes currently carry over to other emerging sources of health-related data, ranging from health sensor data to routine health data, to socioeconomic, demographic and health surveillance data, to health proxy data from remote sensing, or to smartphone and smart home data (see Box 1).

Figure 1(a). One-size-fits-all healthcare may not fit all.

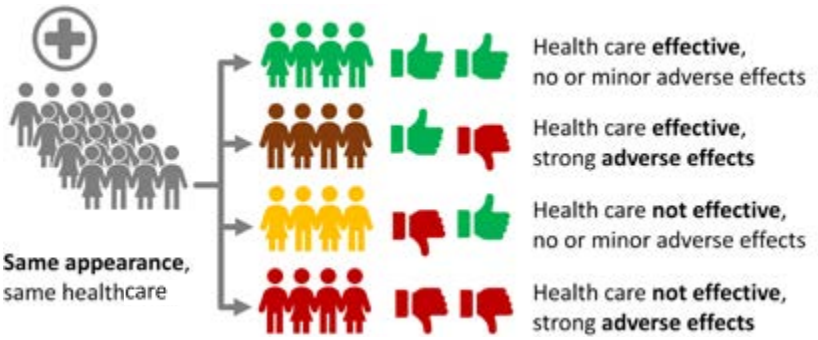

Figure 1(b). Precision health aims to use health-related data to better target healthcare. *Stefan Kohler*

A focus of current applications of precision medicine as well as most development of new precision medicine approaches have been, and continue to be in the field of cancer medicine (oncology). Few successful applications of personalised drug therapy have been discovered in areas other than the pharmacotherapy of cancers [4]. In Germany, for instance, 53 approved drugs were considered personalised medicine in 2017. Of those, 41 (77%) were for cancer treatment and only 12 (23%) in other areas of application (Figure 2). The fundamental idea of applying medicine more precisely, however, is neither restricted to drug therapy nor to cancer medicine (oncology). Precision medicine approaches can be pursued in all areas of health, from disease prevention to health promotion, including health interventions on the population and public health levels.

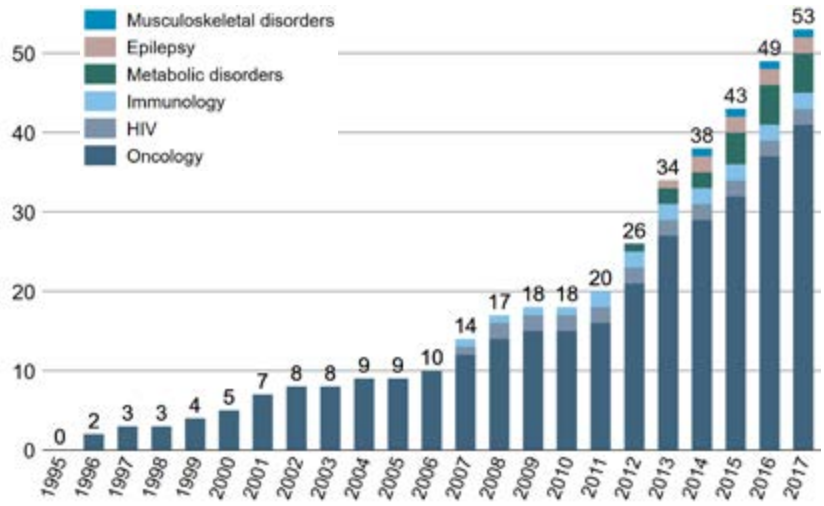

Figure 2. The number of personalised medicines in Germany has steadily increased. Drugs are classified as personalised medicines if a biomarker pre-test for efficacy or adverse drug effects is either required or recommended in the German prescribing information. *Stefan Kohler*

FROM PRECISION MEDICINE TO PRECISION HEALTH

'Precision health is a way of improving overall lifelong health, while precision medicine is generally not implemented until an individual becomes ill [5]. Precision medicine emphasises the targeted medical treatment of people who have fallen ill. However, the risk of disease is already influenced by biologic, social, environmental and economic processes, which affect different people in different ways. In other words, whether someone is healthy or remains healthy, is co-determined by the person's individual circumstances and environment. Figure 3 shows the main determinants of health. Knowledge and awareness about the determinants of health can be used to target preventive health interventions (Box 2).

Disease prevention and early detection of health changes by monitoring health and disease based on an individual's risk is the focus in the emerging field of precision health [6]. As new tools and technologies allow us to collect more data about the various determinants of health, e.g. genotyping at or before birth, health monitoring via health sensors or during clinic check-ups, or surveys about people's socioeconomic status and environmental risk exposure, such information, can be used to predict and prevent disease in health interventions that specifically target those with increased risk of specific diseases.

FROM PRECISION HEALTH TO PRECISION POPULATION HEALTH

Precision health principles can also be applied at the population level (Box 3) to deliver the right population health intervention, at the right time, to the right population.

Health programmes by the government or other organisations complement the work of nurses, doctors and other health workers, by aiming to improve population health. Population health is the health of whole groups or communities of individuals. The health of a population is

BOX 1

PERSONALISED MEDICINE: HOPE OR HYPE?

Examples of successes and setbacks in targeted drug treatment based on genetic markers are described in a *Nature Education* article by Leslie Pray [3]. Her examples continue to represent today's status and challenges of personalised pharmacotherapy.

The *Her2/neu* gene and response to breast cancer treatment – a success

The *Her2/neu* gene can be successfully used as a predictor of breast cancer patients' responses to a drug called trastuzumab (brand name Herceptin). In consequence, trastuzumab is only prescribed to women which have a type of breast tumour in which the cancer cells make too many Her2 receptors (caused by an overexpression of the *Her2/neu* gene). As trastuzumab increases the risk of heart dysfunction, drug regulatory authorities, like the European Medical Agency or the US Food and Drug Administration, typically recommend or require that only patients tested for an 'Her2-positive tumour' are treated with trastuzumab.

The *CYP450* gene and response to antidepressants – a setback

The information our body needs to produce a family of proteins known as the cytochrome P450 enzymes is encoded on the *CYP450* gene. Different forms of the *CYP450* gene have been associated with the function and strength of a commonly prescribed class of antidepressant drugs called selective serotonin reuptake inhibitors (SSRIs). Depending on their genetic makeup, individuals metabolise SSRIs differently – some quickly, others slowly. While, in theory, it should therefore be possible to predict what dose would be most beneficial, clinical studies could not show benefits from prescribing SSRIs based on *CYP450* gene variations.

Source: Adapted from Pray 2008 [3]

influenced by several of the factors that co-determine individuals' health (Figure 3). Increased knowledge and more data about the determinants of health on the population level can help to target population health interventions better.

For instance, we found in recent study in the Kingdom of eSwatini that younger people, people who do not know their partners' HIV status, or those with low self-perceived HIV risk are less likely than others to continue with oral HIV pre-exposure prophylaxis (PrEP) after one month of taking PrEP (Figure 4) [7]. PrEP is a combination of antiretroviral drugs that can be taken by HIV-negative people to reduce their risk of HIV infection. It is becoming an important additional tool for prevention of HIV infection (Figure 5). Since 2015, the World Health Organization has recommended that PrEP should be made available as an additional prevention choice for people at substantial risk of HIV infection.

Knowing which groups of people in a population may be more likely than others to not continue with a health programme, like PrEP, can help increase the programme's success by allowing programme coordinators to tailor care to the different needs of specific groups of people, like those more likely to drop out of a programme early. Furthermore, PrEP itself can be an example of precision health as well as precision population health.

On the one hand, PrEP offers a new, additional method of reducing the risk of HIV infection that complements other methods of HIV prevention. It can be particularly suitable for some people at a certain time in their lives. For instance, PrEP can be used by serodiscordant couples, that is, couples in which one partner is HIV infected while the other is not, who would like to pause the use of condoms to conceive a child. On the other hand, PrEP is not recommended for everyone, but a targeted recommendation for people who face a high risk of HIV infection (Figure 6). Assessing the individuals' risk for HIV infection, before offering PrEP as an additional HIV prevention option for people at substantial risk of HIV infection as part of a combination of HIV prevention approaches, makes PrEP a targeted population health intervention.

Figure 3. The main determinants of health. *Adapted from Dahlgren and Whitehead (1991)*

OUTLOOK AND CHALLENGES FOR PRECISION HEALTH

The amount and variety of data that may allow better targeting and so improve

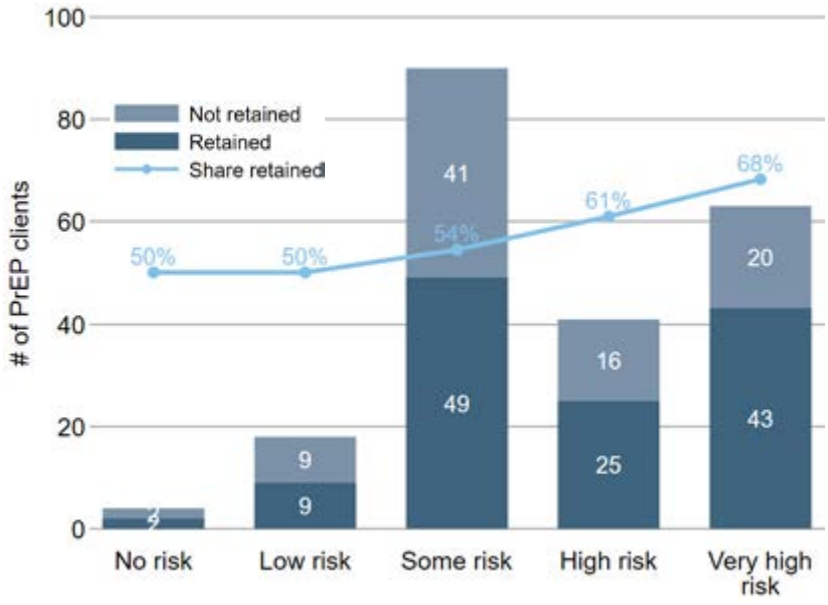

Figure 4: Share of clients retained on HIV pre-exposure prophylaxis (PrEP) after one month increases as self-perceived HIV risk increases. *Data from Hughey et al. 2018 [7]*

BOX 2

WHAT IS THE DIFFERENCE BETWEEN PRECISION MEDICINE AND PRECISION HEALTH?

Precision health leverages the numerous assessments including [the fields of study ending in] omics, immune status, medical imaging, family history, physical condition and standard doctor visits to predict and prevent disease from occurring. Precision medicine uses similar tools, but is primarily focused on patient treatment after the onset of disease. Both health areas have overlap and are complementary in improving patient care. Precision health is a way of improving overall lifelong health, while precision medicine is generally not implemented until an individual becomes ill.

Reprinted from Precision Health and Integrated Diagnostics Center at Stanford [5]

Figure 5. Pre-exposure prophylaxis as part of an HIV prevention package.
Hughey et. al. 2018 [7]

BOX 3

WHAT IS THE DIFFERENCE BETWEEN PRECISION HEALTH AND POPULATION HEALTH?

Population health refers to the health or health outcomes of a group of individuals and this information can be used to improve and learn about the health of a larger group or even the entire population. Precision health, on the other hand, is focused on the health of an individual. However, both precision and population health areas are complementary. The trends of individuals create the average trend of a group, and the trend of a group can be used in conjunction with individual health data to improve the overall predicative capabilities for individual disease prevention and, if needed, early intervention.

Reprinted from Precision Health and Integrated Diagnostics Center, Stanford [5]

healthcare is increasing in all parts of the world. The availability of genomic data has triggered a wave of hope for advances in precision health after the Human Genome Project. Precision health has, since then, experienced successes and setbacks, both of which show that there is still much more to be discovered. Successes achieved by personalised pharmacotherapy are concentrated in the field of cancer treatment, in which often expensive targeted treatments become available for patients with certain subtypes of some cancers. In other areas of health, few effective precision approaches have been found so far. Therefore, precision medicine in the form of genetic information to improve drug targeting is of minor importance for current population health.

To improve population health, at least in the short to medium term, prevention of unhealthy lifestyles and behaviours, as well as universal access to basic diagnostics and care, remain the most important global challenges. Individual- and population-level data on the prevalence of diseases, the determinants of health, access to and utilisation of care, as well as other health-related data, are becoming increasingly available to researchers and health decision makers (see references 6, 11-13). These data offer new opportunities to assess and potentially better predict how care can be provided with more impact through improved targeting in many areas of health, ranging from treatment of diseases and the strengthening of health in populations.

To conclude, precision health principles apply to all areas of health. Challenges are to mainstream precision health thinking in all areas of healthcare and to assess when and which precision health approaches can help to improve health outcomes. If these challenges are overcome, precision health can support health systems globally and allow them to fulfil their core functions, which include providing all people with access to the quality health services they need (see reference 8).

Figure 6. Targeting of HIV pre-exposure prophylaxis at the health facility level.
Stefan Kohler

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GETTING PERSONAL ABOUT PSYCHIATRY: PHARMACOGENETICS IN AFRICA

Why do we all react differently to different medicines? Emma Frickel, Ellen Ovenden, Celia van der Merwe, Louise Warnich, and Nathaniel W McGregor explain

DRUG DOSAGE AND RESPONSE: IT'S PERSONAL

Have you ever wondered why two people with the same symptoms, treated with an identical amount of the same medication, might respond differently? An everyday example would be that of common painkillers, where most of us know people who need to take more pills (higher dosages) than others, for it to have the same effect. You may have also noticed that some people experience the side-effects of drugs, such as drowsiness or nausea, more severely than others. These differences in both drug effectiveness and the experience of side effects, also occur in the case of long-term or life-long medication taken by individuals for the treatment of certain disorders. However, for those who require long-term medication, effective treatment is far more essential than easing a headache, and may even be the difference between life and death in extreme cases. Along with this, the side effects are sometimes so severe that patients will stop taking their medication. This presents a clear need to make the type of drug and drug dosage more specific to each individual. In other words, to personalise the medicine we take.

But let's take a step back and ask ourselves, 'Why do we react differently to certain medications?' At a glance, whether it be hair colour, eye colour, or height; it is easy to see that everyone is different. We also know that these differences between us extend beyond physical appearances in many ways. So what do these differences have in common? The answer to that lies in the story of who we are: it is written in our DNA.

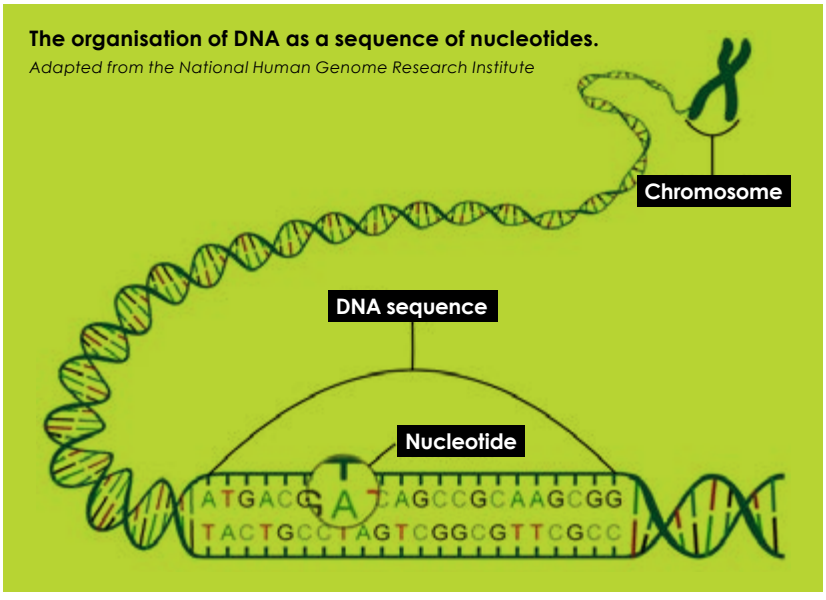
Our DNA is organised as a unique genetic code, which is made up of four 'letters' (A, T, G, and C) called nucleotides.

The order, or sequence, of nucleotides is different for every individual, and determines the functions of our different genes and the resulting differences, and similarities, we see between us. When our DNA sequence is altered by a change in a nucleotide (called a variant), this can sometimes lead to the onset of a disease, or result in a certain reaction to a drug.

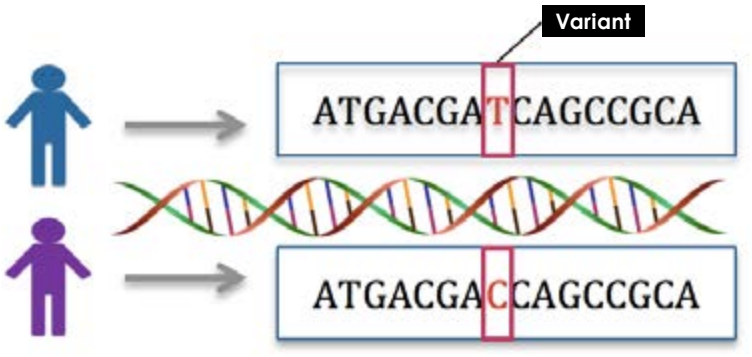
This is usually the result of a number of variants in many different genes. The field of scientific research that focuses on identifying these genetic differences involved in drug reactions is known as pharmacogenetics, and it is now possible to test for variants in our DNA that may cause these different reactions in each individual. This process is called pharmacogenetic testing and is already in use for some medicine prescriptions today: essentially a form of personalised medicine.

Warfarin is a commonly used drug that acts as an anticoagulant (blood thinner) for the treatment of blood clots and to prevent strokes in people with heart disease. The dose response between individuals is highly variable, and excessive bleeding is a common side effect. Pharmacogenetic research has revealed that the majority of this variability in response to warfarin stems from several differences in two genes, *CYP2C9* and *VKORC1*.

The *CYP2C9* gene, part of the cytochrome P450 (*CYP*) gene family, is involved in drug metabolism, which is how the drug is broken down in the body. Individuals with different forms



The organisation of DNA as a sequence of nucleotides.
Adapted from the National Human Genome Research Institute



A nucleotide alteration in a DNA sequence, called a variant.

NUCLEOTIDE:
Organic molecule that serves as the building block of DNA. There are four different nucleotides that can make up a DNA sequence, known as A (Adenine), T (Thymine), G (Guanine), and C (Cytosine).

VARIANT:
An alteration in a DNA sequence. A variant can be harmful, harmless, or have unknown consequences.

PHARMACOGENETICS:
The study of genetic differences which can affect individual responses to drugs, both in terms of drug effectiveness, as well as toxic effects.

of this gene will therefore metabolise warfarin at different rates. *VKORC1* is important for blood clotting through its involvement in the vitamin K cycle. Pharmacogenetic tests are now widely used to determine which forms of *CYP2C9* and *VKORC1* a patient has, and it is the combination of variants in these two genes that determines the optimum dosage of warfarin that needs to be given to a specific individual. This hallmark example is one of many, and the multitude of drugs for which pharmacogenetic indications currently exist can be seen on the Food and Drug Administration's (FDA) website: https://www.fda.gov/Drugs/ScienceResearch/ucm572698.htm.

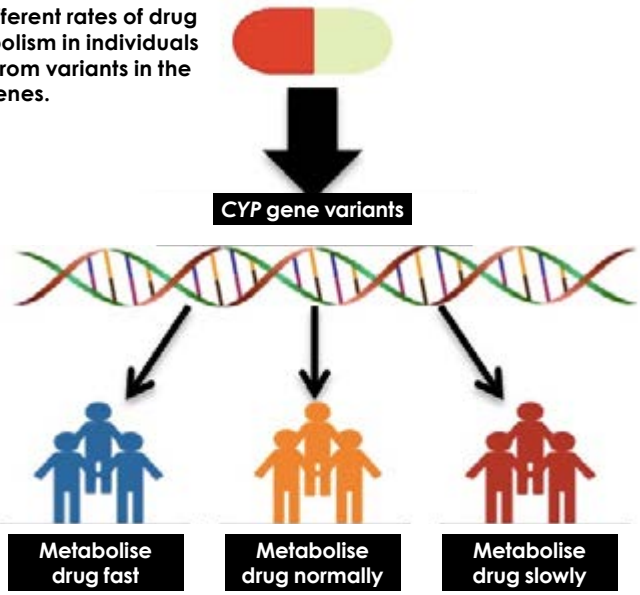
But why is pharmacogenetic testing not already common medical practice? Unlike the success stories, many disorders, and their treatments, have proven to be extremely complex. This is the case for psychiatric disorders (mental illnesses), for which pharmacogenetic research still has a very long way to go, and where personalised medicine remains out of reach, but not out of sight.

MENTAL ILLNESS: IT'S COMPLICATED

Mental illness broadly includes disorders such as depression, anxiety disorders, bipolar disorder, and schizophrenia, among others. Although these disorders show themselves in many different ways, they generally involve a combination of abnormal thoughts, perceptions, emotions, behaviour, and social interactions. Mental illness may not always result in premature death, but patients are sometimes unable to work, or lose their ability to function independently, subsequently requiring people to care for them. It is therefore clear that mental illness severely impacts the quality of life for affected individuals, but exactly how big is the problem? Approximately one billion people suffer from some form of mental illness globally, which includes the 300 million individuals with depression, 60 million with bipolar disorder, and 23 million with schizophrenia. It is therefore not surprising that mental disorders are the leading causes of disability-adjusted life years worldwide, which gives an indication of the years lost due to ill-health, disability, or premature death. Additionally, there is a large economic burden associated with mental illness globally, with the costs for treating these disorders exceeding those for cardiovascular disease, diabetes, and cancer.

The exact causes of psychiatric disorders remain unclear, but decades of research have pointed towards genetics as a major component. Over the years, in an attempt to identify the genes involved in disorders, scientists have looked for genetic variants common in large groups of patients, but uncommon in groups of healthy individuals. This research has revealed that these disorders are much more complex than we first thought. It is now clear that we cannot point the

The different rates of drug metabolism in individuals result from variants in the *CYP* genes.



finger to just a few differences in our DNA sequence. There are in fact potentially hundreds of these genetic variants involved. But why have we still not been able to solve the genetic puzzle of mental illnesses after all these years? It turns out that our genes are not the only culprits.

We must also consider that not all genes are 'switched on' in all cells at all times. The switching on and off of genes is a normal and important part of cell development and function. This is what makes a brain cell different from a liver or muscle cell. This is known as gene regulation.

When this regulation is disrupted in some way, it can lead to abnormal cell functioning, and may contribute to the development of psychiatric disorders. So what can affect the normal regulation of genes? The answer can be uncovered by exploring our environment, factors of which include the food we eat, whether we smoke or take drugs, whether we are exposed to certain chemicals or toxins, or whether we experienced trauma in the early stages of our lives. By interacting with our genes and affecting their regulation, the environment that we are exposed to can increase our risk for developing psychiatric disorders.

Because of these interacting genetic and environmental factors, psychiatric disorders are often complex and extremely difficult to characterise or treat. However, it is imperative that we advance our knowledge of the underlying mechanisms involved, as understanding how and why these disorders exist may help us figure out better ways to treat them. Then, the more we know about how these disorders develop, the more we can learn about the vast differences we see between affected individuals. This will be an important stepping stone in the path towards personalising psychiatric medicine.

GENE REGULATION:
The switching on and off of genes by cellular mechanisms, to increase or decrease the production of specific gene products (i.e. proteins).

REMISSION:
A state or period of time in which the symptoms of a disease/disorder have improved or disappeared.

MEDICINE IN MENTAL ILLNESS: WE SHOULD TAKE IT PERSONALLY

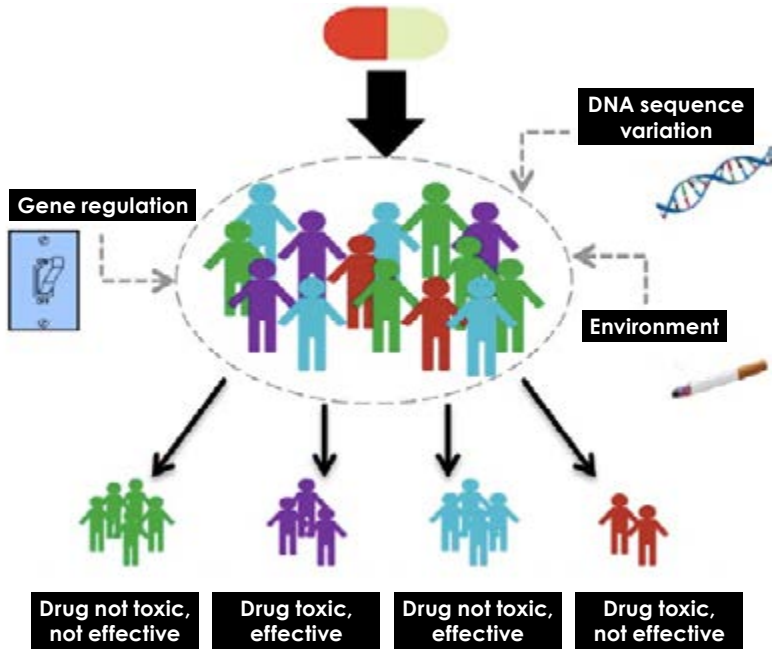
Mental disorders can be treated with psychotherapy (psychological instead of medical means) as well as a range of psychiatric medications. There are several classes of psychiatric drugs, including antidepressants, anxiolytics (including sedatives), mood stabilisers and antipsychotics. However, treatment does not always work as well as we'd like.

Antidepressants are commonly used to treat major depressive disorder (depression), but only 35-45% of patients experience complete remission of symptoms following initial treatment.

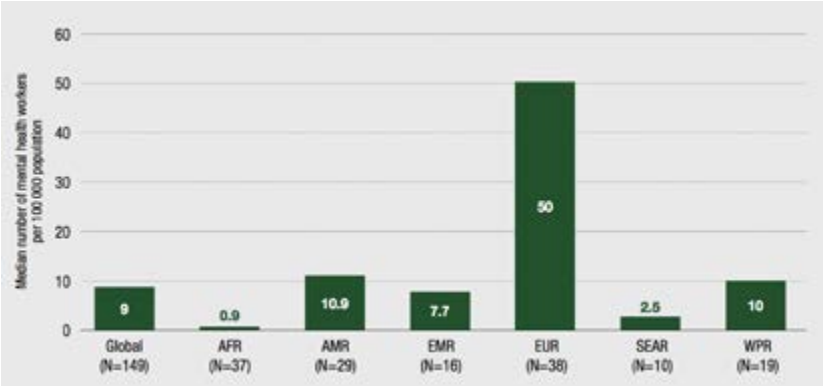
That is to say they get well. Of the patients who didn't respond at first, less than half will get well if given a different antidepressant. In the case of schizophrenia, antipsychotic drugs are used for treatment. But once again, only 50-60% of individuals respond adequately to the first drug they are given. In both depression and schizophrenia, some individuals have to take several different types of medication before they show sufficient improvement, even

Psychiatric drug	Disorders	Common side effects
Antidepressants	Depressive disorders, obsessive-compulsive disorders, anxiety disorders	Nausea, weight gain, disorientation, insomnia, abnormal heart beat
Anxiolytics	Anxiety disorders, insomnia	High blood pressure, abnormal heart beat, suicidal thoughts
Mood stabilisers	Bipolar disorder	Drowsiness, rash, motor dysfunction (tremors), hallucinations
Antipsychotics	Schizophrenia, bipolar disorder, dementia	Dizziness, motor dysfunction (tremors), weight gain, seizures

Psychiatric drugs and disorders they are used to treat, as well as examples of common side effects.



Different drug responder groups based on both drug toxicity and effectiveness, influenced by genetic variants, gene regulation and environmental factors.



Mental health workforce per 100 000 people in different regions. African (AFR) countries have the lowest number of mental health workers of all World Health Organization regions; a tenth of the global average. N=evaluated countries in each region. (AFR – African; AMR – American; EMR – Eastern Mediterranean; EUR – European; SEAR – South-East Asian; WPR – Western Pacific)

Reprinted from Mental Health atlas 2017, World Health Organization, Financial and human resources for mental health, Page 30, Copyright World Health Organization (2018).

though some degree of symptoms may still remain. In some cases, patients are completely resistant to all medication and cannot be treated effectively. Even when treatment is considered successful because remission is achieved, severe side effects are often experienced which can result in worse symptoms than before patients were treated, and often leads to patients stopping their medications. This highlights the urgency for finding new drugs and safer treatments, and emphasises the increasing need to use personalised medicine in the treatment of psychiatric disorders. So how does the complexity of these disorders factor into the treatment?

The range of individuals' reactions to psychiatric medications is as complicated as the disorders themselves. The different drug responses between patients arise from a combination of genetic, environmental, and biological factors. Therefore, in order to effectively apply personalised medicine to psychiatry, all of these factors need to be taken into account. This approach will make use of specific profiles of patients to make certain predictions about potential drug response, in order to make informed decisions about the best treatments to use for each unique individual. This type of approach is the end goal for personalised psychiatric medicine, and does not yet exist despite incredible progress in the field of psychiatric pharmacogenetics. So where are we currently?

Pharmacogenetic research has revealed several genes that have consistently shown some involvement in differential responses to medications. A very well studied set of genes in the context of drug response is the *CYP* gene family. These genes include the *CYP2C9* gene, which was discussed previously in the context of warfarin drug metabolism. All of these genes are involved in determining the rate at which individuals break down drugs in the body, which directly influences the effects of these drugs. Pharmacogenetic testing can be applied with another of these genes, *CYP2D6*, to help determine if the initial dosage of certain antipsychotics should be adjusted, according to how quickly certain individuals will metabolise the drug. Of the medications that have pharmacogenetic guidelines, about 90% involve the *CYP* gene family. Screening for *CYP2D6*, as well as *CYP2C19*, can also be applied to antidepressants, where informed decisions can be made regarding two main types of antidepressant available: tricyclic antidepressants (TCAs), and selective serotonin reuptake inhibitors (SSRIs). SSRIs generally have fewer severe side effects. However, TCAs can still be preferable for the treatment of certain patients. Not disregarding the usefulness of these tests to some patients, drug metabolism is only one aspect of drug response. The ways in which drugs are absorbed and transported around the body are also important factors affected by differences in our genes. Pharmacogenetic testing should capture as many of these known differences as possible to provide a better picture of an individual's response to medication.

Considering the many cellular processes that are involved in drug response, including those that we haven't yet identified, we are still in the process of characterising the full genetic architecture of psychiatric drug response and reaching our full potential for pharmacogenetic testing in psychiatry. This process is impeded by the difficulty in making the jump from finding results in research to using these results in a clinical setting, the so-called 'bench-to-bedside' dilemma. In order to apply findings to medical practice, there needs to be a lot of evidence to support those findings, which includes being able to draw the same conclusions from independent studies. So, while there is an excess of information, the reproducibility of findings between studies remains a challenge. This can be due to the many factors that differ between studies around the world, including vast differences between patient groups, as well as the subjectivity involved in diagnosing psychiatric disorders, as this is based on assessments by many different clinicians, and a lack of standardised criteria. But one of the biggest challenges in pharmacogenetic research is that people of different ethnicities and population groups differ genetically in ways that can affect treatment outcome. This means that genetic findings pertaining to mental illness and drug response cannot readily be applied to all populations. So, what does this mean for Africa in terms of research for personalised medicine in psychiatry?

CURRENT CHALLENGES IN THE AFRICAN CONTEXT

Undeniably, psychiatric illness is an immense problem worldwide: five of the top 20 causes of the global burden of disease are mental illnesses, and it's estimated that they are responsible for about 14% of deaths globally each year. Unfortunately, the situation is even worse on the African continent. Africa is home to the highest global burden of both communicable (infectious) and non-communicable (non-infectious) diseases, including mental illnesses. Because African public healthcare systems are already under huge strain from diseases like HIV/AIDS, tuberculosis and malaria, governments are geared towards trying to solve these crises rather than focusing

on mental illness. In fact, 70% of African countries allocate less than 1% of their already small healthcare budget to mental illness. This means most African countries are severely under-equipped to treat these disorders. Shockingly, the number of psychiatrists on the African continent is less than the number in the state of Massachusetts in the USA.

In Africa, stigma and discrimination contribute to the imbalance between the clear burden mental illness causes and the attention it receives. This makes people reluctant to seek treatment, and individuals are often cut off from their communities and restricted from healthcare, education, employment and social support. This often means a shorter life of poorer quality. These hardships are intensified by poverty, and research has shown that impoverished regions have higher rates of mental illness.

Pharmacogenetics offers the possibility of improving mental healthcare in Africa by laying the foundations for personalised medicine. Proactively designing treatments tailored to the individual will drastically improve quality of life and reduce stigma related to these disorders. Importantly, successful treatment and fewer side effects means less strain on healthcare resources as treatments will no longer be a chronic battle needing constant monitoring and care.

In spite of Africans suffering the highest disease burden, they are one of the least studied population groups in medical genetic research. Over 80% of large-scale genetic studies have been on European people, and only 3% on those of African heritage. Principally a lack of funding, resources and genetic research infrastructure within Africa is to blame for this inequality. Historically, even when well-funded international researchers collaborate with African scientists, there is no investment in researcher training or resource development.

Moving forward, it's essential for researchers to include under-represented populations to ensure that the benefits of research are extended to all and not just a privileged few. More importantly, this must happen in order for medical research to be globally applicable, because our ancestry and our genetic make-up are closely linked. Certain genetic differences between people of African, European or Asian descent mean that the drug response of standard medication will be experienced differently across these ancestral groups; and could in fact result in extreme side effects for some. There are many examples in several psychiatric disorders where differences in particular genes that are connected to the disorder in a European sample group are not the same as those discovered in African individuals. These include the previously discussed *CYP* genes, which play a major role in drug metabolism. For example, there are two variants in *CYP2D6* that hinder drug metabolism, and these are very common in African but not European populations. As discussed, *CYP2D6* is a gene that is employed for psychiatric drug screening. Without inclusion of African individuals in research, personalised psychiatry cannot be a global solution.

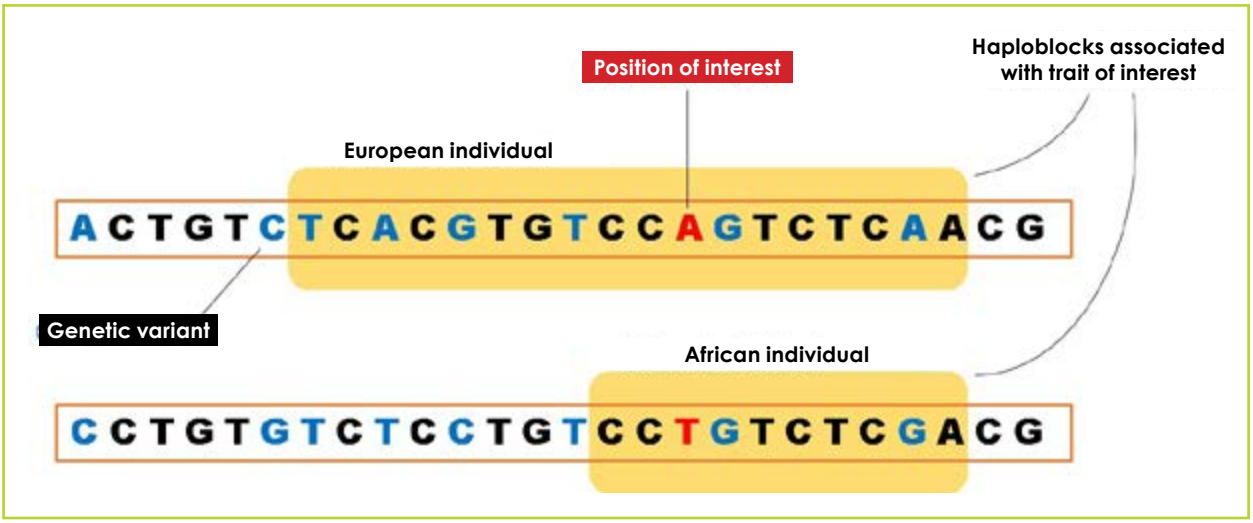
The first step to establishing true personalised medicine is to investigate the pharmacogenetics of the population in which it will be applied – the 'personal' aspect of personalised medicine has a lot to do with ancestry. But what is it that makes Africans genetically different to other populations?

WE'RE NOT SO DIFFERENT AFTER ALL

Our focus here is genetic variation, but keep in mind that all humans are 99.9% genetically similar. The remaining 0.1% equates to about 3 million nucleotides of DNA that differ from person to person. These differences map out our evolutionary and geographic history. Most genetic variants are shared between population groups, but differ in how common or rare they are. Interestingly, research has shown that two people within a population can in fact be more genetically distinct than two people from different populations.

HARNESSING THE POWER OF AFRICAN GENETICS

It is common knowledge that Africa is the cradle of humankind. The 'Out-of-Africa' theory states that all humans originated in Africa and subsequently broke into smaller groups that migrated across the globe. In the creation of every



Example of haploblock differences between populations. Shorter blocks in African populations make it easier to pinpoint the variant of interest.

new generation, genetic information from each parent is recombined or 'shuffled' to result in offspring with unique, new DNA made up from both parents. This means that the older a population is, the more times recombination has occurred, and the more genetic variation this population has accumulated.

Because people have lived in Africa longer than anywhere else, it is also the continent harbouring the most genetic diversity in the world. Since personalised medicine is all about looking for genetic differences, Africa is in fact the best place on earth to discover the genetic bases of complex diseases and treatment outcomes.

Further emphasising the need to study African populations, the rich genetic diversity of African individuals makes it easier to pinpoint exact genetic differences – down to single variants – that are connected to a specific treatment outcome.

This is because of the nature of haploblocks in African populations. A haploblock is a segment of DNA that usually sticks together and stays unchanged during genetic recombination, such that the nucleotides in this sequence are inherited together from one parent. Over a long period of time, these haploblocks become smaller and smaller through more and more recombination events. Since African populations have been around the longest, their DNA contains the smallest haploblocks. The fewer nucleotides or variants in a haploblock, the easier it is to discern which exact nucleotide is the one you're interested in, that is, which one has a true relationship with the treatment outcome. With larger haploblocks, such as those in European individuals, there are many variants to choose from in a block, and no way of pinpointing the culprit. One can think of these haploblocks of African ancestry as being at a 'higher resolution': more detailed and informative than corresponding sequences of European origin.

RECOMBINATION:
Exchange or shuffling of the DNA from each parent to produce offspring with unique genetic material. This process maintains genetic diversity.

HAPLOBLOCK:
A segment of DNA that is usually inherited together as a chunk from one parent, i.e. the genetic material is not recombined.

The genetics of African populations are currently still an untapped resource for scientists investigating disease. The catch is that high genetic diversity also means DNA that's trickier to study with methods traditionally applied to DNA of European ancestry. Nonetheless, the field is quickly advancing its technology and statistical approaches to handle African genetic data. Shifting our focus to previously under-represented ethnic groups with understudied diversity could yield a multitude of new genetic findings. This could completely shift our existing knowledge of the human genome and accelerate discovery that can ultimately be applied to clinical testing.

There are several large-scale initiatives that have been recently formed to address the sparsity of genetic data on African individuals, some with specific focus on understanding disease genetics. These include:

- The Human Heredity and Health in Africa (H3Africa) Initiative (https://h3africa.org/)
- The African Genome Variation Project (https://www.sanger.ac.uk/science/collaboration/african-genome-variation-project)
- Neuropsychiatric Genetics in African Populations (NeuroGAP) (https://www.broadinstitute.org/stanley-global/neuropsychiatric-genetics-african-populations-neurogap)
- Developing Excellence in Leadership, Training and Science Initiative (DELTAS Africa) (https://www.aasciences.ac.ke/aesa/programmes/deltas/)
- The Multi-Ethnic Global Array (MEGA) Consortium (https://emea.illumina.com/science/consortia/human-consortia/multi-ethnic-genotyping-consortium.html?langsel=/za/)

These projects represent collaborative efforts with the goal of training African scientists and increasing available resources to promote the study of African genetics. For the African continent to advance in the field of personalised medicine, it is essential for funding bodies, government, and researchers to work together to build research capacity and genetic databases that can rival the abundance of European data available today. This will ensure that countries with the largest public health needs are not the last to benefit from important genetic research.

Improved treatment will translate to a better quality of life for the individual, their family, community, and society as a whole. In fact, pharmacogenetic testing will likely produce economic benefits for Africa too. Genetic technologies are both rapidly advancing and decreasing in cost. In the future, tests that can be cheaply and specifically designed for diagnosis or drug prediction in specific ancestry groups will be a reality. In the long term, the money saved by avoiding relapses, hospitalisations and hit-and-miss treatments is predicted to far outweigh the cost of genetic screening. What's more, a price cannot be put on the countless additional benefits personalised psychiatric care will bring. Genetic discoveries will lend evidence to research in other populations and will be applicable to diseases that share genetic roots with mental illnesses and responses to other drugs that share common mechanisms. Both the scientists and the policymakers have a long way to go before all of this can be achieved, but there is certainly hope for personalised mental healthcare in Africa.

Emma Frickel was born in Durban, KZN, where she completed her schooling. She then moved to Stellenbosch, Western Cape, to study at Stellenbosch University, where she has remained since. She completed her Bachelor of Science degree in 2016, and in 2017 she obtained her Honours degree in Human Genetics. This was where her passion for neuropsychiatric genetics was realised, and where her focus remains. She is currently in the first year of her Master's degree, researching the genetic, neuroanatomical, and environmental influences of antipsychotic treatment response in schizophrenia, and she hopes to one day obtain a PhD in this field. When Emma is not in the lab, she can probably be found at home, absorbed in the latest crime or drama series, otherwise reading Harry Potter for the hundredth time. She also enjoys being with friends, appreciating the unique wine culture that Stellenbosch has to offer.

Ellen Ovenden is originally from Johannesburg but has lived in the Western Cape for almost ten years. Ellen is currently completing her PhD in Genetics at Stellenbosch University. In 2015, she obtained her Master's degree, focusing on the complex genetic regulatory mechanisms related to antipsychotic treatment response in schizophrenia. Ellen's PhD expands on this research by adding epigenetic regulation to the mix, a component of psychiatric illness that has recently come to the fore as a key player. Ellen considers herself a mental health advocate and has always been interested in biological psychiatry and debunking myths about mental illness. In her spare time Ellen fosters her obsession with film and enjoys experimenting with new dishes in the kitchen.

Dr Celia van der Merwe attended Stellenbosch University for her undergraduate BSc degree in Human Life Sciences in 2007. Thereafter, she completed her Honours degree in Medical Physiology, and went on to obtain her Masters and PhD in Human Genetics from Stellenbosch University with a focus on the genetic aetiology of Parkinson's disease. Currently, Celia is a postdoctoral research fellow at the University of Cape Town. She has an interest in understanding the complexity of the genetic concordance between psychiatric disorders, the underlying downstream common biological pathways thereof, and how this can be applied in unique African populations.

Prof. Louise Warnich is a professor in Genetics and Dean of the Faculty of Science, Stellenbosch University. Her current research interests focus on genetic variation in pharmacogenes in South African populations and the application of pharmacogenomics to optimise therapies in schizophrenia and HIV/AIDS. She obtained both her MSc and PhD in Human Genetics from the Stellenbosch University

Dr Nathaniel McGregor graduated with a BSc in Molecular and Cellular Biology in 2006, a BSc Honours in Genetics in 2007, and an MSc (cum laude) in 2009, all at Stellenbosch University. He then spent a year and a half managing the laboratory of a molecular diagnostics company after embarking on his PhD (Psychiatry) where he focused on identifying new candidate genes which may be involved in anxiety disorders. After 18 months as a postdoctoral researcher in neuropsychiatric genetics he was appointed as a faculty member in the Department of Genetics at Stellenbosch University where he now co-runs the Human Genetics laboratory with Prof. Louise Warnich and is co-founder of the System's Genetics Working Group. Additionally, he is a member of the Schizophrenia Research Group (headed by Prof. Robin Emsley) in the Department of Psychiatry at Stellenbosch University, the US/ UCT MRC Unit on Risk and Resilience in Mental Disorders, and is a fellow of the Global Initiative for Neuropsychiatric Genetics Education in Research (GINGER) programme of the Harvard TH Chan School of Public Health and MIT.

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Scientists peep deep into a diamond crystal to get information about the nature of its defects

A multinational team of researchers, including a scientist from Wits University, have taken a deep look into a diamond to see how the atoms in its platelet defects are arranged in the hardest natural material known to man.

Using two processes, namely transmission electron microscopy and electron energy-loss spectroscopy, the scientists probed the spatial arrangement of carbon and nitrogen atoms forming the core of the defects. The nature of the bonds between the atoms was also determined.

Like voids and inclusions, platelets are known as 'defects' or imperfections in diamonds. Where the carbon atoms in diamonds are in perfect periodic arrangement, a platelet defect disrupts the periodic arrangement of the carbon atoms, resulting in a defect that looks like a tiny straight line inside the gem stone when imaged with an electron microscope along a specific direction in the diamond crystal.

Research on the nature of defects in a diamond has been going on for many decades, but the breakthrough came when an atomic resolution aberration corrected transmission electron microscope at the Centre for High Resolution Microscopy at the Nelson Mandela University was used to image and analyse the platelet defects. The microscope was operated in scanning transmission electron microscopy (STEM) mode, using a high angle annular dark field detector together with electron energy loss (EEL) spectrum imaging, says Professor Mervin Naidoo from the Wits School of Physics. An article on the team's work that included scientists from the Nelson Mandela University, Free State University, Oxford University in the UK and the Max Planck Institute in Germany, was recently published in the journal, *Nature Materials*.

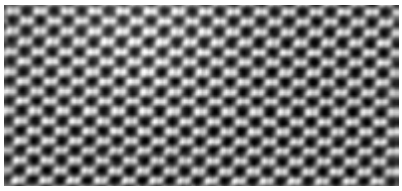
Thin diamond sections for STEM analysis were prepared by using a focused ion beam (FIB) to cut sections of 5 × 10 microns with a thickness of about 20-50 nanometres (a nanometre is a billionth of a metre). The sections were then investigated in an atomic resolution electron microscope by passing a focused beam of electrons with a well-defined energy through the thin diamond section. The interference pattern formed by the electron 'waves' after passing through a thin diamond section generates an image of the spatial arrangement of the carbon atoms in the diamond crystal as well as the carbon and nitrogen atoms in the platelet defect. The corresponding electron energy-loss data provides information about the chemical composition of the platelet and the nature of the chemical bonds between the atoms.

'By juxtaposing these images onto each other, we were able to create a unique image of the platelet,' says Naidoo.

While many theoretical models of the atomic arrangement of atoms in the platelets were proposed in the past, the current study was the first ever that succeeded in imaging the exact atomic positions in the platelets and matching that to one of the theoretical models proposed earlier.

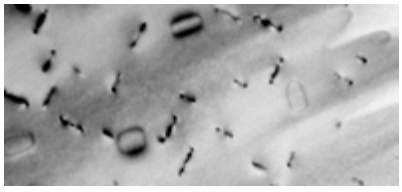
Carbon atoms in a diamond are arranged in a periodic three-dimensional lattice. The platelet defect interrupts the periodic arrangement of atoms by introducing a type of extended planar defect, containing mostly carbon and some nitrogen atoms. The atoms in the platelet are arranged in a zigzag ordering of defect pairs along the defect line.

'Diamonds are messengers from the deep. The knowledge of the structure and composition of a platelet defect could tell us how diamonds are formed in the Earth and which processes are involved in their formation,' says Naidoo. 'In other words, the current knowledge now allows researchers to formulate a dynamic model of the possible point defect interactions that eventually formed this platelet structure.'



A scanning transmission electron microscopy image of a diamond. At this resolution you 'see' the individual dumbbells formed by two carbon atoms at the face centred cubic lattice points of the diamond structure. *Jaco Olivier*

A high-resolution transmission electron microscopy image showing a single platelet. *Jaco Olivier*



A bright field transmission elelctron microscopy image of platelets in a diamond. *Jaco Olivier*

Platelets can also now be produced in synthetic diamonds, which would allow scientists to compare the nature of platelets in natural diamonds to their synthetic counterparts.

These results also revealed that platelets do not consist of nitrogen atoms only, but it showed that platelets do contain nitrogen and the nitrogen atoms most likely play a role in the formation kinetics of the platelets.

'We have uncovered a mystery. We have answered by atomic resolution electron imaging techniques the question of the atomic arrangement of atoms in platelet defects in diamond. This study now opens up other exciting research avenues,' says Naidoo. 'This is not the end of the story.'

Issued by: Schalk Mouton, Senior Communications Officer, Wits University

The Universe is right next door

The South African Astronomical Observatory (SAAO) brings the Universe closer to home.

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NRF National Research Foundation | SAAO South African Astronomical Observatory

Science Clubs

The missing link in our science education and communication efforts

Massive efforts geared at improving levels of scientific literacy and increasing the numbers of learners choosing science- and technology-based studies and careers have been undertaken since the dawn of democracy. These have been mainly led and supported by the Department of Science and Technology, science research councils, science centres, universities and the private sector. During events such as the National Science Week, National Science Festivals and science centre-based programmes, learners are informed, amazed, excited, inspired about science and technology. However, questions that beg to be answered are: *How do we retain the inspiration and interest acquired during these events? How do we develop the interest further after these events? How do we sustain and transform the awareness developed to continuous active performance and participation in science and technology?* These preceding three questions speak to issues of continuity, sustainability and development. The most powerful response to those questions is Science Clubs.

Science clubs can increase the frequency of science- and technology-based activities at schools and in communities. They can augment the intensity of science engagement activities among our learners. Science clubs can shift the site of science activities from science centres and universities to schools and communities. They can facilitate the culture of science appreciation and science-based recreation in our schools and communities.

The South African Astronomical Observatory has, for the last decade, been involved in promoting the formation of science clubs. This has been done in various ways, which include facilitation of workshops for school teachers and learners, training of science centre personnel and department of education in the formation and supporting of science clubs, presentations at various conferences on the need for establishment of science clubs and how to establish these clubs. This has also included development of science club brochures, website and newsletters. Jive Media has also been involved in the promotion of science clubs through its Science Spaza programme and website, Science Spaza Newspaper and science-based competitions. The South African Association of Science Centres and Technological Centres (SAASTEC) and the South African Agency of Science and Technology Advancement (SAASTA) have also been initiating and supporting these efforts.

So what are these science clubs? Science clubs are school- and learner-based organisations aimed at providing opportunities for learners to explore science. They are usually supported by science teachers and interested parents during their nascent stages. These clubs can enhance positive experiences that learners have with science. They can help learners develop problem-solving skills, confidence and communication. Science clubs can challenge gifted and talented learners, while appealing to and motivating struggling learners. They can also serve as links between schools and industry; schools and universities; schools and communities; and lastly between schools and research institutes and councils.

Science clubs can undertake a number of activities. These include educational excursions to science-based facilities such as science centres and research councils and industry; hosting speakers and debates; facilitating peer tutoring and entering competition and science expos. Completing problem solving exercises and puzzles can also be part of the science club programme. Reading and discussion of articles from science-based magazines such as *Quest- Science for South Africa* can boost the knowledge and interest of science club members. See the SAAO brochure in this link on how to start and run a science club. https://scienceclub.saao.ac.za/wp-content/uploads/sites/90/2015/09/Science_Club_brochure_web_1_.pdf

Education organised by SAAO and Ithemba Labs – budding chemists. *SAAO*

Experience in the formation and in supporting science clubs has shown beyond doubt that support from scientists, engineers, researchers and post graduates is needed to keep science clubs vibrant and to ensure that they are a success. Scientists can support science clubs as guest speakers and can provide talks based on their fields of study. They can do demonstrations and experiments and can also share career related information. Scientists can also write articles for science club newsletters and act as experts and be available to be consulted on queries over telephone and by email.

Everyone can contribute in the establishment of science clubs. You can introduce, initiate or inspire learners to form their own club. You can adopt or support an already-existing club. You can encourage your colleagues or acquaintances to present at a local science club. There are many ways in which we can contribute in the establishment of science clubs.

Having active and vibrant science clubs at our schools and communities can contribute positively towards attracting our youth into science and technology. Science clubs can also improve the level of scientific interest and literacy in our communities.

Relevant links and contacts:

Websites : www.scienceclubs.org.za
https://jivemedia.co.za
www.saasta.ac.za
www.livingmaths.co.m

Contacts:

Sivuyile Manxoyi ; sivuyile@saao.ac.za
Simon Rametse ; simon@saasta.ac.za
Buzani Khumalo ; buzani@saao.ac.za

First tetrapods of Africa lived within the Devonian Antarctic Circle

The first African fossils of Devonian tetrapods (four-legged vertebrates) show these pioneers of land living within the Antarctic circle, 360 million years ago.

The evolution of tetrapods from fishes during the Devonian period was a key event in our distant ancestry. New-found fossils from the latest Devonian Waterloo Farm locality near Grahamstown in the Eastern Cape, South Africa, published recently in *Science*, force a major reassessment of this event. 'Whereas all previously found Devonian tetrapods came from localities which were in tropical regions during the Devonian, these specimens lived within the Antarctic circle,' explains lead author, Dr Robert Gess of the Albany Museum in Grahamstown, and co-author Professor Per Ahlberg of Uppsala University in Sweden. The research was supported by the South African DST-NRF Centre of Excellence in Palaeosciences, based at the University of the Witwatersrand, and the Millennium Trust.

South Africa's rich natural resources

The Minister of Science and Technology, Mmamoloko Kubayi-Ngubane, says South Africa is richly endowed with natural resources, and the country's fossil wealth dates back more than three billion years.

'It is uniquely expansive for any one country, and many internationally significant fossil discoveries have been made in our country and are stored in South African Museum collections,' says the Minister.

She says the country's geographic advantage as a global provider of information on the evolution of life and humanity on Earth stands alongside the country's biodiversity and geographic advantage in astronomy and the science of the southern oceans.

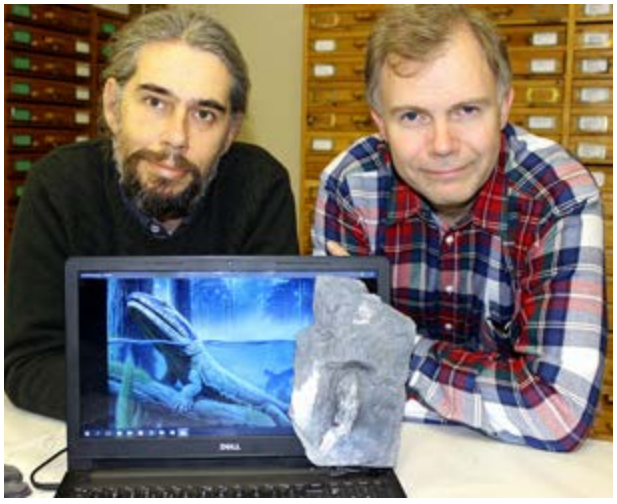
Work on South African paleosciences is of crucial national and international importance, because it provides proof of our shared human origins, the mutual roots that bind all people within a common humanity. It also provides answers as to what occurred before humans existed, including the evolution of plant and animal life.

The Minister congratulated Dr Gess, saying this groundbreaking discovery places South Africa at the forefront of the study of the evolution of land-living vertebrate animals, including the ancestry of all the wildlife we see in the country's game parks.

The first African Devonian tetrapods

Two new species, named *Tutusius* and *Umzantsia,* are Africa's earliest known four-legged vertebrates by a remarkable 70 million years. The approximately metre-long *Tutusius umlambo* (named in honour of Archbishop Emeritus Desmond Tutu) and the somewhat smaller *Umzantsia amazana* are both incomplete. *Tutusius* is represented by a single bone from the shoulder girdle, whereas *Umzantsia* is known from a greater number of bones, but they both appear similar to previously known Devonian tetrapods. Alive, they would have resembled a cross between a crocodile and a fish, with a crocodile-like head, stubby legs, and a tail with a fish-like fin.

The Waterloo Farm locality (where the tetrapods were discovered) is a roadcut first revealed in 2016 after controlled rock-cutting explosions by the South African National Roads Agency (SANRAL) along the N2 highway between Grahamstown and the Fish River. This cutting exposed dark grey mudstones of the Witpoort Formation that represent an ancient environment of a brackish, tidal river estuary that contain abundant fossils of animals and plants.



Dr Rob Gess (left) and Prof Per Ahlberg (right) with the cleithrum of Tutusius and an image of a Devonian tetrapod. *Steven Lang*

Full reconstruction of Waterloo Farm, including *Tutusius* and *Umzantsia*. *Maggie Newman*

The first tetrapod found outside of tropical regions

The real importance of *Tutusius* and *Umzantsia* lies in where they were found.

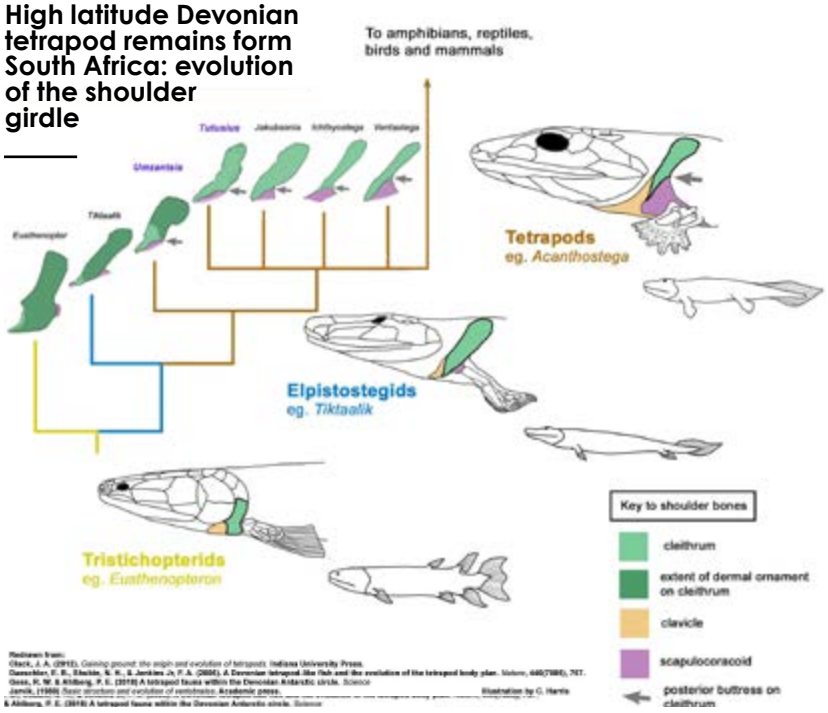
Devonian tetrapod fossils are found in widely scattered localities. However, if the continents are mapped back to their Devonian positions, it emerges that all previous finds are from rocks deposited in the palaeotropics – between 30 degrees north and south of the equator. Almost all come from Laurussia, a supercontinent that later fragmented into North America, Greenland and Europe.

The much larger southern supercontinent, Gondwana, which incorporated present-day Africa, South America, Australia, Antarctica, and India, has hitherto yielded almost no Devonian tetrapods, with only an isolated jaw (named *Metaxygnathus*) and footprints, being found in eastern Australia. Because Australia was the northernmost part of Gondwana, extending into the tropics, an assumption developed that tetrapods evolved in the tropics, most likely in Laurussia. By extension it was assumed that movement of vertebrates from water onto land (terrestrialisation) also occurred in the tropics. Attempts to understand the causes of these major macroevolutionary steps therefore focused on conditions prevalent in tropical water bodies.

The Waterloo Farm tetrapods not only come from Gondwana, but from its southernmost part: reconstructed to have been more than 70 degrees south, within the Antarctic circle. Abundant plant fossils show that forests grew nearby, so it wasn't frozen, but it was definitely not tropical and during winter it will have experienced months of complete darkness. This finding changes our understanding of the distribution of Devonian tetrapods. We now know that tetrapods occurred throughout the world by the Late Devonian and that their evolution and terrestrialisation could realistically have occurred anywhere.

South Africa now adds insights into the emergence of land animals to its incredible fossil record, which also includes transition to mammals from reptile-like ancestors and the evolution of humans. There is probably not another country on the planet that so fully documents the long and dramatic evolutionary history of our own lineage.

High latitude Devonian tetrapod remains form South Africa: evolution of the shoulder girdle

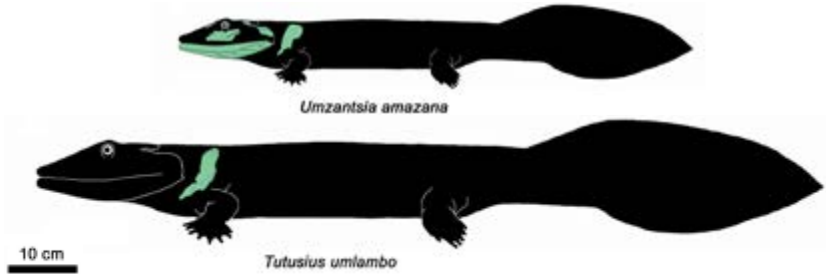


Infographic of evolution of the shoulder girdle across the fish to tetrapod transition. Includes the proposed position of the cleithra of *Tutusius* and *Umzantsia*. High latitude Devonian tetrapod remains from South Africa: evolution of the shoulder girdle. *Rob Gess and Per Ahlberg*

Waterloo Farm tetrapod cleithra

1. Cleithrum of *Umzantsia amazana* (scale = 1 cm)
Rob Gess and Per Ahlberg

2. Cleithrum of *Tutusius umlambo* (scale = 1 cm)
Rob Gess and Per Ahlberg



Silhouettes of Devonian tetrapods showing (in green) the life positions of tetrapod bones recovered from Waterloo Farm. *Rob Gess and Per Ahlberg*

Issued by: Kimberleigh Tommy, Science Communications Officer, DST-NRF Centre of Excellence in Paleosciences.

Precision Medicine for Africa: Challenges and opportunities

Michèle Ramsay explains the basics of precision medicine

Imagine a future where you visit your local healthcare clinic in Soweto. A friendly receptionist leads you to a computer where she can access all your information, since birth. She explains how to enter information on your current health and lifestyle. You meet with a health counsellor who explains what tests can be performed and what the possible outcomes could be. You sign a consent form indicating what information you would like to receive and what you would rather not know. For example, you may wish only to receive information on medical conditions that can be treated. She provides you with a tube to collect some of your saliva. The saliva is sent to a laboratory where the DNA is extracted and the tests performed. Two weeks later you return and see the doctor who makes an accurate diagnosis of your illness, and prescribes the most effective treatment to restore you to good health with minimal side effects. She provides information to prevent future ill health.

In this world money is no obstacle, all your data is safely stored and your identity protected, but most of all, we have the knowledge to make direct and accurate connections between the test results and your present and future health.

WHAT IS PRECISION MEDICINE?

Precision medicine is an approach to healthcare that uses modern technologies to generate information that takes into consideration your individuality (including your health, lifestyle, diet, family history of disease and ethnic origin) to ensure that you receive the correct treatment at an optimal dose at the right time to ensure your best health.

HOW DOES THIS DIFFER FROM CURRENT MEDICAL PRACTICE?

It builds on our current evidence-based medical practice by using additional information that will make it possible to provide a direct link between your genetic makeup, your behaviour, environment and lifestyle, and your health. In addition, it will guide treatment, by providing information on possible medication to avoid adverse reactions, to predict the most effective drug dose and to minimise side effects. It will therefore be less of a hit-and-miss or trial-and-error approach and will ensure that the most appropriate drug for the best outcome is prescribed without delay.

HOW CLOSE ARE WE TO A PRECISION MEDICINE APPROACH IN AFRICA?

The most important aspect of precision medicine is the knowledge needed to understand the relationship between genetic variability, lifestyle and environment, and your health. This relationship has been studied extensively in populations of European and Asian ancestry, but there is not much information about African populations. There are some great success stories, but in general there is not enough knowledge from African populations to fully understand the relationship between your genetic variability and your risk for developing diseases. So, we need a lot more knowledge before we can effectively implement precision medicine programmes for Africans.

WHAT ARE THE AREAS OF MEDICINE THAT ARE CLOSEST TO THE INTRODUCTION OF PRECISION MEDICINE?

There are essentially three areas where precision medicine is already having an impact on healthcare. They are:

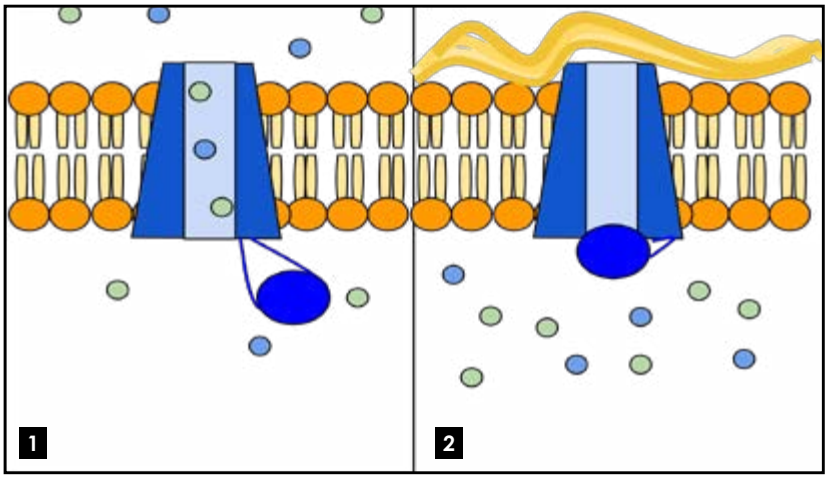
1. Precision medicine approaches for the diagnosis and treatment of genetic diseases that are caused by mutations in single genes (Mendelian diseases).
2. In the area of cancer to improve the accuracy of diagnosis and to choose the right treatment.
3. To guide the safe and efficient use of drugs or medication to minimise adverse events.

Each area is described briefly and illustrated with examples.

Diseases caused by mutations in single genes (Mendelian diseases)

There are an increasing number of Mendelian diseases for which we now know the causal mutations and are beginning to understand how they affect the functioning of the genes. This provides an opportunity to study the biological consequences of mutations and to develop drugs that specifically target the mutant genes. Good examples of diseases where a precision medicine approach has led to novel treatment options are Duchenne muscular dystrophy and cystic fibrosis.

Example: Cystic fibrosis (CF) is a devastating autosomal recessive genetic disease characterised by sticky mucus secretions that cause recurrent lung infections and prevent the pancreas from functioning properly to digest food. If not treated, babies with CF usually die within a year. There is currently good treatment, but this treats the consequences and not the cause of CF. CF is caused by mutations in the cystic fibrosis transmembrane conductance regulator gene (*CFTR*). This gene encodes a protein that sits in the cell membrane and regulates the flow of salt and water across the membrane. Over 1 500 CF-causing *CFTR* mutations have been described and they affect the function of the protein in six different ways. There are some mutations that are common in people of European origin (e.g. *F508del* and *G551D*) and absent in Africans. A precision medicine approach has been used specifically to treat patients with the *G551D* mutation with a drug called ivacaftor, which improves the flow of salt and water across membranes. In addition it was found that two drugs in combination, ivacaftor and lumacaftor, can be used to treat patients with the common *F508del* mutation, which then improves salt and water flow across membranes even more. Together these two mutations are present in ~90% of CF patients of European origin and they can potentially benefit from these drugs. These mutations are, however, rare or absent in people of African origin as they have a different common mutation (3120+1G>A) and people with this mutation would not benefit from the above medications as the problem with the *CFTR* protein is different. This highlights the importance of detecting the actual gene mutation to understand how to develop effective precision medicine treatments for CF. Furthermore, it also points to ethnic differences in gene mutations that cause the same disease and can influence the treatment options for the patients.

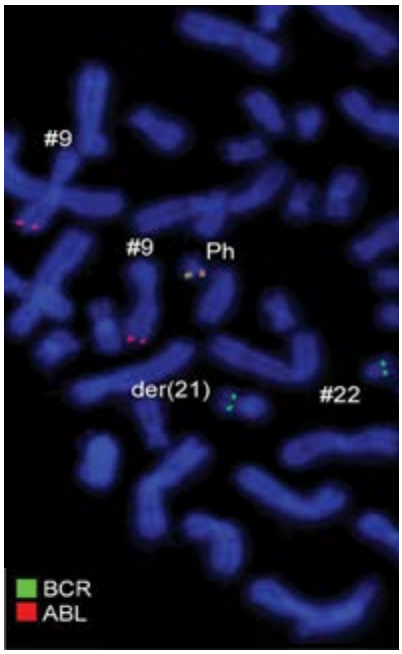


The *CFTR* protein is a channel protein that controls the flow of H_2O (water) and Cl^- ions (chloride ions in salt) into and out of cells inside the lungs. When the *CFTR* protein is working correctly, as shown in Panel 1, ions freely flow in and out of the cells. However, when the *CFTR* protein is malfunctioning as in Panel 2, these ions cannot flow out of the cell due to a blocked channel. This causes cystic fibrosis, characterised by the buildup of thick mucus in the lungs. *Wikimedia Commons*

Cancer diagnosis and treatment

Cancer is a very complex disease and develops as an accumulation of mutations in cell lineages (cells that are derived from the same original cell through cell divisions). They usually affect a single organ (primary site) and can sometimes spread to other organs or regions of the body (secondary sites). Each cancer is different, but some groups of cancers have specific signatures or profiles. By comparing the DNA from the cancer with the DNA from non-cancerous cells from the same person, we can detect the cancer profiles. Sometimes when we understand what the profiles mean in terms of causing the abnormal cell growth in the cancer, we can specifically target the cancer cells by using a precision medicine approach. Because this is targeted to the actual problem, it has a higher likelihood of success.

Example: Chronic myeloid leukaemia (CML) has been studied for a long time and in the 1960s it was discovered that the cancerous blood cells of patients with CML carry a small abnormal chromosome called the Philadelphia chromosome (named after the city in which it was first discovered). This chromosome was shown to be a combination of chromosomes 9 and 22. At the region where the parent chromosomes have broken and re-attached incorrectly (a process called translocation) two different gene segments were placed next to one another to form a hybrid gene (BCR-ABL) giving rise to an abnormal hybrid protein. This hybrid protein has a special pocket that allows other proteins to dock and then adds phosphate molecules to those proteins, thereby altering their function and triggering a process of abnormal cell division, and eventually this causes CML. In the late 1990s, a molecule was identified that would competitively dock into the pocket of the hybrid molecule thus preventing other proteins from being phosphorylated. This drug, called imatinib (or sometimes glivec) was dubbed the golden bullet in the fight against cancer, and is one of the earliest examples of a precision medicine approach to treating cancer.



The Philadelphia chromosome showing the *BCR-ABL* hybrids.
Spandidos Publications

Pharmacogenetics

It has long been known that not every person reacts to a specific drug in the same way. A drug that seems to cause a miracle cure in one group of patients may cause severe and life-threatening reactions in another group. Pharmacogenomics refers to the ability to detect specific genetic mutations that will provide information on which patients are likely to benefit from a drug, who will not benefit and who is likely to have a very bad reaction to a specific drug. In practice in some parts of the world, patients need to be tested for specific variants before a doctor is permitted to prescribe certain drugs. There is relatively little pharmacogenomic research specifically performed in Africans, but some studies have shown that many Africans have more severe side effects when taking specific anti-retroviral drugs when they are infected with HIV.

Example: Why is it that some people find immediate pain relief when taking codeine (a common active ingredient found in pain killers) and this same drug, when take by a mother who is breast feeding her baby, can put her baby's life in danger? The reason is that some people have genetic variants or mutations in specific genes that provide the code for enzymes (specialised proteins) that break down certain drugs in order to convert them to their active ingredients. The mutations can either cause the speeding up of the breakdown process, meaning that the person very quickly gets a very high dose of the active ingredient, or can slow down the process, meaning that the person derives little benefit from the drug because they do not get a high enough dose of the active ingredient to minimise their pain. Mothers with specific mutations in their *CYP2D6* genes that cause them to be ultra-rapid metabolisers, could put their babies at risk of excessive exposure to high levels of codeine.

HOW COULD ONE APPLY PRECISION MEDICINE TO COMMON COMPLEX DISEASES?

At a population level, the causes of the greatest morbidity and mortality are the common complex diseases, also referred to as non-communicable diseases (NCDs). They include cancer, diabetes, lung disease and cardiovascular disease (including stroke and hypertension). The reason is that they affect many people and cause premature death, often in the most economically active people in a population. These NCDs result from a complex interaction between genetic and environmental risk factors and often there is an accumulation of events that finally leads to a disease diagnosis. The most important preventative measures or delaying strategies involve a healthy lifestyle. A balanced diet, sufficient exercise and enough sleep, while avoiding smoking and excessive alcohol consumption. The most indicative factors include a family history and early signs of the disease. Precision medicine in this case is seldom helpful as tests would include over a hundred different genetic variants that together can only predict 1-4% of the variability of the risk factor or trait (e.g. the genetic risk for obesity). On a population level, genetic risk scores for NCDs can be used to place people in categories from high to low risk. Cut-off points may then be used in a public health scenario to recommend certain prevention or screening programmes for individuals with the highest genetic risk. For example in the United Kingdom a test of about 100 genetic markers would identify the 1% of women in the population at highest risk for breast cancer and they will be offered free mammography screening from an early age.

Several companies offer genetic tests for dozens of DNA markers and promise to give you information on your risk for developing many different conditions, including NCDs They often market their tests directly to the public without the need to consult a doctor. These tests however, have little or no predictive value at the individual level and have seldom been validated in African populations. It is important not to be misled by their seductive advertising. Your health would be better served by adjusting your lifestyle and seeing your local general practitioner or visiting your local clinic.

INTERPRETING DNA SEQUENCE DATA CAN BE A CHALLENGE AND RAISES IMPORTANT ETHICAL ISSUES

Precision medicine often involves determining the DNA sequences of individuals. Generating accurate data and interpreting what the DNA variants are likely to mean with respect to disease can be challenging. There are many software programmes that have been developed to interpret DNA sequence data and to predict whether specific variants are likely to contribute toward causing diseases. A vast amount of information is stored in databases that link DNA variants with phenotypes but they are far from comprehensive and particularly lack adequate data from Africans. The information that comes from sequencing whole genomes or whole exomes (the protein coding regions of the genome representing ~1.5% of the genome) poses some very interesting ethical dilemmas.

Variants of unknown significance

A variant of unknown significance (VUS) is a variant for which it is difficult to predict whether it has a link to a disease or phenotype or is completely neutral in its effect. It may also be a variant for which there is conflicting information in different databases where one database suggests it causes disease and another indicates that it has no effect on your health. Perhaps in a few more years, additional information will come to light that will firmly place the variant in the category of disease causing or alternatively, as benign. There are several interesting questions that arise.

- Should the scientists report VUSs when they write their reports?
- Should a doctor share this information with a patient?
- Could such information cause unnecessary anxiety and worry for the patient?
- Who should be responsible for checking, from time to time, as more information becomes available on a VUS?
- Who should cover the costs of keeping the information up to date and contacting the patient if there is new information that could be useful to the patient?

Efavirenz tablets

Wikimedia Commons

Incidental findings

When a test is done that provides information on a whole exome or whole genome sequence, with a view to identifying variants related to a specific disease, there is a very high likelihood that you will find variants related to medically important genes that may cause a completely different disease. This is an incidental finding, something you were not looking for, but which you observe.

- Should the scientist write the incidental findings in the report if the doctor did not request the information?
- Should the doctor tell the patient if they know about the variant?
- Should you only tell the patient if there is a strong link between the DNA variant and the likelihood of getting the disease?
- Should you only tell the patient if there is a treatment for the disease that the patient is likely to develop?

An example of an incidental finding is if the doctor is treating the patient for cancer and is looking for the genetic cause of the cancer. The data from the test then reveal that the patient has a high likelihood of developing Alzheimer's disease (adult onset dementia). Another example is of a doctor treating a young girl for a serious muscle disease and requesting a whole genome sequencing test to identify the mutation that causes the muscle disease. The data then reveal that the girl has only one X chromosome (instead of the normal two) and will be infertile. Should the doctor tell the parents about this finding?

The role of genetic counsellors

Doing sequencing tests that could potentially reveal far more information than only what the doctor is looking for in order to diagnose, or to find the cause of disease, requires careful communication with the patient and their family. Genetic counsellors are trained to convey genetic information to patients and to help them make decisions by telling them about all their options. They are also trained to convey information in cases where there is not complete certainty, such as the detection of VUSs. It is therefore important for patients and their families to receive counselling before they have genetic or genomic tests done so that they understand what might be found and can state their preference as to what kind of information they wish to receive. It is then equally important to follow up with counselling when the test results are returned so that patients and their families can get information to understand the implications of a result and the options that are available to them.

To read about the journey of a journalist who had his own genome sequenced follow the link 'Game of Genomes': https://www.statnews.com/feature/game-of-genomes/season-one/

IS IT POSSIBLE TO APPLY THE CONCEPT OF PRECISION MEDICINE TO A POPULATION, RATHER THAN AN INDIVIDUAL?

Recently the concept of precision public health has come to the fore. Public health is about ensuring the greatest benefit to the largest number of people in a population.

For example vaccination is a form of preventative public health. How then does precision medicine, which is aimed at matching the most effective treatment to an individual, apply to a population?

In countries that do not have large resources to cover the medical care of all their people, one could ask how they could be able to afford the expensive precision medicine tests and approaches? One may, on the other hand, argue that they cannot afford NOT to invest in a precision public health programme that would, in the long run, lead to more cost effective treatment for the majority of the population.

Here is an example. A common form of anti-retroviral therapy (ART) to treat HIV infection is efavirenz. It is usually given at a single daily dose of 600 mg per day. It was discovered that efavirenz has serious side effects in many individuals of African descent. The side effects include dizziness, nightmares, insomnia, nervousness, cognitive dysfunction, depression, suicide ideation and anxiety, and therefore many patients simply stop using the medication. Through a precision medicine approach it was discovered that a genetic variant in the *CYP2B6* gene causes efavirenz to be broken down (or metabolised) much more slowly by the body of individuals who have this genetic variant. That keeps the dose of the medication too high causing the side effects. Up to 50% of Africans have this variant. A simple public precision health intervention was to remove the drug and use an alternative set of ARV drugs, as was done in Botswana, or to produce pills that contain only 200 mg of efavirenz, which means that it is far less likely to cause side effects, even in patients with the slow metabolising genetic variant.

THE PROMISE OF PRECISION MEDICINE FOR AFRICA

What could be done in a middle-income country like South Africa to ensure that we do not miss out on the promise of precision medicine? As we look to the future there are five simple things that we could do now to make a difference to the lives of our children and their children.

1. Accurate counting: Register every birth and every death and record cause, age and place of death.
2. Build laboratory infrastructure: It is important to make an accurate diagnosis of disease by implementing affordable and accurate tests.
3. Tracking diseases in communities: This will help us understand infectious epidemics and disease transmission.
4. Invest in skills development: Make sure that enough people are trained in specific areas to perform and interpret tests and to support our health system.
5. Communicate clearly and effectively: We need to create a political will to have a larger proportion of the national health budget devoted to the development of smarter interventions that include precision medicine research and translation.

The unique genetic variants in African populations could lead to important discoveries to help improve the health and well-being of not only Africans, but of the global community.

Michèle Ramsay (PhD) is the director of the Sydney Benner Institute for Molecular Bioscience at the University of the Witwatersrand, Johannesburg, professor in human genetics and South African Research Chair holder in Genomics and Bioinformatics of African Populations. As a member of the Human Heredity and Health in Africa Consortium (H3Africa) she leads the AWI-Gen study on the genetic and environmental contributions to obesity and cardiometabolic disease risk in six centres across four African countries. Her research aims to shed light on the role of African population genomic variation in susceptibility to diseases and translational research to contribute toward a precision medicine approach in Africans.

CURRICULUM CORNER

OUTCOMES LIFE SCIENCES

Cell unit of life (Grade 10)

DNA code of life (Grade 12)

In the gaping mouth of ancient crocodiles

The mouth of today's crocodilians inspires fear and awe, with their wide gape and the greatest known bite force in the vertebrate animal kingdom. However, this apex predator of today and its modus of attack (its mouth) had humble beginnings. The very earliest crocodilians were very different to the beasts we know well today, they were much smaller bodied, slender and had longer legs. And it is thought that their lifestyle was very different.

A new study by a team of international experts, led by University of Witwatersrand PhD candidate Kathleen Dollman and Professor Jonah Choiniere published today in the *American Museum Novitates*, endeavoured to further explore the mouth of one of the earliest occurring and least understand groups of crocodilians, the shartegosuchids. In 2010, Choiniere was a part of a field team working in the Late Jurassic (±160 mya) exposures in the western Gobi in Mongolia, when he found the fossil of a small snout of a shartegosuchid. This work was co-authored by researchers based at the American Museum of Natural History, the George Washington University and the Institute for Vertebrate Palaeontology and Palaeoanthropology.

The snout was later CT scanned at the American Museum of Natural History, exposing an unusual, closed secondary palate. Crocodilians are one of only a few groups of animals that evolve a completely closed, bony secondary palate (along with turtles and mammals). A closed secondary palate has many biological implications for crocodilians, including breathing while under water and reinforcing the skull to allow for their incredible bite force.

Coauthor Prof. Mark Norell standing at the field site where the fossil was found. *WITS University, Jonah Choiniere, Kathleen Dollman, Viktor Radermacher*

This study showed that these early crocodilians, the shartegosuchids, are important because they evolved a completely closed secondary palate much earlier than previously thought. This is an interesting example of convergent evolution, whereby a similar feature evolves independently in two completely unrelated groups. The advent of a convergent evolutionary event allows scientists to test questions about why that feature evolved and even the function of that feature, which in this case is the first step in understanding the purpose of a closed secondary palate in crocodilians.

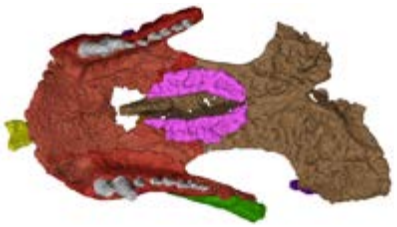
'I was surprised to find that there were many features in the palate and snout that were completely different between shartegosuchids and extant crocodilians' says Dollman. Shartegosuchids have a thickened and sculptured palate together with a tall and short snout, whereas extant crocodilians have a smooth palate with a long and broad rostrum.

'We would expect to see the same palatal structures and snout shapes in both shartegosuchids and extant crocodiles if they were using it for similar functions and had evolved a closed palate for similar reasons', says Dollman. 'The observed differences tell us that shartegosuchids likely had predation practices to which there is no modern analogue in crocodilians'.

'It's been nearly 10 years since we collected this fossil after driving five days across the Gobi Desert,' said Choiniere, 'and I am delighted that it's formed a part of Kathleen's PhD.'

Issued by: Kimberleigh Tommy, Science Communications Officer, DST-NRF Centre of Excellence in Paleosciences.

Reconstruction of *Shartegosuchus*. *Artist: Viktor Rademacher*



Digital reconstruction of the palate of the fossil. *WITS University, Jonah Choiniere, Kathleen Dollman, Viktor Radermacher*

Digital model of the skull still enclosed in matrix. *WITS University, Jonah Choiniere, Kathleen Dollman, Viktor Radermacher*

Basics for Precision Medicine

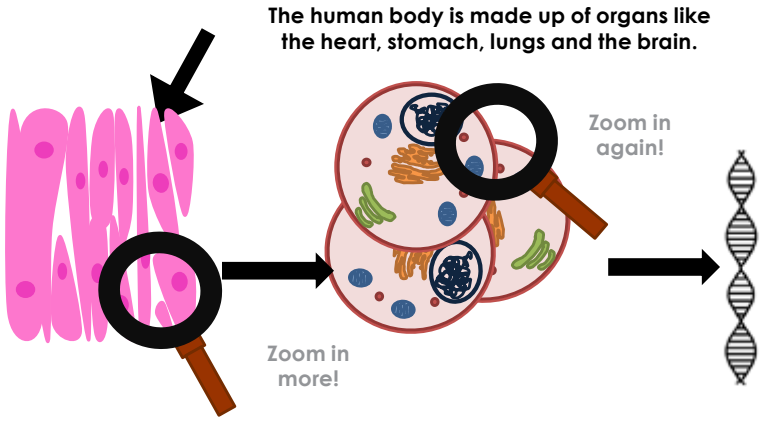
From DNA to Doctor

by Jorge da Rocha and Mahtaab Hayat

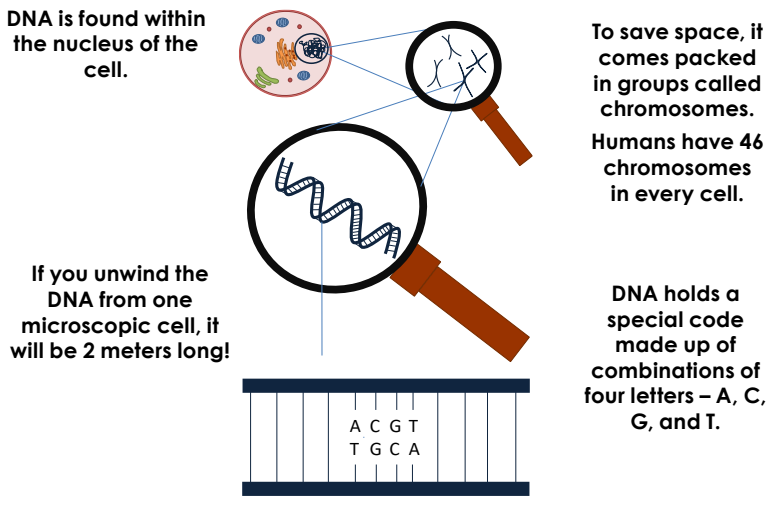
Everybody gets sick every now and then, and it is usually resolved with a quick visit to the doctor, some medication and some rest. Still, most of us have had, or know someone who has had problematic responses to their medication. This is called an adverse reaction and some of these are related to changes in DNA.

But what if your doctor could know beforehand what medicine to use based on your DNA sequence? This is one aspect of an approach called precision medicine. Genomic science can be used to help make medicine safer and more effective. If you were curious to know how this works, you would also need to know some of the basics about genetics.

WHAT IS A CELL?



WHAT IS DNA?



BUILDING BLOCKS OF LIFE

DNA is an information molecule. It is deoxyribonucleic acid – a chemical blueprint that encodes who we are, what we look like and much more. Most cells in the human body contain our DNA. The DNA carries instructions to build cells and to give them specific functions. The diagrams explain what cells look like, where they are, and where DNA is located within them.

DNA can be interpreted as a code made up of four letters, each corresponding to a chemical group forming the bases of the molecule. These chemical groups are called nucleotides. They are named Adenine (A), Cytosine (C), Guanine (G) and Thymine (T). Across the two DNA strands, they match as pairs, A-T and G-C, and these pairs form the backbone of the familiar DNA double helix or ladder. Sections of DNA that form physical products are called genes. Each gene corresponds to a different protein product, which has a unique DNA sequence of A, C, G, T within the gene.

GENES AND MUTATIONS:

A gene could be interpreted as a mini blueprint, a section of information that is needed to form a bigger machine, take for example the car. Changes to the DNA, referred to as variants or mutations, can cause changes to the parts. Though the example shows a 'mutation' leading to a car with square

wheels, most human variants are benign (make no difference to our health), and some can even be advantageous.

The information stored in DNA is linear, it is a long line of code, which is useful to store so much information in a such a small place. But how does DNA form the 3D structures that build up our body, called proteins? DNA guides the synthesis of proteins by directing combinations of amino acids (protein building blocks) in a particular order. An example of how these processes work is shown. As it is impractical for DNA to leave the nucleus, a message is sent in the form of RNA molecules.

RNA, ribonucleic acid, is a temporary guide used to link amino acids together into long chains, which then fold to form proteins. Protein shapes are critical to their function, so any change in DNA, could lead to a different amino acid placed in the sequence, which may change the final shape of the protein.

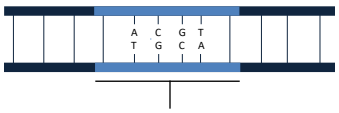
DNA CAN EASILY BE EXTRACTED FROM CELLS:

If you would like to extract your own DNA, a handy guide is displayed in the diagrams below. Saliva is an easy-to-use source of DNA, as it contains cheek cells. A soap, such as dishwashing liquid is used to break down the cell membranes, freeing the DNA. At this point, DNA is still soluble (dissolved), so we won't be able to see it until we cause it to precipitate out. Salt is used to help this process. It causes DNA (which is negatively charged) to bind to the positively charged sodium ions. Meat tenderiser can be used to help clarify the final product of DNA, as this will degrade proteins which were present in the cheek cells and saliva. If you don't have meat tenderiser, a drop of contact lens solution will do instead. Surgical spirits are used to force DNA out of solution so we can see a white globby mass form. This is a crude extraction, but similar principles are used to extract DNA from many different types of cells around the world!

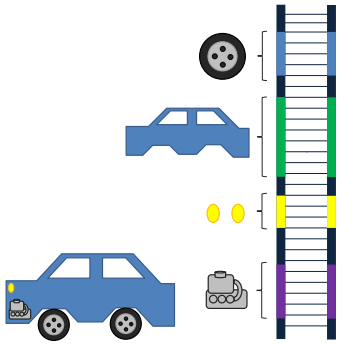
HOW DO WE IDENTIFY THE MUTATIONS OR VARIANTS THAT ARE PRESENT IN OUR DNA?

DNA analysis technology has developed rapidly in the past 20 years. The process began with a technique known as Sanger sequencing. Sanger sequencing uses a series of chemical reactions to copy a DNA strand, and to capture the base that is added to the growing strand, thus revealing its sequence. This technique, though accurate, is expensive and slow, so it is currently used only for short sequences or for validation of variants. Other more automated technologies, such as the genotyping array and next generation sequencing,

HOW DO THESE CODED MESSAGES WORK?



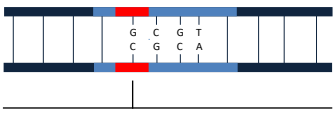
Sections of DNA that code for specific things are called genes.



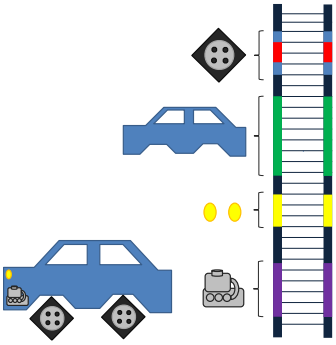
Think of genes as mini blueprints needed to put together one big project. In this example, lets imagine building a car.

Each gene has the code for different parts. These parts come together to make a whole car.

WHAT IF THERE WAS A CHANGE IN THE CODE?



Sometimes, mutations occur in our genes – a change in the blueprint.

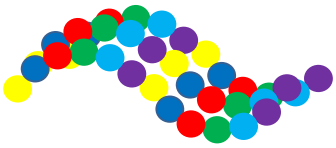


A mutation in one gene can have big effects on the end product.

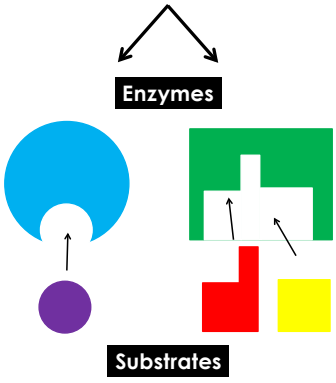
In this case, the mutation changes the shape of the tire. This change affects the shape and function of the protein.

WHAT ARE AMINO ACIDS & PROTEINS?

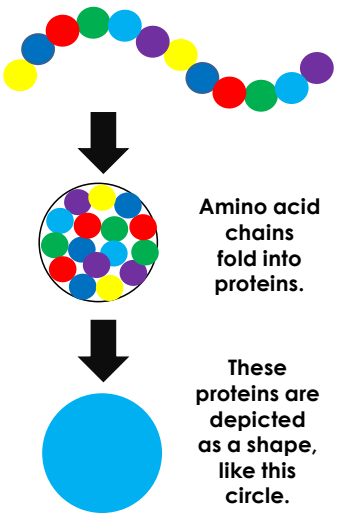
Enzymes are proteins that help complex reactions occur everywhere in life.



Enzymes are very specific and only work with specific substrates.



FOLDING OF PROTEINS



DNA EXTRACTION

You will need:

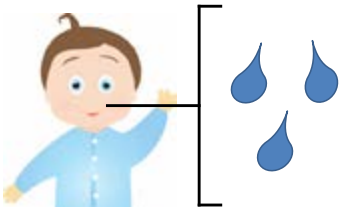
Dishwashing liquid

Table salt

Meat Tenderiser

Surgical Spirits

You will also need a special ingredient – a source of DNA!



The easiest way to get a good amount of DNA containing cells for this experiment is via saliva.

STEP 1: Swirl your saliva around in your mouth until you have about 2 ml, then spit into a small container or glass.

STEP 2: Add one or two drops of dishwashing liquid to the saliva, and swirl gently.

STEP 3: Take a pinch of salt in your fingers and add it to the mixture, one small pinch is enough.

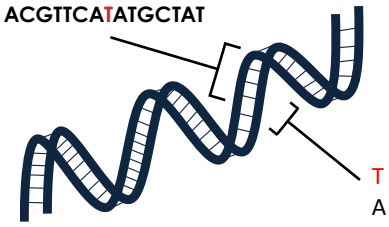
STEP 4: Add a small pinch of meat tenderiser to your mix, then swirl or stir gently.

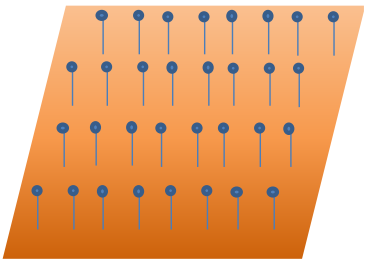
STEP 5: Now slowly add about 4-5 ml of surgical spirits to your mixture. Give your container a gentle shake or stir the mix slowly.

Are you seeing a sticky, white, slimy form in your mix? **That's your DNA!**

DNA GENOTYPING ARRAYS

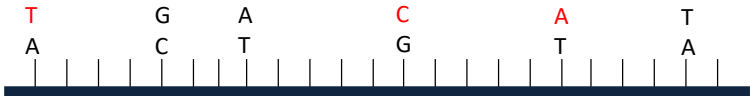
As DNA is microscopic, special machines are used to determine the sequence for scientists to interpret.





Specialised microchips: genotyping array chips capture DNA variants at specific positions across the genome, targeting variants of interest.

Each marker on the chip corresponds to a DNA variant site. These can be used to assess variants across the genome.



These chips are affordable, and can return substantial genomic information for a low price. But as these chips can only capture previously known variants, Next Generation Sequencing (NGS) technology must be used to discover new variants.

have a much higher throughput, meaning they provide large amounts information in a short amount of time. These methods have allowed genomic data and science to expand rapidly.

DNA genotyping array, is used to identify the variants that an individual has at predetermined regions of the DNA. It can tell us whether a person has inherited the same base at a specific position from their mother and father, and is therefore 'homozygous' at that position, or has inherited two different alleles, one from their mother and one from their father, in which case they are 'heterozygous' at that position. DNA sequencing ensures that each position in the DNA sequence is determined and all the variation can be detected, including variants that have never been discovered before.

FROM DNA VARIATION TO PRECISION MEDICINE

Precision medicine uses many different laboratory techniques to gather information which is combined with a doctor's assessment of a patient to make an accurate diagnosis and to develop a treatment that will be most effective in that specific patient.

WE PRESENT TWO DIFFERENT SCENARIOS FOR PRECISION MEDICINE BELOW

Firstly we look at how precision medicine is used to ensure that we give a patient the medicine that is best suited to the way in which their genes work, and secondly we give an example for targeted therapy for a specific cancer.

Pharmacogenetics is a new field aiming to characterise the relationship between genetic variants and reactions to pharmaceutical drugs. Just as medicines have a chemical impact on our body, our body induces chemical modifications to the medicine molecules in order to move them around, break them down, or remove them from the body. The machinery required for these modifications are proteins, and as protein coding and expression are controlled by DNA, any change to DNA could lead to changes in the pathways which a given medication will take. The figures and descriptions (below) describe how changes in DNA can result in changes in protein structure, and how this could lead to a poor drug response. By understanding the relationship between genetic variants and drug pathways, it is possible to predict the response before treatment is given.

There is much more work to do in Africa before we could use pharmacogenetics here, as African populations have not yet been genetically characterised to the same extent as others around the world.

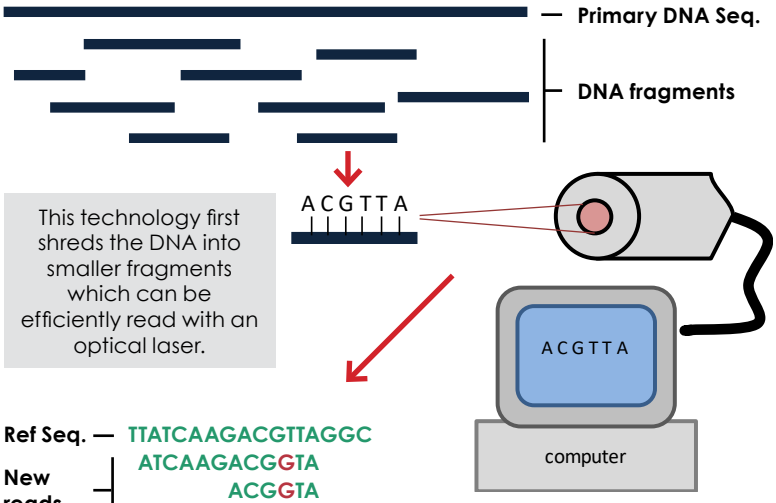
THE SECOND EXAMPLE IS OF THE USE OF PRECISION MEDICINE IN TREATING CANCER

Cancer is a disease that begins when cells grow uncontrollably in the body. This can be caused by genetic and environmental factors. Variants in certain genes can cause many cancers such as breast cancer and leukaemia. Environmental factors include smoking, exposure to radiation and stress. Because there are many different types of cancers that occur in different organs of the body, it is a difficult condition to treat. However, with the advancement in genome sequencing, doctors are able to decide on specific treatment regimens based on your genetics, or the genes the cancer cells express. Scientists have discovered that if a patient has certain variants in their DNA, or a chromosomal rearrangement, it can be targeted for therapy. Targeting mutated proteins that arise because of chromosomal rearrangements is used in the treatment of some types of leukaemia.

Chronic myeloid leukaemia (CML) can arise through a chromosomal

DNA SEQUENCING

To characterise the entire sequence of DNA a sequencer is used to scan multiple copies of the DNA strand in parallel. Specific regions or whole genomes can be sequenced using NGS technologies.



This technology first shreds the DNA into smaller fragments which can be efficiently read with an optical laser.

A computer stores all the information for the millions of DNA fragments.

These short sequence 'reads' are then aligned to a reference genome. This process can be used 'assemble' regions of DNA and to find variants. This is a very computationally intensive process that involves multiple bioinformatics steps.

A whole genome sequence captures all variation that a person may have. It holds a wealth of information that can be used for multiple downstream assessments.

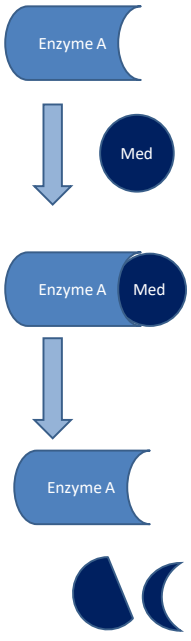
BREAKING DOWN MEDICINE

Enzymes are biological machines that catalyse reactions. They lower the activation energy needed to let chemical reactions occur. These reactions include the breakdown of medicines.

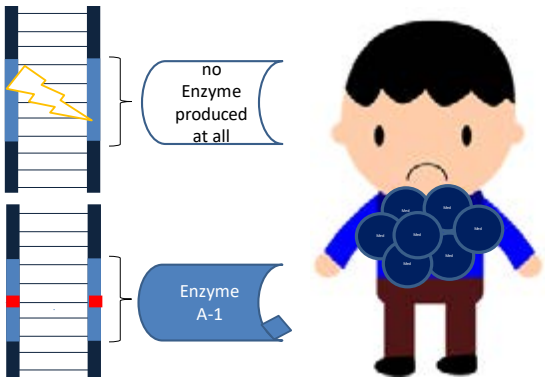
The unique shape of enzymes is what makes them very specific to what they bind to. Take for example our Enzyme A – its shape is specific to the medicine it breaks down.

Enzyme A is able to bind the medicine quite well, and once it is bound, chemical bonds in the medicine are broken and the pieces are small enough to be removed effectively from the body, or to fit other enzymes along that path.

Special enzymes are necessary to do these jobs because, without them, the medicine will build up inside our bodies. Once too much builds up, toxic effects are likely to occur.



VARIANTS IN THE ENZYME A GENE



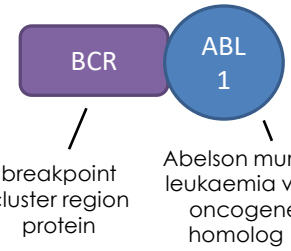
Some genetic variants can fully disrupt the function of a gene. These may cause the protein to be formed incorrectly, or in abrupt pieces, which have no active ability to bind and break down medicines.

Other variants can change the shape of the enzyme. These modified enzymes (e.g. Enzyme A-1) may be able to bind and work, but would do so far more slowly.

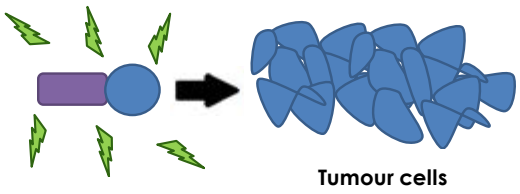
Without the enzyme available, or if it is not working at the necessary rate, the medicine can accumulate in your body, causing adverse reactions, which can make you feel worse rather than better!

TREATING CANCER - LEUKAEMIA

A chromosomal translocation is when two pieces of two different chromosomes break off and swap places. A chromosomal translocation between chromosomes 9 and 22 is known to cause leukaemia – a cancer of the blood.

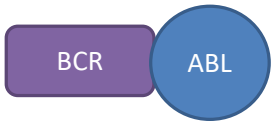


The translocation produces a fusion protein of BCR and ABL.

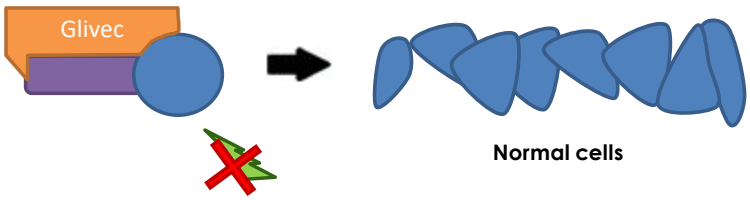


The BCR-ABL fusion protein is a kinase protein that sends signals to cells to promote abnormal cell division, and cause cancer.

If a leukaemia patient has this translocation, then the product of the gene, the BCR-ABL protein, can be targeted.



Glivec is a medicine given to leukaemia patients. This medicine blocks the BCR-ABL protein from sending signals to the cell, preventing abnormal cell growth.



Glivec is a medicine given to leukaemia patients. This medicine blocks the BCR-ABL protein from sending signals to the cell, preventing abnormal cell growth.

translocation that results in a fusion protein that promotes cell division. This leads to cancer. In the figure below, the protein that promotes extensive cell division in the cancer cells is inhibited by targeted treatment (using Glivec- also referred to as Gleevec or Imatinib). The targeted medicine is made to fit the shape of the protein, ensuring that it prevents the mutated protein from sending growth signals to the cells, therefore stopping cell growth.

These artworks and descriptions were developed by the Sydney Brenner Institute for Molecular Bioscience and Wits Division of Human Genetics Community Outreach Programme (SCOP). This is a student-driven initiative that aims to educate learners about genetics and how this science is used to advance health, medicine and much more. They are trying new methods to reach learners, such as school presentations and an app which should be available soon. If you would like to contact them with questions or to invite them to your school (limited to Gauteng and surrounding areas), please reach out at: scop.students@gmail.com

Jorge da Rocha (MSc), is a PhD student at the Sydney Brenner Institute for Molecular Bioscience, University of the Witwatersrand. His work involves trying to understand and characterise African genetic variants of relevance to pharmacogenomics. He is an avid member of SCOP, the departmental outreach programme, whose main goal is to share knowledge about genomics and inspire learners to find out more about this exciting field.

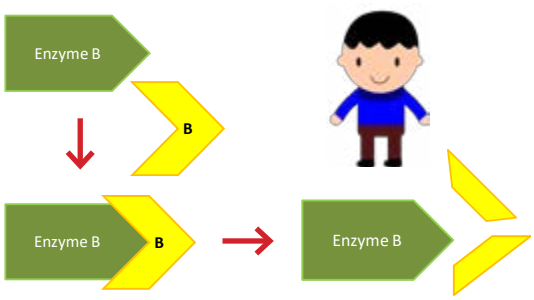
Mahtaab Hayat is currently a PhD student at the Sydney Brenner Institute for Molecular Bioscience (SBIMB), University of the Witwatersrand, Johannesburg. She is an executive member of the outreach programme at the SBIMB, as well as the South African Society for Bioinformatics Student Council. Her current research aims to explore the genetics of breast cancer in Black, South African populations.

HOW CAN PRECISION MEDICINE HELP?

By learning about the variants that can cause this, we can assess what medicines are safest for you to use, to prevent this from happening.

If we know you have variants in the Enzyme A gene that affect its function, we could give you medicine that gets broken down by Enzyme B instead, right from the start.

You'd be well on your way to getting better and not worried that your medicine was making you worse.



Cranium of a four-million-year-old hominin shows similarities to that of modern humans

The 'virtual' revisiting of a fossil described as 'the oldest evidence of human evolution in South Africa' shows surprising results.

A cranium of a four-million-year-old fossil, that, in 1995 was described as the oldest evidence of human evolution in South Africa, has shown similarities to that of our own, when scanned through high resolution imaging systems.

The cranium of the extinct *Australopithecus* genus was found in the lower-lying deposits of the Jacovec Cavern in the Sterkfontein Caves, about 40 km North-West of Johannesburg in South Africa. Dr Amelie Beaudet from the School of Geography, Archaeology and Environmental Studies of the University of the Witwatersrand and her colleagues from the Sterkfontein team scanned the cranium at the Evolutionary Studies Institute, based at the University of the Witwatersrand, in 2016 and applied advanced imaging techniques in 'virtual paleontology' to further explore the anatomy of the cranium. Their research was funded by the Centre of Excellence in Palaeosciences, the Claude Leon Foundation and the French Institute of South Africa and was published in the *Journal of Human Evolution.*

'The Jacovec cranium represents a unique opportunity to learn more about the biology and diversity of our ancestors and their relatives and, ultimately, about their evolution,' says Beaudet. 'Unfortunately, the cranium is highly fragmentary and or much could be said about the identity nor the anatomy of the Jacovec specimen before.'

Through high resolution scanning, the researchers were able to quantitatively and non-invasively explore fine details of the inner anatomy of the Jacovec specimen and to report previously unknown information about the genus *Australopithecus*.

'Our study revealed that the cranium of the Jacovec specimen and of the *Ausralopithecus* specimens from Sterkfontein in general was thick and essentially composed of spongy bone,' says Beaudet. 'This large portion of spongy bone, also found in our own cranium, may indicate that blood flow in the brain of *Australopithecus* may have been comparable to us, and/or that the braincase had an important role in the protection of the evolving brain.'

In comparing this cranium to that of another extinct group of our family tree, *Paranthropus*, that lived in South Africa along with the first humans less than two-million-years ago, their study revealed an intriguing and unexpected aspect of the cranial anatomy in this genus.

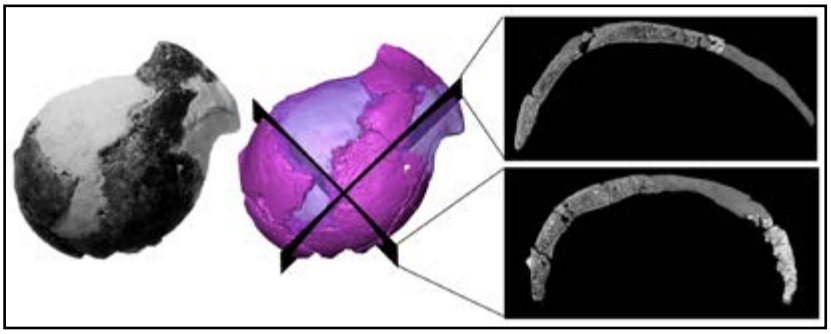
'We also found that the *Paranthropus* cranium was relatively thin and essentially composed of compact bone. This result is of particular interest, as it may suggest a different biology,' says Beaudet.

Situated in the Cradle of humankind, a Unesco World Heritage Site, the South African paleontological sites have played a pivotal role in the exploration of our origins. In particular, the Sterkfontein Caves site has been one of the most prolific fossil localities in Africa, with over 800 hominin remains representing three genera of hominin recovered since 1936, including the first adult *Australopithecus*, the iconic 'Mrs Ples' and 'Little Foot', the most complete single skeleton of an early hominin yet found.

'The Jacovec cranium exemplifies the relevance of the Sterkfontein fossil specimens for our understanding of human evolution,' says Beaudet. 'Imaging techniques open unique perspectives for revisiting the South African fossil assemblage.'

Issued by: Schalk Mouton, Senior Communications Officer, Wits University

Dr Amelie Beaudet
Wits University

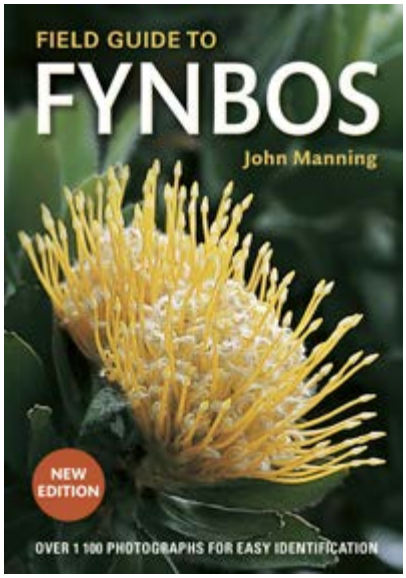


Original picture (left) and virtual rendering of the Jacovec cranium (middle) with two sections revealing the inner structure (right). *Amelie Beaudet*

BOOK REVIEW

THE EXTENSIVE FYNBOS

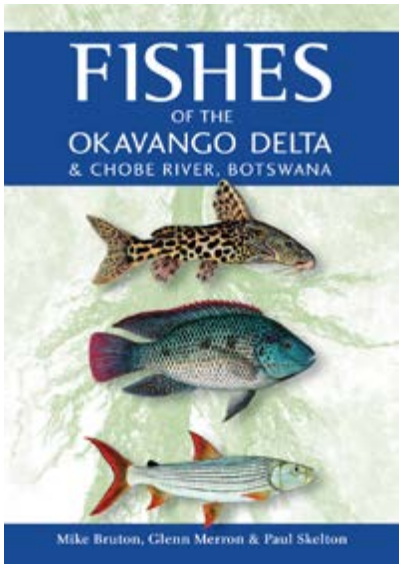
Field Guide to Fynbos. By John Manning. Cape Town. Struik Nature. 2018



This is the second edition of this invaluable field guide to the fynbos, arguably one of our richest floral kingdoms. The fynbos vegetation group extends from north of Clanwilliam in the west, to Port Elizabeth in the east. Most fynbos vegetation is contained within the boundaries of the Cape Floristic Region, but suitable soils support smaller portions of fynbos well beyond its borders. This book provides a complete guide to the many plants in this wonderful vegetation.

The introductory chapters of the book contain a full ecological description of fynbos, its communities, the climate that it is found in, the topography and soil types and the diversity of the vegetation types. Plant structure and adaptations and the role of fire in the maintenance of community diversity are also covered.

As a field guide, the book explains how it is to be used, how to find the right group of plants and descriptions of fynbos families. Each group is distinguished by a coloured tab on the page edge. All species are photographed in full colour, with a full description and a distribution map. A must for any enthusiastic botanist.



FLY FISHING IN THE OKAVANGO

Fishes of the Okavango and Chobe River, Botswana. By Mike Bruton, Glenn Merron and Paul Skelton. Cape Town. Struik Nature. 2018

This slim volume is the only dedicated guide to the fishes of this region and offers a comprehensive guide. As with all the Struik Nature books, the guide starts with an excellent introduction to the region, covering the structure and ecology of the Okavango Delta, and its aquatic habitats. The ecology and behaviour of the fish are also covered, including habitat preferences, feeding behaviour and predator-prey relationships, breeding strategies, and survival tactics. Rare and endangered species are singled out. There is an introduction to angling in the Delta and on how to identify a fish.

Each species acount is accompanyed by a colour illustration and a full species description. This guide will be invaluable for local fishermen, naturalists and conservationists as well as tourists visiting the area.

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A portion of Theewaterskloof dam, Cape Town's main water supply, close to empty in March 2018. Droughts continue to this day.

Zaian, Wikimedia Commons

WE ARE IN THE MEGHALAYAN AGE

We are living in a newly named geologic age – the Meghalayan – which started 4 200 years ago. This is one of three newly designated ages dividing the Holocene Epoch, a geological time period that started off 11 700 years ago by the end of the Ice Age.

First there was a warming period, now called the Greenlandian Age. Then about 3 800 years the Northgrippan age began with freezing weather that continued to about 4 000 years. Finally, the Meghalayan started 4 200 years ago with a devastating 200-year worldwide drought. This marked quite a serious collapse of human agricultural civilizations. The megadrought triggered human crises and migrations, which took place from China to the Middle East to India.

A stalagmite from a cave in the northeastern Indian state of Meghalaya acts as the official time stamp marker for the start of the age. The drought is also recorded in other geologic sediments and at archaeological sites around the world.

The Meghalayan is the first formal geological time interval in Earth's 4.6-billion-year history that began at the same time as a worldwide, climate-driven cultural event.

Source: Science Magazine

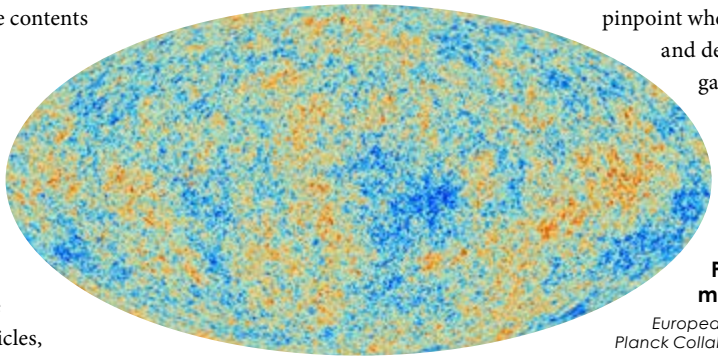
THE OLDEST LIGHT IN THE COSMOS

Scientists have just unveiled the final result from the European Space Agency's Planck Satellie, which observed the oldest light in the Universe – the cosmic microwave background – from 2009 to 2013. Since the satellite was launched, Planck has helped scientists work out a detailed story of the start of the Universe, its life history and current properties. This includes everything from the contents of the Universe, to its age, to how fast it is expanding and when the first stars formed. But the bottom line is that we still don't understand what makes up most of the Universe.

Before Planck, the theory was that the Universe was made up of various particles, including the mysterious unidentified dark energy and dark matter. Dark matter is thought to be a type of sub-atomic particle, so far only detectable via its gravitational effect on visible matter, while dark energy drives the accelerating expansion of the Universe. Planck's observations suggest that this is in fact the case – meaning that the Universe's matter and energy are divided into about 68% dark energy, about 27% dark matter and only about 5% normal matter. And it is only normal matter that we know anything about!

So while Planck has revealed several interesting facts – the Universe is slightly older than we thought – and has helped to pinpoint when the first stars appeared and detailed how structures like galaxies and galaxy clusters form, we still know very little about what makes up the Universe.

Source: Science Magazine



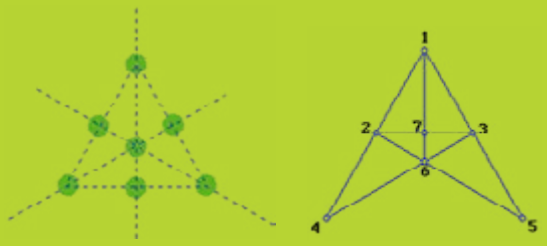
Planck maps the microwave background

European Space Agency, Planck Collaboration

QUEST MATHS PUZZLE NO. 46

Find a number ABCDEFGHIJ such that A is the count of how many 0s are in the number, B is the number of 1s, and so on.

Answer to Maths Puzzle no. 45:



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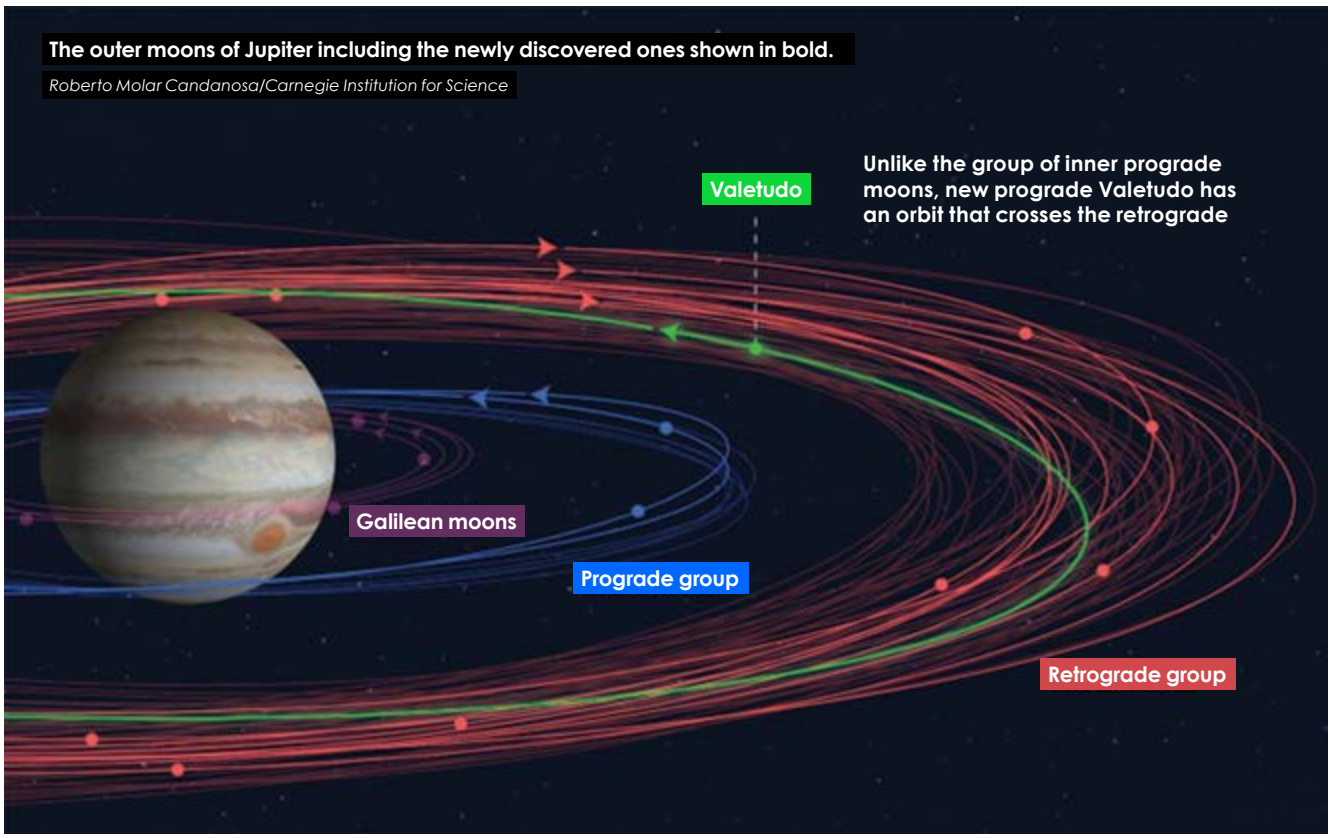
JUPITER'S MANY MOONS

There are 12 more moons around Jupiter than astronomers previously thought – and one is seriously strange. Eleven of the moons orbit in the same direction as each other, but one is oribiting in the opposite direction, potentially putting it on a collision course. There are 79 moons already orbiting around Jupiter, the inner moons probably formed from a disk of gas and dust that orbited the giant planet in the early days of the Solar System. The outer moons were probably free-floating space rocks captured when they came too close, and their opposite orbit was set by the direction that they approached Jupiter from.

The rock that is going in the opposite direction is called Valetudo and is tiny – only about a kilometre across. It orbits in the same direction as Jupiter's spin, but alongside the further out retrograed moons. Valetudo may be the last remnant of a bigger object that has already been involved in several collisions, or maybe part of a family of moons, the rest of which have been smashed completely.

Source: Science News



The outer moons of Jupiter including the newly discovered ones shown in bold.

Roberto Molar Candanosa/Carnegie Institution for Science

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