What next for anti-doping: EVOLUTION OR REVOLUTION?

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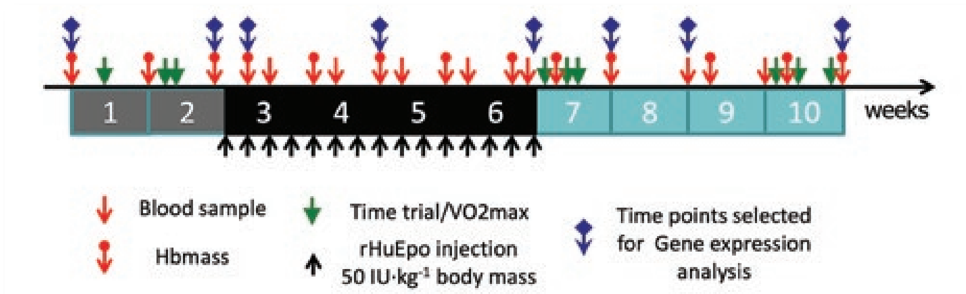
THE ISSUE

Unfortunately, doping is a well-known problem in sport. The use of performance-enhancing drugs (PEDs) is widespread in elite and amateur level athletes. The World Anti-Doping Agency (WADA), created in 1999, implemented the World Anti-Doping Code in 2004 in order to regulate doping control and provide educational strategies to avoid doping[1]. The Code documents the anti-doping rules, regulations and policies worldwide, which proposes 1.) to protect the fundamental right to participate in doping-free sport, consequently promoting health, fairness and equality for athletes worldwide and 2.) to promote effective anti-doping programmes at international and national level in order to detect, deter and prevent doping [2].

However, more than 20 years since the founding of WADA and a decade after the implementation of the Code, the magnitude of sports doping has not substantially abated [3]. The true prevalence of doping is unknown, but some studies estimate a prevalence of 14–39%, which is far from that provided by doping control test results (estimate of doping: 1–2% annually)[3].

The principles cited in the Code for doping control are: Education, Deterrence, Detection, Enforcement and Rule of Law[2]. As this requires an effective testing system, the Athletic Biological Passport (ABP) was implemented in 2009, as a strategy for blood doping detection, and a few years later in 2011, the urinary steroidal model was also implemented[4]. However, dopers continue to use PEDs and/or illegal methods to obtain an unfair advantage.

For example, analysis of blood samples collected during the 2011 and 2013 World Athletics Championships revealed evidence of blood doping[5].



Above: Figure 1 Experimental design of EPO study[9]. Grey: Baseline; Black: during rHuEpo administration; Blue: post rHuEpo administration

Since 2004, the WADA has stored samples collected during Olympic Games for long-term retrospective re-analysis with more advanced analytical techniques. A total of 138 medals were impacted by doping, with the majority of positives (72%) identified retrospectively, which took 6.8 ± 2.0 years to be announced. The most detected type of PEDs is the Anabolic Androgenic Steroids (AAS). Amongst the most difficult AAS to be detected is testosterone, which generally is used together with a variety of other anabolic steroids such as nandrolone, stanozolol, oxandrolone, drostanolone, metenolone and mesterolone[6].

THE PROMISING "GAME CHANGER" DETECTION METHOD

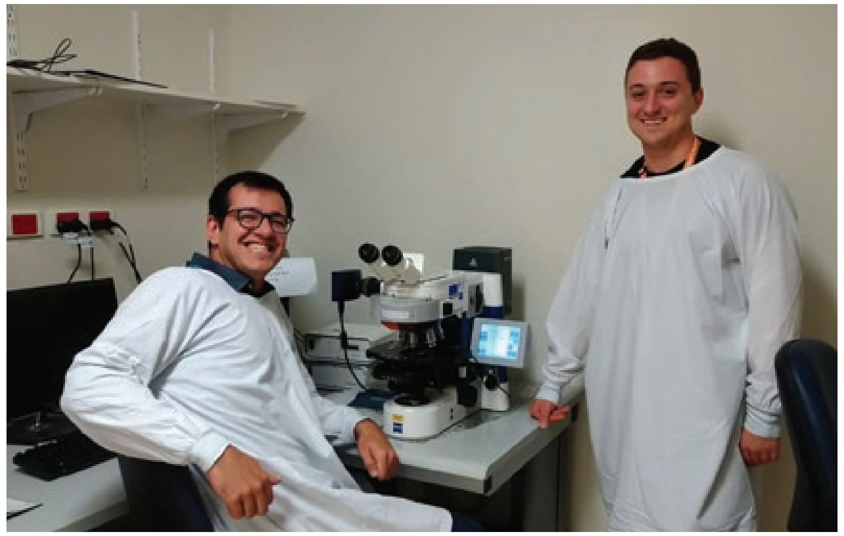
First requirement for new game changing advances in anti-doping science to improve testing sensitivity and specificity is the need to adopt the most effective technologies available and not be satisfied with what one can afford or has access to.

For instance, authors writing in the journal Nature in 2017, predict the impact of DNA sequencing will be on a par with that of the microscope[7]. It is essential therefore that anti-doping science is able to use such powerful technologies and to keep up with rapid developments to increase the chances of finding the best possible solutions. Given this technology is routinely being used in biomedical research and precision medicine applications such as for cancer, stroke, Alzheimer's, and understanding COVID-19 and its spread, then vital lessons can be learned and applied to anti-doping research. We have recently published this aspiration[8].

IOC RESEARCH GRANT

Thanks to a research grant from the International Olympic Committee (IOC) we were able to travel to Illumina (San Diego, California in August 2017), one of the company leaders in next generation sequencing, to plan and oversee the analysis of a subset of samples from a high dose recombinant human erythropoietin (rHuEPO) study previously conducted and funded by WADA (*See Figure 1 for the study design*)[9]. This was an EPO intervention study with samples collected at numerous time points in 39 individuals – representing the largest study of its kind.

Fourteen months later (October 2018), we travelled to BGI, a competitor sequencing company based in Shenzhen, China, to test the same samples on what the Chinese are calling the *'Ultimate Sequencer'*. The same sequencing technology is having a big impact on the management of Covid-19. Sequencing is helping decipher not only how the virus is spreading in a particular location, but its origins and how it got there in the first place[10]. Sequencing is also



Above: Figure 2 Biopsy surgery from Trapezius muscle

Above, right: Figure 3 Students whose PhD project is part of the MAASS Study during immuno-histochemistry analysis - Giscard Lima and Alexander Kolliari-Tuner

being used to understand why some individuals are more prone to getting seriously ill, or dying when infected with Covid-19. The results of the sequencing of the anti-doping research samples from our rHuEPO study were most exciting (manuscript in preparation, G. Wang et al.). Briefly, we were able to identify distinct patterns across the time points using the RNA-seq data from either sequencer thereby capturing genes reflecting the response to EPO. As Covid-19 has delayed laboratory progress due to months of enforced lockdown, new funding is currently being sought to continue this exciting research.

Here lies the problem. WADA has committed US $80 million into scientific research since their formation. This funding support from WADA is much less than the transfer fee of one professional football player, such as Neymar (€220 million), Mbappé (€180 million), Philippe Coutinho (€145 million) and others. The research budget of WADA has also been considerably reduced over the last 10 years with almost US $7 million (£5 million/€5.7 million) spent in 2006 compared with US $1.5 million (£1.07 million/€1.22 million) in 2018, a reduction of more than 78% in a 12-year period. The undisputed reality is that "omics" technologies, despite massive potential to revolutionise anti-doping, has not been properly researched and tested. Anti-doping urgently needs new partners.

The need for a concerted "omics" research initiative in anti-doping is also evident by the recent award of the largest research grant ever made in the history of the Partnership for Clean Competition (PCC) - $1 million awarded to Professor Rob Roach from the University of Colorado, USA[11]. This award and the "omics" results we (and others) have generated to date, in the context of what is happening in medical/disease diagnostics, confirm that it is only a matter of when, rather than if, "omics" methods will revolutionise anti-doping. However, a paradigm shift in terms of funding will only expedite this process and save money and pain in the long term.

A GAME CHANGER

The inspirational speech of the IOC president, Thomas Bach, at the fifth WADA world conference in Katowice, Poland, and the pledge of $10 million for new anti-doping approaches with particular focus on genetic sequencing, Dried Blood Spots (DBS), and an ambitious long-term storage and re-analysis programme, could be game changing and represent the turning point in the fight against doping in sport and the protection of the clean athlete[12].

The cornerstone of the IOC president's action plan was to increase the deterrence factor, and as such the IOC extended the storage time of samples and the subsequent re-analysis using new testing methods such as genetic sequencing as these became available. Specifically, the IOC has initiated a global long-term storage and re-analysis programme, also for samples collected during the pre-Games testing period.

This means that these samples also should be stored for up to ten years, as the IOC already does for the samples taken during the Olympic Games. For this to happen, there is a need to revise the blood sample collection criteria set out by WADA to permit the use of tubes for stabilisation of RNA.

A particular focus of our research in Eastbourne is to generate the evidence needed to justify a revision of the blood sample collection criteria approved by WADA to permit the use of tubes for stabilisation of RNA. Failure to revise the blood sample collection protocols in the run up to the Tokyo Olympics would represent a major victory for doped athletes. Despite this unprecedented (in recent times) investment in anti-doping science by the IOC (with particular focus on storage and re-analysis), there would be no real prospect for meaningful reanalysis of samples for blood doping methods as new analytical methods become available.

In summary, implementation of this very promising *"game changer"* detection method is expected to result in increased detection rates of blood doping without an increase in the cost of anti-doping. This outcome is expected to bring a culture change in terms of promoting clean competition. This overall success is also expected to intensify research efforts that involve state-of-the-art technologies such as next generation sequencing (i.e., RNA-Seq) and to advance newer approaches such as artificial intelligence (AI), machine learning, and deep learning to identify new and more robust signatures of doping[13].

THE APPROACH TO SUPPORT HARSHER DOPING SANCTIONS – MAYBE LIFE BANS?

The consensus in the limited scientific literature is that supra-physiologic levels of testosterone stimulates muscle growth and consequently an increase in muscle mass and strength[14]. The suggested mechanism for the increase in muscle hypertrophy and potentially the performance-enhancing properties induced by testosterone is an increase in the number of satellite cells and myonuclei[15].

There are large numbers of myonuclei in skeletal muscle fibres and according to the notion of the "myonuclei domain", each controls a limited cytoplasmic area called "domain"[16]. When a muscle fibre increases in size, satellite cells are activated and are able to proliferate and subsequently differentiate to form new myonuclei[16]. Most available evidence would indicate that muscle fibre hypertrophy, induced by resistance-type exercise training, is accompanied by a rise in myonuclear and satellite cell content[17].

The premise of the "muscle memory" hypothesis is that myonuclei acquired by exercise and/or testosterone administration during hypertrophy are not lost after a period of detraining and atrophy[18]. A "muscle memory" hypothesis could explain the observation that strength training adaptations induced by an increase in muscle mass are significantly enhanced in previously trained individuals despite a prolonged detraining period[19]. In particular, the formation of extra myonuclei could be the local "memory" mechanism in muscle[18,19].

The significance of this idea is that either a long or short-term exposure to AAS will have a sustained effect on muscle morphological changes, leading to improved performance and an enhanced future training effect. Given the persistence of muscle nuclei, the use of AAS combined with training will have a greater impact on muscle hypertrophy than either training or steroid use alone.

> **"Considering the long-term effect of muscle memory, it is possible that athletes are benefiting from a history of AAS use during their Olympic careers. A better understanding of the "muscle memory" mechanism could justify longer suspensions to end this abuse."**

The long-term effect of "muscle memory" has important implications for anti-doping policies and penalties. At least 120 athletes with a history of doping offences and who had been suspended for a doping violation competed at the 2016 Rio Olympics. Thirty-one of these individuals, approximately 25%, won medals[20]. Eight of these were powerlifting athletes who were suspended from March of 2013 up to October of 2015 for Anti-Doping Rule Violations (ADRVs)[21]. Considering the long-term effect of muscle memory, it is possible that athletes are benefiting from a history of AAS use during their Olympic careers. A better understanding of the "muscle memory" mechanism could justify longer suspensions to end this abuse. The aforementioned data suggests that the dopers are steps ahead of the anti-doping system.

There is an urgent need to change this scenario with a higher investment in anti-doping policies.

AN URGENT NEED

Despite some advances in the detection of AAS, there is an urgent need to develop new approaches that are resistant to the ever-increasing number of methods to mask the use of AAS, including the detection of novel designer AAS.

New advances in biotechnology enable the use of powerful tools which have been successfully applied to diverse fields such as the diagnosis of cancer[22] and rare diseases with clinical and genetic heterogeneity[23], treatment for specific genetic diseases and to match transplant recipient and donor.[24].

Considering the efficacy of the new "omics" technologies, this approach can be used to enhance current anti-doping testing, as shown in previous studies that investigated the blood transcriptional signature after administration of rHuEPO in endurance trained athletes[9,25]. Transcriptional profiling showed that transcripts were altered by rHuEPO and the expression pattern was observed up to 3 weeks after the last rHuEPO injection[9]. A validation study using micro-dose of rHuEPO provided evidence that transcriptional biomarkers may be used to prolong the detection window of blood doping [25].

Three of these genes (ALAS2, CA1, and SLC4A1) were also investigated in other studies that used RNA-based methods to monitor erythropoiesis after blood withdrawal and autologous blood transfusion showing significant lower expression of all three genes after 9 days of the transfusion and lower expression of ALAS2 and SLC4A1 after 15 days[26]. Given the short window detection of testosterone, studies investing molecular mechanism of long-term effects of the AAS usage has potential to identify possible biomarkers that can be used in new doping testing.

In order to achieve this goal, the Muscle Memory and Anabolic Androgenic Steroids (MMAAS) Study is an international collaborative study developed by the University of Brighton (UK), University of Rome 'Foro Italico' (Italy) and Murdoch Children's Research Institute - MCRI (Australia). These studies have been conducted in an attempt to replicate the previous findings with particular reference to AAS use and molecular effects on skeletal muscle. In addition, investigating the "muscle memory" mechanism in humans, monitoring human AAS users over time, may also allow the identification of novel molecular markers of AAS that can subsequently be integrated to enhance the new steroidal module of the ABP. The proposed research may also help anti-doping authorities make informed decisions on the length of bans for such doping offences.

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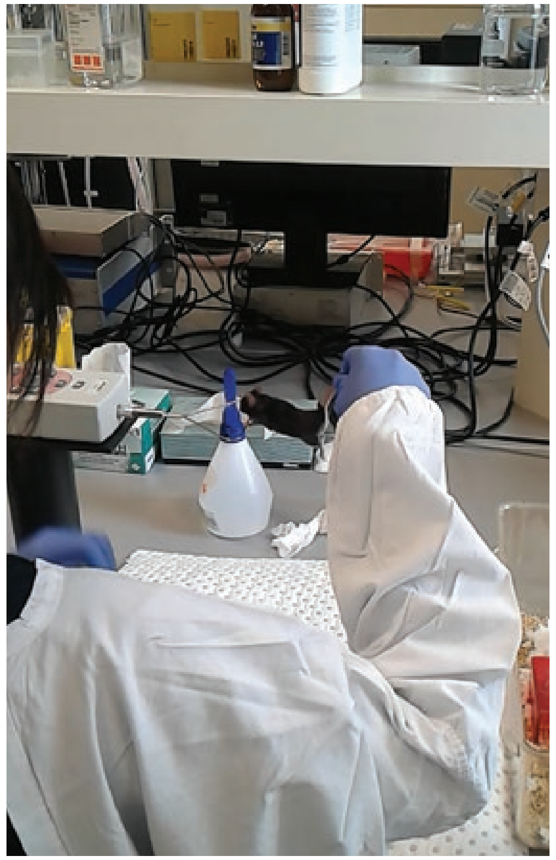


Above: Figure 4 Mice grip strength evaluation carried out at the MCRI laboratory

> **"A second study using animal model (in collaboration with MCRI) has investigated the effect of AAS regarding to gender and time of AAS exposure."**

Two complementary studies have been developed to investigate the "muscle memory" mechanism. To the best of our knowledge, we have created the largest research biobank with human tissue samples of muscle, blood, urine and saliva from resistance trained AAS users, resistance trained non-AAS users and controls. The Trapezius muscle immunohistochemistry (IHC) analysis from 43 volunteers revealed that participants currently under AAS usage have significant higher fibre cross-sectional area (CSA) compared with previous AAS users, resistance trained non-AAS users and non-trained individuals (*Figure 2, previous page*).

In order to investigate the long term effects of AAS usage, the 19 participants were invited to return for a second visit after 20 weeks without AAS use, but most volunteers reported that after their cycle they did not wish to stop the use of AAS, even those subjects that reduced their AAS dose to levels eliciting hormonal levels higher than normal physiological levels.

Only 5 of the 19 participants self-reported that they ended AAS use and declared their intention to return to the laboratory for further testing. Of the 3 subjects tested, IHC revealed that two participants had a decrease of fibre CSA, however the myonuclei number per fibre did not change and one participant had an increase of fibre CSA and myonuclei per fibre, which is consistent with the existence of the "muscle memory" mechanism. (*Figure 3, previous page*).

A second study using an animal model (in collaboration with MCRI) is ongoing and investigating the sex and time of exposure effects of AAS. Female and castrated males presented higher anabolic response to AAS administration compared to male mice (*Figure 4*). This finding, albeit preliminary, is envisaged to have important implications for female athletes, time of anti-doping suspension, and could inform an open, fair, and scientific based recommendation for the integration of transgender athletes in elite sport (see Blair Hamilton's article in this series). The time of exposure to AAS (and in this case the dose as well) also influenced the biological response; data already demonstrated in humans. When athletes are caught doping with AAS, the dose and duration of drug use should be considered where possible to determine the length of suspension as the effects of AAS on the "muscle memory" mechanism looks to be more pronounced with higher AAS dose. (*Figure 4*).

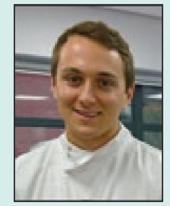
Due to the Covid-19 pandemic, the activities of the MMAAS Study were paused. Gradually, a few experiments have resumed and the main aim of the project is to conclude the RNA-Sequencing analysis to investigate molecular mechanisms involved in the "muscle memory" phenomenon and explore possible implications for anti-doping. It is worth noting that the investigation of the "muscle memory" mechanism creates a valuable link between the MMAAS study and the Tavistock Transgender Athlete Study (TTAS) (both under Professor Yannis Pitsiladis supervision, at the University of Brighton).

Meanwhile, the MMAAS study is engaged in the fight against doping and the TTAS aims to provide a better understanding of the impact on "muscle memory" of the hormonal treatment for individuals with Differences of Sex Development (DSD) or gender-affirming treatment for gender dysphoria. Also the effects of subsequent cross-sex hormone therapy on biological responses to exclude.

In addition, how the existence of the "muscle memory" phenomenon influences the inclusion of these athletes into elite sports (see more in the section *"Integrating Transwomen and DSD Athletes Into Elite Women's Sport: The Tavistock Transgender Athlete Study"*.

CONCLUDING POINTS

- Lessons, the pandemic provides an unprecedented opportunity to learn vital lessons from Covid-19, to develop creative and long-lasting anti-doping solutions.
- A paradigm shift is needed, new game changer approaches are needed to enhance anti-doping.
- Use the best tools available, sequencing technology, artificial intelligence, machine/deep learning and other approaches proven effective to deal with Covid-19.
- New partners, anti-doping needs new partners.
- Use Olympic/Anti-doping assets, better use of anti-doping resources to enhance anti-doping (science).
- Collaboration, large international anti-doping collaborations are needed.



Alexander Kolliari-Turner graduated from the University of Oxford with a BA in Biological Sciences in 2015. He achieved the highest 2:1 in his year group and was awarded the Heron-Allen Academic Scholarship from Lady Margaret Hall. **Email address:** *A.Kolliari-Turner@brighton.ac.uk* **Qualification:** PhD **Timeframe:** November 2017- November 2024

Thesis title: Implications of RNA-seq in the detection of anabolic steroid use and the harnessing of the molecular mechanism(s) of muscle memory

My research: Studies in both humans and mice have demonstrated that anabolic-androgenic steroids (AAS) can increase the number of nuclei within muscle fibres. This accretion of "myonuclei" is how AAS increase hypertrophy via enhanced rates of protein synthesis. In a mouse model these myonuclei have been demonstrated to be retained after AAS usage has ceased and these subsequently elevated levels facilitate muscle re-growth and thus enhance "muscle memory". These findings indicate that the benefits of AAS usage are long lasting and suggest that if an athlete serves a ban and returns to sport they may have a permanent advantage in their ability to build muscle - even when they are no longer taking AAS. Previous studies on powerlifters who took AAS in the past (PREV group), but are currently drug free, have demonstrated that these individuals have more myonuclei in their trapezius muscle than powerlifters who are currently using AAS (PAS group), clean powerlifters (P group) and controls (C group). Additionally, the number of myonuclei within the vastus lateralis was comparable between the PREV and P groups.

This data suggests that the myonuclei obtained via strength training and AAS usage are retained in humans and therefore could provide long term advantages to AAS users, but more data is needed to confirm this hypothesis. This thesis aims to recruit similar groups to further investigate muscle memory. Additionally, RNA-Sequencing will be conducted on blood samples to explore the possibility of a transcriptomic signature of doping that could enhance AAS detection strategies.

Funder: World Anti-Doping Agency **Supervisors:** Professor Yannis Pitsiladis, Fergus Guppy and Dr Guan Wang

Giscard Lima concluded his graduation in Sports Science and achieved the title of Master of Science in his country, Brazil. Also worked as strength condition trainer of the paralympic athlete Antonio Tenorio, in winning of silver medal in Rio 2016. Currently, he is a fellow PhD candidate at University of Rome 'Foro Italico', Italy (beginning on Oct 2017 ending on January 2021), and his PhD project is part of an international collaboration to investigate the implications of anabolic steroid use in the molecular mechanism of muscle memory and applications for anti-doping testing. Throughout his PhD course, he was affiliated at University of Brighton, UK, and joined the Prof Yannis Pitsiladis research group, in order to develop the project the Muscle Memory and Anabolic Androgen Steroids (MMAAS) study, which investigate the effects of steroid abuse in resistance-trained individuals.

He also was affiliated at Murdoch Children's Research Institute (MCRI), Australia, for another collaboration to investigate the effect of anabolic steroids, but using animal model in the group of Prof Kathryn North. His research interesting is focused in using of RNA-Seq technology to improve the testing for doping detection, in samples that will be collected in further competition as well as to validate a method the assess samples that has been stored for a long term waiting for an more effective test (which he truly believes that can be the omics technologies).

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The use of technology to protect the health of athletes during the heat of Tokyo

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Tokyo will host the Summer Olympics from July 23rd to August 8th 2021, with averaged air temperatures surpassing 30°C and humidity levels above 70%[1]. Notably, forecasts indicate increments in the intensity and consistency of heatwaves globally because of environmental change[2]. In recent years there has been an increasing number of heat illness cases in Tokyo, with over 65 deaths recorded in only one week in August 2018[3]. Interestingly, daily air temperatures during the summer of 2020 have been remarkably low when contrasted with the past two years.

Despite the fact that this is by all accounts an abnormal season characterised by a broadened rainy period, 2021 is expected to face more intense heat and humid conditions, based on the La Niña forecasting models (i.e., powerful winds moving the hot waters of the Pacific Ocean from South America towards Indonesia). These predictions point towards warm irregularities that could probably be present in Japan during June-August 2021[4].

Heat stroke is a life-threatening illness characterised by an elevated core body temperature that rises above 40°C, associated with central nervous system disturbances and multiple organ system failure[5]. Policies to prevent classical heat stroke are not adapted for exercise-related heat stroke and exertional heat illness (EHI). Indeed, the primary risk factor for EHI is exercise itself as a result of the metabolic heat production of the contracting muscles. Due to differing factors and characteristics such as exercise duration, rules, clothing, intensity, muscle mass, each sport is likely to offer a unique risk pattern, and each discipline within a sport can also have specific thermoregulatory demands. It is therefore necessary to characterise the thermoregulatory responses of athletes to each sport to adapt the current policies to the needs of athletes.

There is also a need to develop innovative wearable devices capable of collecting, analysing and integrating a wide range of multidisciplinary parameters for application in elite sports. It is absolutely essential, however, that any mounted devices are unobtrusive and in no way hinder the performance of athletes or indeed endanger the health of any competitors. With this goal in mind, our group (i.e., a team of scientists, engineers, elite athletes and industry partners) have developed the "Sub2 mobile application" which is a state-of-the-art application for monitoring and analysing interdisciplinary data in real-time during sporting events such as marathon racing[6] (*Figure 1*). This application can also be applied as a preventive tool to inform on the health of athletes exposed to extreme environmental conditions with the collection of a wide range of biochemical, biomechanical, physiological and mechanical variables.

EXCITING POTENTIAL

This timely development has exciting potential applications given the Tokyo 2020 where this technology could help in the management of athletes during a medical emergency (e.g., collapse) allowing for an earlier identification and intervention. For example, this application would have benefited Scottish runner Callum Hawkins who collapsed a mile from winning the marathon at the Commonwealth Games at the Gold Coast (Australia, April 2018). Early recognition and diagnosis are imperative. Gastrointestinal temperature via ingestible devices is the only surrogate to rectal temperature[7] and real time core temperature monitoring may save precious minutes. In our group, we recently developed and used this real-time technology as a "hub" to aggregate a range of data feeds to assist athletes[8]. Our research team has extensive experience in using this technology during various international events (e.g., Major City Marathons, UCI and IAAF/WA World Championships, Dakar rally, World Rugby 7 Series).

The need to include such applications, not only within elite sport but also workers and attendees during a sporting event, is clearly reflected by the dramatic environmental conditions which occurred in the World Athletics Championships 2019 (Doha, Qatar), where approximately 1/3 of the female athletes could not complete the marathon race held in extreme temperatures of >30°C and high levels of humidity >80%[9].

Data collected from such applications would be of particular interest in a wide range of sports, especially during events held in similar extreme conditions such as the World Beach Games which were also recently held in Doha, Qatar (12 Oct - 16 Oct 2019) and involved 1240 athletes from 97 nations participating in a total of 13 sports (e.g., open water swimming, beach volleyball, beach handball, beach football)[10].

In light of the above, it would be scientifically invaluable to better understand the impact that these technologies and innovations could have in athletes, workers, and all attendees at the Tokyo Olympics, where the environmental conditions are predicted to be as severe and extreme as those encountered at the 2019 World Athletics Championships in Doha (Qatar) or worse.

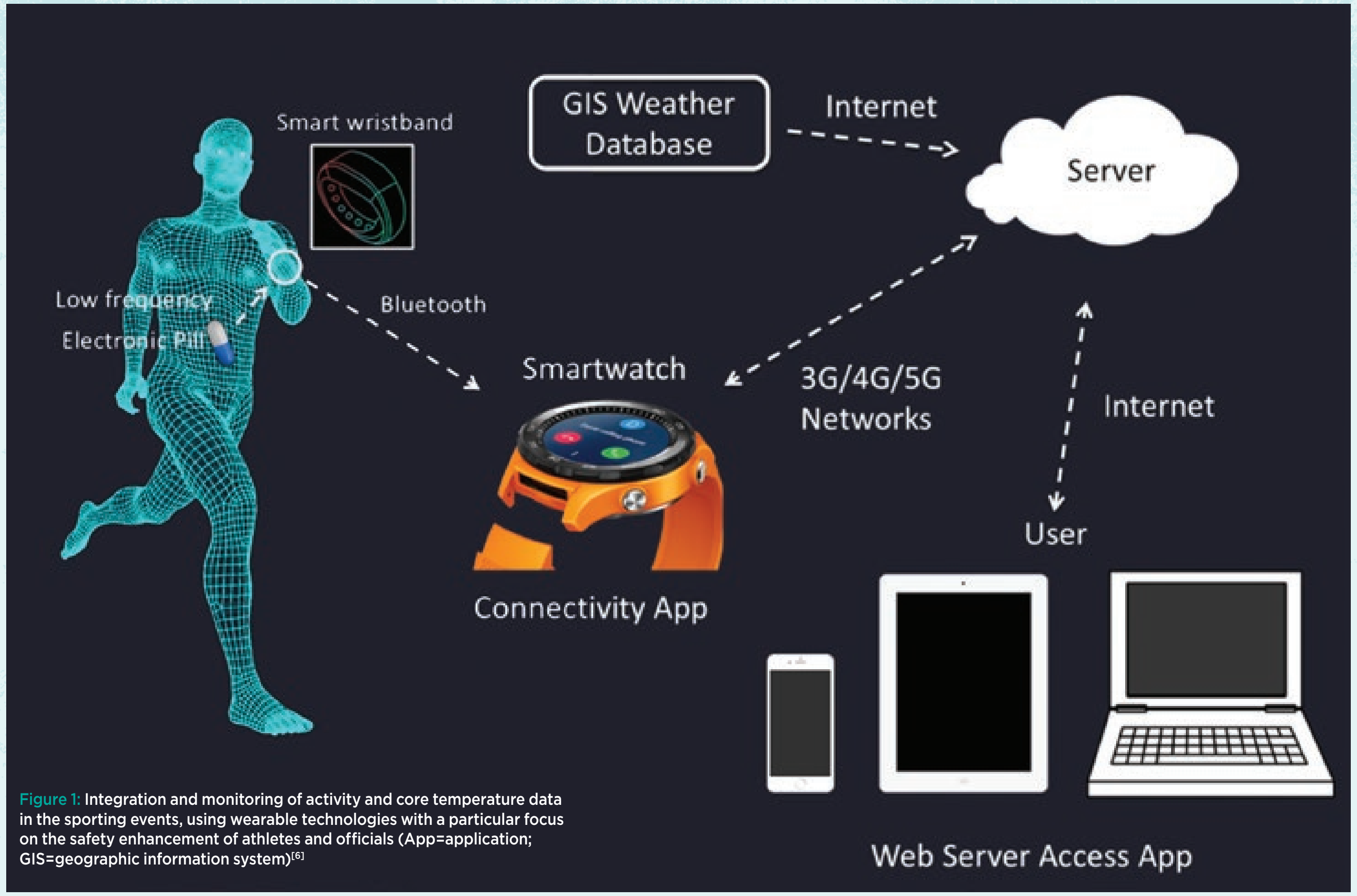

Figure 1: Integration and monitoring of activity and core temperature data in the sporting events, using wearable technologies with a particular focus on the safety enhancement of athletes and officials (App=application; GIS=geographic information system)[6]

A concerted effort is currently underway by our group to ensure the necessary developments of these wearable technologies and innovations are validated in time to allow accurate monitoring and analysis of physical responses in real-time, to better protect the health of athletes and optimise sports performance.

EXPERT WORKING GROUP

The knowledge, experience and competencies at Eastbourne/ Brighton are highlighted in this special edition and have been instrumental in guiding the efforts of Professor Yannis Pitsiladis (and his multidisciplinary research team and partners) who is a member of the IOC Medical and Scientific Commission and member of the Adverse Weather Impact expert working Group for the Olympic Games Tokyo 2020.

As part of this IOC expert working group, numerous outcomes are being generated including athlete brochures aids such as *Beat the Heat: Olympic Games Tokyo 2020* *https://d2g8uwgn11fzhj.cloudfront.net/wp-content/uploads/2019/08/20102016/2019_A365_BeattheHeat2020_8a.pdf*, educational and research symposia/ workshops (e.g., *https://ioc-preventionconference.org*

"Heat injury and illness prevention for Tokyo 2020: What is the IOC doing?" and *"How wearables can protect the health of athletes during sporting competitions in the heat"*) and research that can help protect the health of athletes competing in the heat in Tokyo is ongoing (and a small research grant awarded by the IOC entitled *"Protecting athletes' health through the prevention of heat illness during the 2020 Tokyo summer Olympics. $50,000.00. 2020-2021*). The Brighton marathon serves as one of the numerous test events to test these developments using a variety of different experimental protocols conducted in an ecologically valid environment, preceding the Tokyo Games (albeit the 2020 edition of the Brighton marathon was cancelled due to Covid-19).

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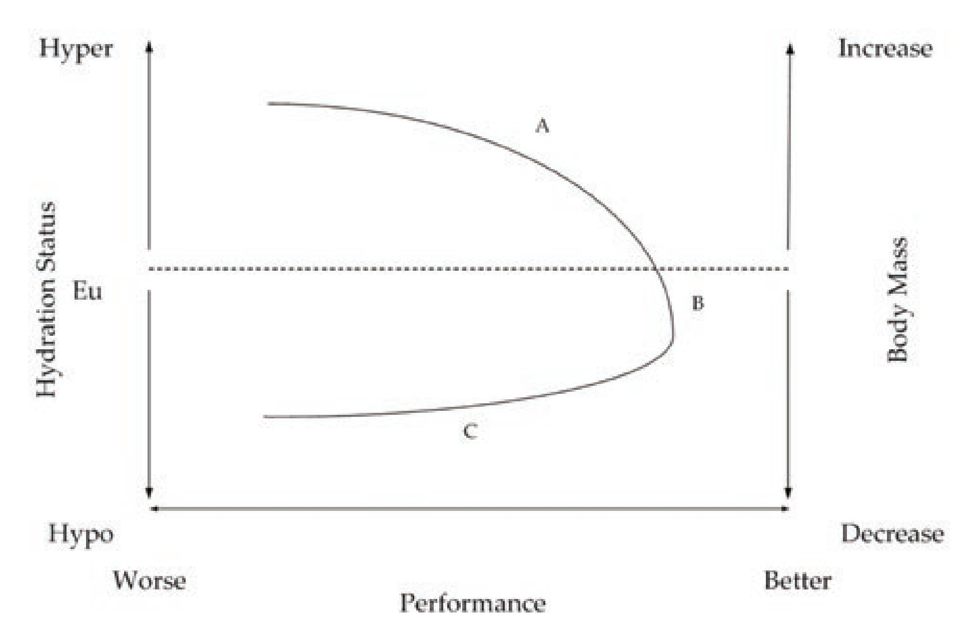
DEHYDRATION AS AN ERGOGENIC AID

ARTICLE BY **SHAUN SUTEHALL**[1], **ANDREW BOSCH**[1] AND **YANNIS PITSILADIS**[2]

1. Division of Exercise Science and Sports Medicine, University of Cape Town, Cape Town, South Africa;
2. Collaborating Centre of Sports Medicine, University of Brighton, Eastbourne, United Kingdom



Above: Figure 1 Theoretical model illustrating effect of varying rates of fluid ingestion (i.e., A: an excess fluid intake; B: an *ad libitum* fluid intake and C: no fluid intake) on running performance. Illustration courtesy of Dr Barry Fudge.

"Absence of evidence is not evidence of absence"

Martin Rees, British astrophysicist

The above is a popular phrase, often cited to describe the concept that disproving the existence of something is extremely difficult and at times, impossible. In sports research and performance, advice often given to many athletes, at all levels (amateur to professional) is that dehydration that results in the loss of bodily fluid of >2% body weight must be avoided[1].

This advice stems from many studies, some from as early as 1968, demonstrating a decrease in exercise performance when dehydration results in a reduction in body mass by ≥ 2%[2-4].

What has been assumed for decades, albeit with some resistance [5], but without evidence supporting such a notion, is that findings from these laboratory-based research studies, usually with non-elite athletes and under "non-normal" test conditions (i.e. in heat chamber, use of diuretics or long "pre-loads") apply to elite athletes during competition. In this instance, the absence of any evidence has been assumed to indicate athletes must also prevent dehydration in excess of ~2% body mass loss.

Here we address the potential for dehydration to be used by athletes and their support staff as an ergogenic aid and make the reader aware of a common misconception regarding dehydration and heat stroke.

ECOLOGICAL VALIDITY

The fundamental concept that must not be overlooked when interpreting the available literature, is the ecological validity of the study to the situation of interest.

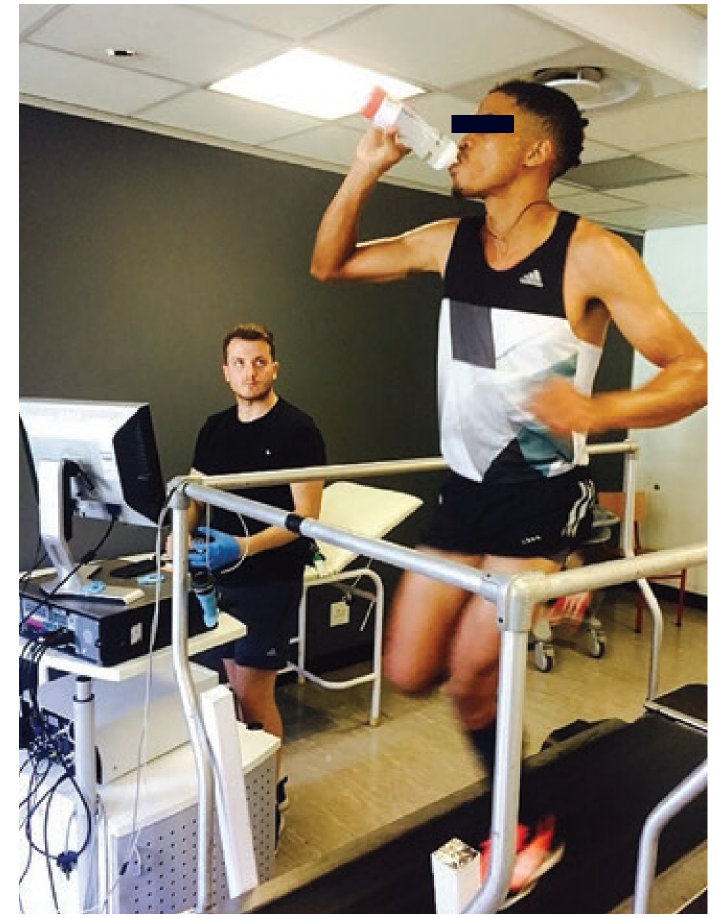
For example, if the performance of an athlete, after ingesting a diuretic and urinating excessively and who subsequently begins an endurance task, is compared with an athlete who prepares normally, then dehydration may indeed be shown to impair performance[6].

It is, however, difficult to elucidate from such research which was the cause of the decreased performance: 40 mg of furosemide or the associated dehydration.

Other studies, performed during competition, have demonstrated no negative effects of dehydration, with athletes regularly exceeding 2% body mass loss and at times >10%[7]. This apparent ability of athletes to perform prolonged endurance exercise while "dehydrated" is further demonstrated by two separate case studies of Olympic marathoners, Haile Gebrselassie and Alberto Salazar, who had body mass losses of 9.8% and 8.1%, respectively, during competition[8, 9].

See Figure 1 for a theoretical model illustrating the effect of varying rates of fluid ingestion (i.e., A: an excess fluid intake; B: an ad libitum fluid intake and C: no fluid intake) on running performance we developed in 2006 together with Dr Barry Fudge – then a PhD student in our laboratory in Glasgow, Scotland.

In a pilot study conducted by the authors and others, we demonstrated an average body mass loss of 4.2±1.0% in 16 well-trained Kenyan runners, during a 25 km training run at an average running speed of 3:48 min.km^{-1} at



~2,000m above sea level, with fluids consumed every ~5 km ab libitum, with no sign of impairment of performance or well-being due to dehydration[10].

See "*Endurance*" episode of "*Enhanced*" series for ESPN and Alex Gibney/Jigsaw Prods (*https://vimeo.com/281090972*).

While it is possible to argue that these athletes could have performed better had they not "dehydrated" to such an extent, it must also be noted that Haile Gebrselassie completed his marathon in 2:05:29 (hr:min:sec), just 36 sec slower than his winning time in the previous year and 40 sec faster than his winning time in the following year[11].

Regardless of the debatable improvement in performance with an attenuated reduction in body mass, these athletes demonstrate it is possible to compete at elite-level with significant levels of hypohydration. Clearly, there is a mismatch between evidence from laboratory-based studies (*i.e. Figure 2 and Figure 3*) and what has been observed in competition by elite athletes.

EFFECT OF ADDED WEIGHT

While the effect of altering the level of hypohydration in elite athletes during competition is currently unknown, the effect of **added** weight on endurance has been investigated[12].

It was found that an increase of 10% in "non-functional" body mass resulted in a ~10% increase in performance time. Using data from this study, we estimated running speed from 0% (15 min . 5km^{-1}) at the start of a marathon to 10% (16.5 min . 5km^{-1}) at the end of a marathon, assuming a linear change in mass over the duration of the marathon and compared this with an athlete who has no "impairments" from added weight (15 min . 5km^{-1}).

In this example, the unimpaired athlete runs a marathon in 2:00:36, whereas the impaired athlete will complete the marathon in 2:06:52. Should this athlete carry just 3% of excess, "non-functional" body mass, the resulting marathon time is still significantly impaired (2:02:28).

If we assume that the reverse applies i.e., losing weight during a marathon due to fluid losses results in a similar effect on times, but improvement rather than a reduction in running speed, then these simple calculations demonstrate the potential importance of shedding all "non-functional" body mass.

If it is possible to lose significant amounts of water without causing a detriment to the body's physiological processes, this may have a significant impact on performance times, especially at elite level.

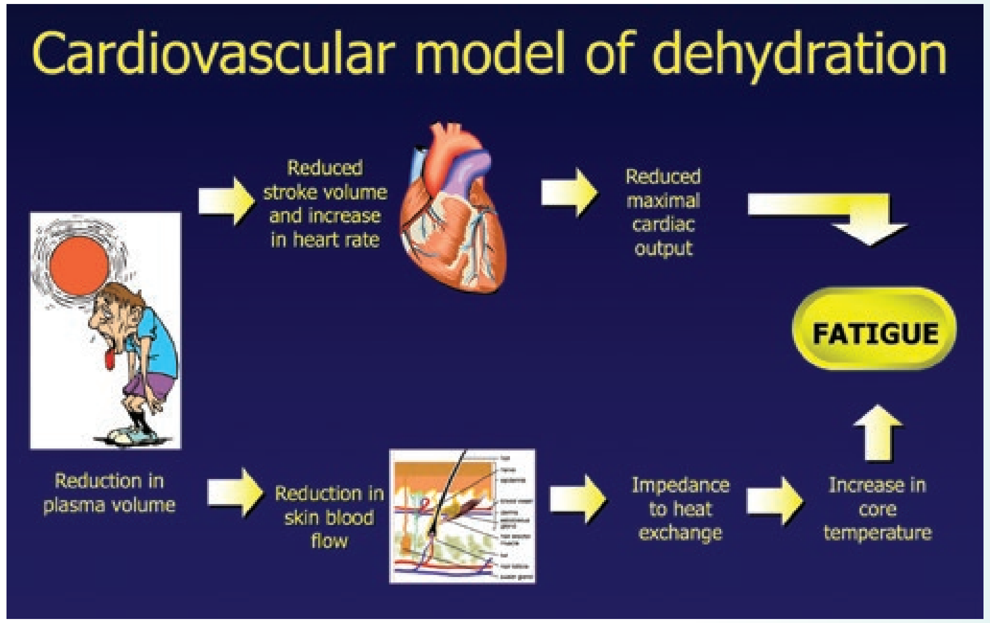
EXERTIONAL HEAT STROKE

A reason often cited for preventing significant hypohydration during competition is the associated risk of developing exertional heat stroke. This is a process in which heat is accumulated within the body, primarily through a rise in metabolic heat production and an inability to dissipate this heat at a sufficient rate to the environment to maintain homeostasis.

It is at times, falsely, believed that dehydration exacerbates this process and that it is a health risk to allow dehydration during competitions[2].

Left: Figure 2 A South African athlete with cardio-respiratory variables being measured during an exercise trial (ca. 2000)

Above: Figure 3 A South African athlete in the same laboratory as in Fig 1, 20 years on, testing new concepts in sports nutrition and PhD student Shaun Sutehall conducting the experiment



Above: Figure 4 The cardiovascular model of physiology. Illustration courtesy of Professor Tim Noakes

This concept has been disputed[13] and one that is based on a simplistic reasoning of the cardiovascular model of physiology (*see Figure 4*).

In this model, it is suggested that, during exercise, dehydration reduces plasma volume to such an extent that skin blood flow is restricted (reducing heat loss via sweating) and ultimately cardiac output is reduced, requiring the athlete to reduce heat gain or risk collapse due to insufficient blood pressure.

Firstly, it must be recognised that the occurrence of heat stroke is often higher in shorter distance races (i.e. <21 km) compared with the marathon, where metabolic heat production is very high but, due to the relatively short exercise time, the level of dehydration is often low[14].

Secondly, that the occurrence of collapse immediately following the completion of a race is seldom due to dehydration or heat stroke but rather postural hypotension[15].

While hyperthermia is a risk to athletes, especially those competing in the heat, if recommended practices to minimise heat gain (i.e. cold fluid ingestion, adequate hydration at beginning of the race etc) are followed, it is unlikely that hypohydration in the levels likely to be achieved (e.g. -2-8%) will be a major contributor to the development of heat stroke.

Prof Andrew Bosch:
Andrew Bosch is a Professor in the Division of Exercise Science & Sports Medicine at University of Cape Town. His research interests centre around fluid delivery, carbohydrate and protein to improve performance and recovery, and he enjoys applying laboratory findings in these areas to Olympic and other elite level athletes.

He is co-leader of the Sub2hrs Marathon Project (*www.sub2hrs.com*) and Heads the Sports Nutrition of the project. Andrew has published extensively and presented at international conferences.

Mr Shaun Sutehall:
A PhD student at the University of Cape Town, investigating novel techniques applied to traditional methods of improving performance. Particularly focused on the effects of adding sodium alginate and pectin to a carbohydrate beverage and applying transcriptomics to altitude training.

Shaun has been on several research trips around the world including Ethiopia, Kenya, Scotland, USA and Greece and has worked with many elite, East African runners as part of the Sub2hrs Project (*www.sub2hrs.com*).

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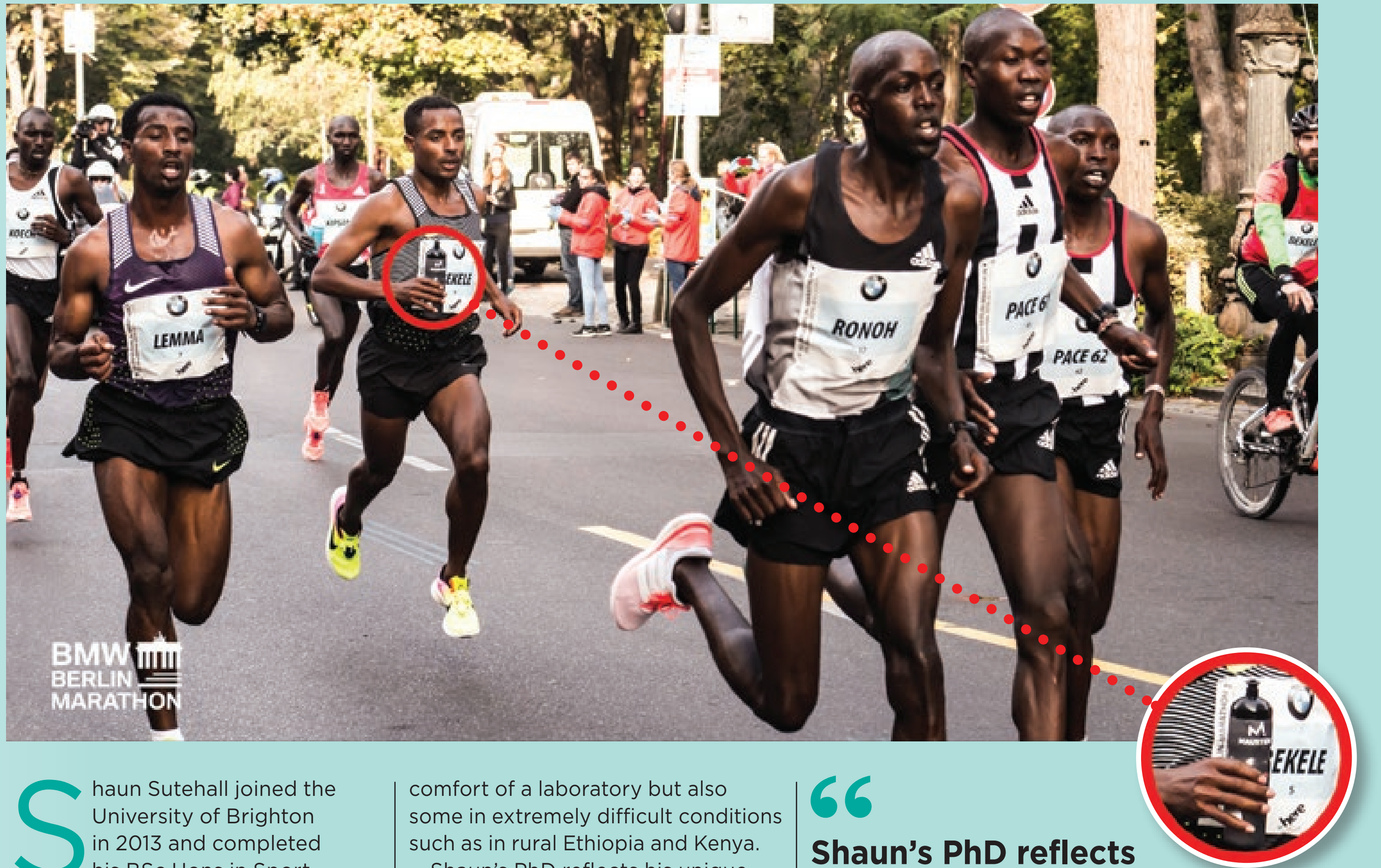
Applying novel techniques to traditional methods of improving performance

A closer look at the research studies conducted by PhD Student, Shaun Sutehall



Above: Figure 1 Kenenisa Bekele conducting a field experiment at the 2016 Berlin Marathon which he won in 2:03:03; Kenenisa's winning time of 2:03:03 was an Ethiopian record and the second-fastest time in history on a record-eligible course

Shaun Sutehall joined the University of Brighton in 2013 and completed his BSc Hons in Sport Science in 2016. Upon completion of the BSc and research project conducted under the supervision of Professor Pitsiladis, Shaun applied and was accepted for a PhD in the Department of Human Biology Sports Science at the University of Cape Town (UCT) to conduct his PhD under the supervision of Andrew Bosch (internal supervisor) and Yannis Pitsiladis (external supervisor); Yannis has a long standing collaboration at UCT with Andrew Bosch but also with other good friends such as Tim Noakes, Malcolm Collins, and Jeroen Swart.

EXPERT SUPERVISION

Under their expert supervision, Shaun has conducted numerous research studies, some in the relative comfort of a laboratory but also some in extremely difficult conditions such as in rural Ethiopia and Kenya.

Shaun's PhD reflects his unique ability to conduct research in the most challenging environments. His PhD thesis, *"Applying novel techniques to traditional methods of improving performance"* comprises a series of field and lab-based studies such as a 3-month research field trip to South Africa and Ethiopia, where he led 14 South African runners on a 4-week altitude training camp to Sululta, Ethiopia while collecting blood and saliva samples for transcriptomic analysis.

The aim of this study funded by the World Anti-Doping Agency (WADA) and South African Institute for Drug- Free Sports (SAIDS) was twofold: to determine the transcriptomic response (i.e., gene expression response) to altitude to allow differentiation from prohibited methods of enhancing performance and to determine if transcriptomics can be used to individualise altitude training[1].

> **"Shaun's PhD reflects his unique ability to conduct research in the most challenging environments."**

Shaun has also received funding from Maurten AB (a Swedish Start-up) and the Sub2 Foundation (*www.sub2hrs.com*) to investigate the efficacy of adding sodium alginate and pectin to a carbohydrate beverage, given to athletes during prolonged endurance exercise.

Figure 2: Celebration of the Sub2 marathon team in Berlin, 2016

Figure 3: Shaun Sutehall assessing the impact of carbon fibre plate running shoes versus a preferred training shoe on the running economy of the greatest distance runner of all time - Kenenisa Bekele. The test is being conducted at the Sub2 laboratory at 2,800m above sea level (Suluta, Ethiopia)

ELITE ATHLETES

This research began with Shaun attending many high profile international marathons (i.e., New York City, Berlin, Dubai and London) to work with elite athletes (and often the winners of these marathons, e.g., *see Figures 1 and 2*), providing scientific support and careful monitoring of the potential of sodium alginate and pectin to enhance carbohydrate ingestion.

See (2) for some of the publicity surrounding this innovative research. This field work and a pilot study[3] was followed by two laboratory research studies performed at the University of Stirling, Scotland under the direct supervision of Dr John Leiper and Professor Stuart Galloway. Here Shaun investigated the effect of sodium alginate and pectin on the gastric emptying rate of a 500 mL bolus of carbohydrate drink[4] and the oxidation rate of ingested carbohydrate during prolonged exercise[5].

Alongside these PhD studies, Shaun has led or supported numerous other research projects related to anti-doping [6, 7], wearable technology [8, 9] prevention of heat-related illness during competition using technology[10] and implications for the use of carbon fibre plates in running shoes – a fair innovation or technological doping? (*see Figure 3*)[11].

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Establishing a Global Standard for Wearable Devices in Sport and Fitness

ARTICLE BY **IRINA ZELENKOVA**[1], **BORJA MUÑIZ-PARDOS**[1], **KONSTANTINOS ANGELOUDIS**[2] AND **PROFESSOR YANNIS PITSILADIS**[2,3]
ON BEHALF OF THE INTERNATIONAL FEDERATION OF SPORTS MEDICINE (FIMS) COLLABORATING CENTRES OF SPORTS MEDICINE

1. GENUD research group, Faculty of Sport and Health Sciences, Department of Physiatry and Nursing, University of Zaragoza, Zaragoza, Spain
2. Collaborating Centre of Sports Medicine, University of Brighton, Eastbourne, UK, **3.** International Federation of Sports Medicine (FIMS), Lausanne, Switzerland

The market of wearable technology is continuously growing and was valued at USD 15.74 billion in 2015 and is expected to reach USD 51.60 billion by 2022, at a CAGR of 15.51% between 2016 to 2022. Notably, the growth of the market is increasing in developed and developing countries and expected to grow even more now due to COVID-19.

Wearable devices are largely used worldwide in health monitoring, telemedicine and fitness industries. Global companies such as Fitbit (U.S.), Apple, Inc. (U.S.), Xiaomi Technology Co., Ltd. (China), Garmin, Ltd. (U.S.), Samsung Electronics Co. Ltd. (South Korea) and others are developing wearable technology.

Despite the high speed growth of the sector, there are several concerns shared amongst the scientific community regarding the use of wearable devices. These concerns include their accuracy, reliability, accessibility, quality assurance, population-specific validation, privacy, data interpretation and presentation to consumers, and standardisation of data for technical purposes. The absence of regulation in the field of sport and fitness wearable devices creates the need for the implementation of a global standard for sport and fitness wearables[1].

Figure 1: Overview on the wearable market as defined by Wearable Technologies (*http://www.wearable-technologies.com*)

IOC RECOGNISED

As the only formally recognised by the International Olympic Committee (IOC) sports medicine federation and a key organisation in the field of sport and exercise medicine, the International Federation of Sports Medicine (FIMS) together with its 26 Collaborating Centres of Sports Medicine (FIMS CCSM)[2] established a task force in association with our partner Wearables Technology[3] and headed by Professor Yannis Pitsiladis to address the need for a quality assurance standard for wearable devices guiding companies to achieve these aspects and educating consumers to critically consider them (*Figure 1*)[4].

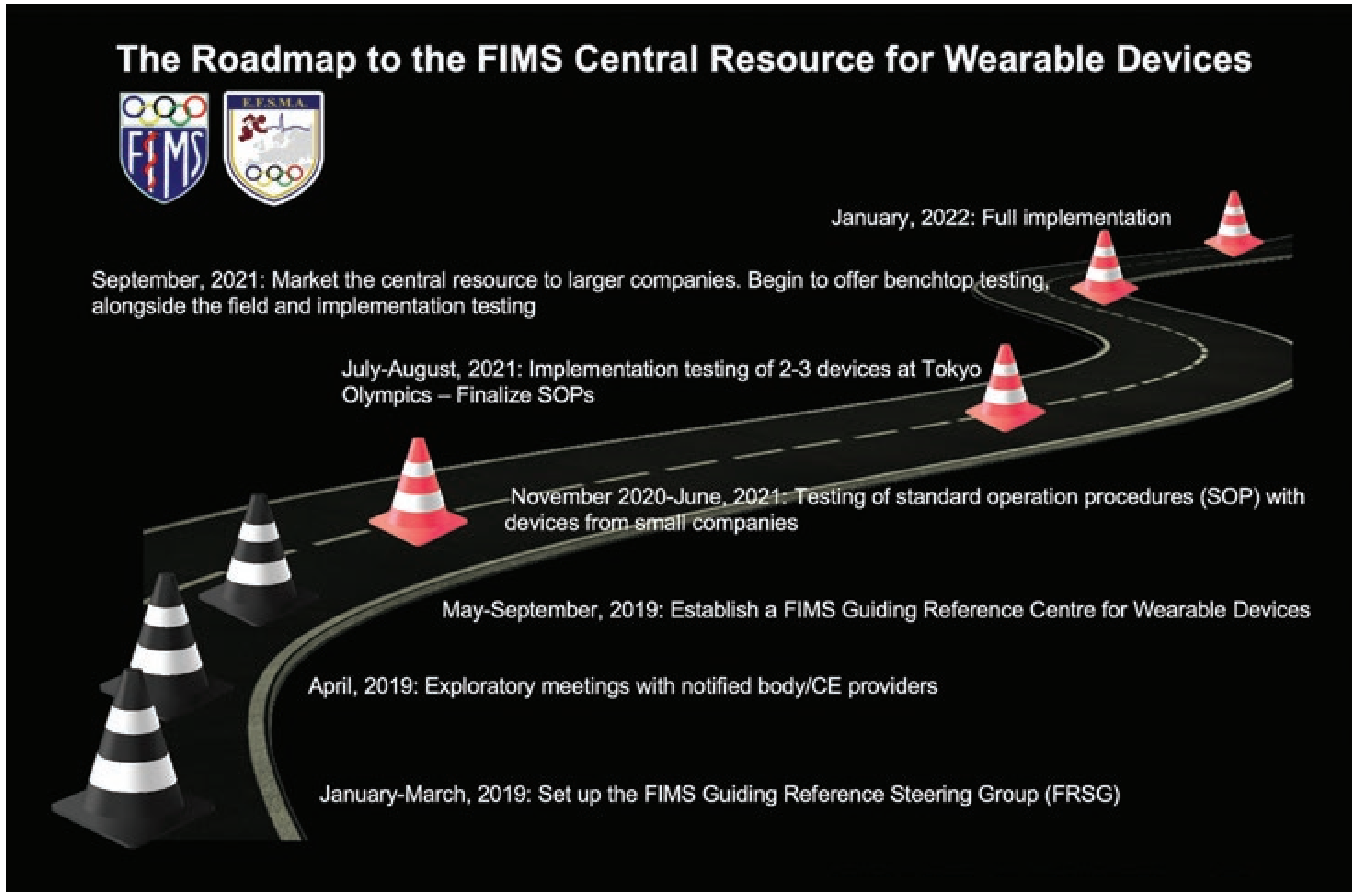
The roadmap to the FIMS central resource for wearable devices for establishing protocols and standard operating procedures for the testing and certification of wearable devices has been drafted and currently being implemented (*Figure 2, next page*).

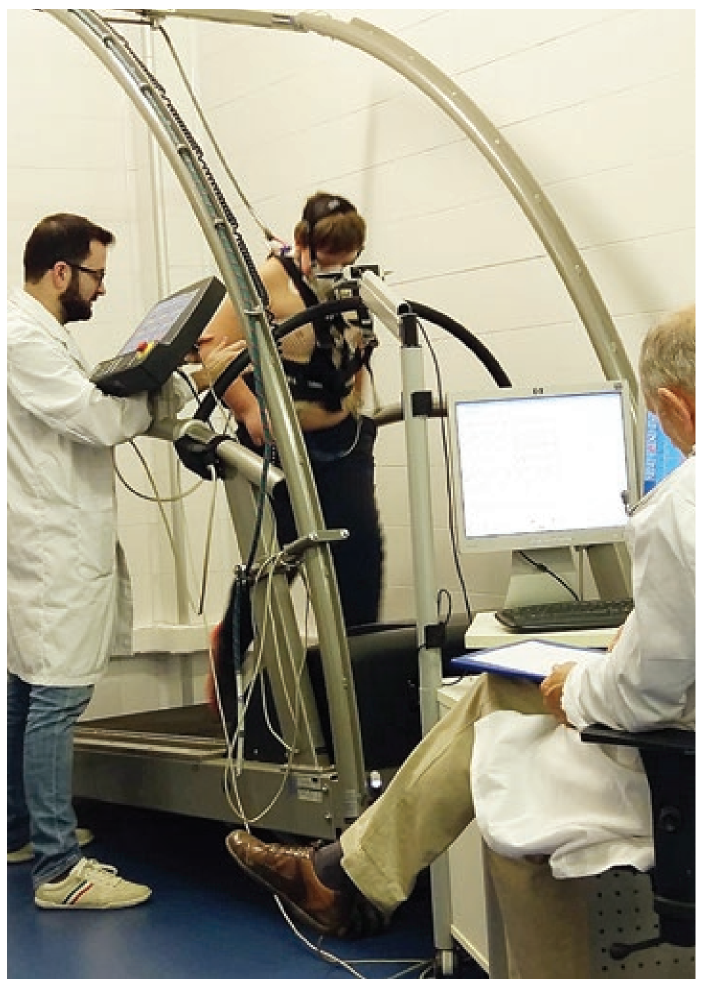
Briefly, some highlights include the setting up of the Guiding Reference Steering Committee (FRSG) in January – March 2019. In September 2019, the first FIMS Collaborating Centre for Wearable Devices was established in the Growth, Exercise, Nutrition and Development (GENUD) Research Group at the University of Zaragoza (Zaragoza, Spain).

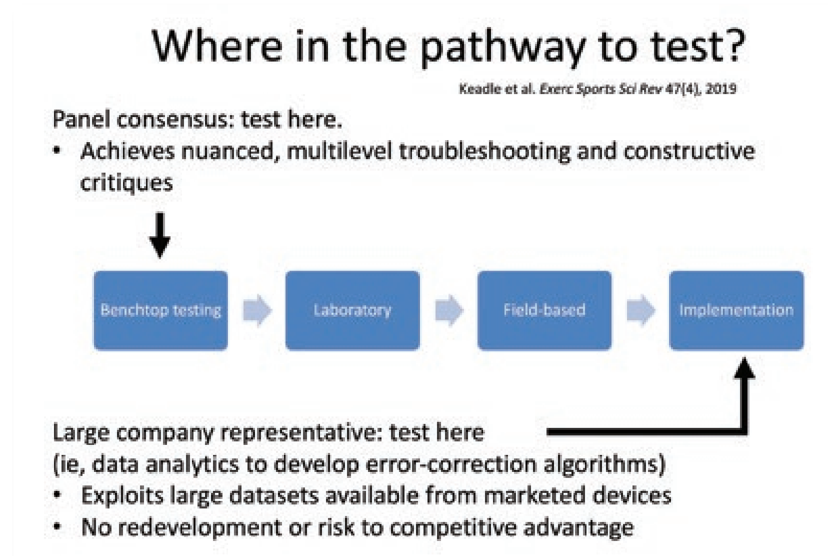
The multidisciplinary GENUD Lab has been successful in designing and implementing interventions that combine a nutritional-physical activity-medical approach. GENUD has experts in assessing body composition and indirect calorimetry and has a long-standing record of performing clinical and public health investigations in collaboration with medical doctors, nurses, dieticians, and sports scientists. GENUD also has extensive experience with the use and method validation of wearable technology (e.g., camera-based systems to measure movement velocity, accelerometers, brain stimulation wearables, and foot-worn inertial sensors) focusing on body composition, physical activity, and athletic performance assessment in both trained and sedentary children, adolescents, adults, and elderly individuals. (*See Figures 3-5 for the key members of the GENUD laboratory on the next page*).

SECURED FUNDING

It is worth pointing out that funding for this ambitious project has been secured, in part at least from fundraising efforts by FIMS which are beginning to bare fruits with over €100,000 secured from MW Shakhnovskyy Foundation, and FIMS CCSM in Latvia (Sports Medicine and Physical Health Centre, Riga) and Italy (Instituto di Riabilitazione Riba, Torino) with generous infrastructure support from the GENUD-FIMS







Opposite page:
Figure 2
The roadmap to the FIMS central resource for wearable devices

Figures 3-5
GENUD team at the University of Zaragoza, Spain

Left:
Figure 6
Testing pathway for the device implementation

CCSM at the University of Zaragoza, Zaragoza, Spain. The aim in the near future is for each of the FIMS CCSM that qualify for accreditation to deliver the FIMS Global Standard to be self-sustaining within 24 months.

CONSULTATION PROCESS

It is imperative that an initiative like establishing a global standard for wearable devices in sport and fitness considers the views of all likely stakeholders, and especially industry.

With this in mind, numerous interactive events are being held around the world (despite the restrictions due to Covid-19) to solicit the input of the stakeholders. Interesting insights are emerging from these events such as from the open forum held at the Annual Meeting of the New England Regional Chapter of the American College of Sports Medicine (ACSM) in November 2019 in Providence, Rhode Island, USA[4] but also more recently, the panel discussion as part of the Yale Centre for Biomedical Data Science Digital Health Monthly Seminar Series in September 2020 (manuscript in preparation).

> **"It is envisaged that the technical and quality assurance developments to be implemented by the new global standard will undoubtedly accelerate the integration of wearable sensors into recreation and competitive sports."**

In attendance at the Yale event were representatives from industry (Xsensio, Google Health, VivoSense), societies/associations (FIMS, European Respiratory Society, Digital Health Working Group, Consumer Technology Association), academics (Yale University - medicine, nursing, computer science, University of Connecticut, Southern Connecticut State University, University of Massachusetts, University of Brighton, Hong Kong Baptist University) and clinicians (Yale-New Haven Hospital, Veterans Affairs Healthcare System).

At this event, the testing pathway for device implementation (e.g., the model presented by Keadle and colleagues[5]; *see Figure 6*) was presented and the roadmap to establishing the global standard for wearable devices in sport and fitness was redefined (*see Figure 2*) in light of the overall discussions.

Given this extensive consultation process (including consultations at other select events such as the virtual MEDICA MEDICINE + SPORTS CONFERENCE 18-19 November, 2020; *www.medicine-and-sports.com/virtual/?v=f214a7d42e0d*), it is envisaged that the technical and quality assurance developments to be implemented by the new global standard will undoubtedly accelerate the integration of wearable sensors into recreation and competitive sports, while also serving healthcare by providing customers with reliable information about the effectiveness of healthcare devices and products.

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Over 10 years working in the field of professional sports providing scientific and medical support for elite athletes. This includes the highest level competitions (World Championships, World Cup Stages, and Olympic Games).

The main focus of the work is to improve the performance of athletes with integration of the innovative technologies without the use of prohibited substances and methods. Main research focus on the altitude training, adaptation for the heat environment, total haemoglobin mass changes, parameters limiting aerobic performance.

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