Institution: King's College London		
Unit of Assessment: 8 (Chemistry)		
Title of case study: Analytical advances in anti-doping shapes international standards for professional sports		
Period when the underpinning research was undertaken: 2003 - 2019		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Prof David Cowan Dr Mark Parkin Dr Alan Brailsford Prof Denise Syndercombe Court Dr Danielle Moncrieffe	Emeritus Professor Lecturer in Analytical Sciences Head of Laboratory Professor of Forensic Genetics Research Associate	1971 – present 2005 – 2017 2009 – 2020 2010 – present 2018 – present
Period when the claimed impact occurred: 2014 - 2020		
Is this case study continued from a case study submitted in 2014? Yes		

1. Summary of the impact (indicative maximum 100 words)

The Drug Control Centre (DCC) at King's College London plays a leading role in international efforts to combat doping in sports. As the only World Anti-Doping Agency (WADA) accredited laboratory in the UK, the DCC is an integral component in high-profile international anti-doping investigations; including the recent systemic violations by Russia, which resulted in their suspension from the Rio 2016 Olympics and Paralympics.

The DCC provides a pipeline that links novel advances in analytical measurement to the establishment of internationally accredited standards and guidelines. The DCC also plays a direct role in then delivering these standards across UK sports - analysing around 13,000 samples every year. This expertise is widely sought after; both in the development and implementation of new national and international testing standards and policies, and in the planning and delivery of high-profile national and international competitions. Overall this approach, integrating novel science with the hands-on application of our advances has delivered significant societal impact - safeguarding the health of athletes, protecting the integrity of international sport, and establishing the UK as an international leader in this area.

2. Underpinning research (indicative maximum 500 words)

Chemistry at King's is embedded across applied interdisciplinary research centres; strengthened in 2012 by the relaunch of a Department of Chemistry. Analytical chemists in the Department of Analytical, Environmental & Forensic Sciences have played a leading role in the development of new analytical techniques and probe molecules that help deter misuse of substances prohibited by the WADA - expanding detection limits, sensitivity, and evidential quality for compound detection in biological fluids.

For example, King's researchers have advanced isotope-dilution liquid chromatography-tandem mass spectrometry to improve sensitivity and reliability of steroid testing [**1**]. In addition, molecular-imprinted polymers have been created to detect naturally produced steroids present as dopants in biological samples. New applied combustion isotope ratio mass spectrometry methods have also simplified and improved sample purification used for the detection of such steroids [**2**]; for example, to define upper limits for the principal urinary metabolite of nandrolone [**3**]. Volumetric adsorptive micro-sampling has been pioneered, to enable high-precision steroid quantification from dried blood spots using Desorption Electrospray Ionization time-of flight mass spectrometry and developed new analytical methods to improve tandem mass spectrometry for increased sensitivity to quantify and validate amphetamines [**4**].

The use of biomarkers as indirect measures of pseudo endogenous compounds, has been a key research theme. Compounds ranging from small molecules like testosterone and salbutamol, to proteins such as human growth hormone (hGH) using procollagen-3 N-terminal peptide (P3NP) [**5**] have been used to detect doping without requiring a direct measurement of a specific dopant. This indirect approach provides an answer to the increasingly rapid development of new 'designer steroids,' where attempting to targeting the compound directly would be ineffective. We have combined this sensitive chemical testing with new DNA profiling technologies, enabling methods that can link illegal sample manipulation to individual athletes [**6**].

3. References to the research (indicative maximum of six references)

1. Cawood, M. L., Field, H. P., Ford, C. G., Gillingwater, S., Kicman, A., **Cowan, D.**, and Barth, J. H. (2005). Testosterone measurement by isotope-dilution liquid chromatography-tandem mass spectrometry: validation of a method for routine clinical practice. *Clinical Chemistry*, 51(8):1472-9. doi.org/10.1373/clinchem.2004.044503
2. Lopes, F., **Cowan, D**. **A.**, Thevis, M., Thomas, A., and **Parkin, M. C.** (2014). Quantification of intact human insulin-like growth factor-i in serum by nano-ultrahigh-performance liquid chromatography/tandem mass spectrometry. *Rapid Comm. Mass Spec.*, 28(13):1426-1432. doi.org/10.1002/rcm.6908
3. Arthur, K. L., Turner, M. A., **Brailsford, A. D.**, Kicman, A. T., **Cowan, D**. **A.**, Reynolds, J. C., and Creaser, C. S. (2017). Rapid analysis of anabolic steroid metabolites in urine by combining field asymmetric waveform ion mobility spectrometry with liquid chromatography and mass spectrometry. *Analytical Chemistry*, 89(14):7431-7437. doi.org/10.1021/acs.analchem.7b00940
4. Wang, Y., Caldwell, R., **Cowan, D. A.**, and Legido-Quigley, C. (2016). LC-MS-based metabolomics discovers purine endogenous associations with low-dose salbutamol in urine collected for antidoping tests. *Analytical Chemistry*, 88(4):2243-9. doi.org/10.1021/acs.analchem.5b03927
5. Holt, R. I. G., Böhning, W., Guha, N., Bartlett, C., **Cowan, D. A.**, Giraud, S., Bassett, E. E., Sönksen, P. H., and Böhning, D. (2015). The development of decision limits for the gh-2000 detection methodology using additional insulin-like growth factor-i and amino-terminal pro-peptide of type iii collagen assays. *Drug Test. Anal.*, 7(9):745-55. doi.org/10.1002/dta.1772
6. Devesse, L., **Syndercombe Court, D., Cowan, D.** (2015). Determining the authenticity of athlete urine in doping control by DNA analysis. *Drug Test. Anal.,* 7(10):912-918. doi.org/10.1002/dta.1785

4. Details of the impact (indicative maximum 750 words)

Over the last 10 years King's has worked in close partnership with key organisations in anti-doping, including the World Anti-Doping Association (WADA) and UK Anti-Doping (UKAD), to bring our underpinning analytical advances into effective sporting policy and practice. Led by Professors David Cowan (1990-2018) and Kim Wolff (2018-2020), the DCC is the centrepiece of this strategy at King's. The DCC provides a virtuous circle, linking the ongoing development of analytical techniques by King's researchers, through the applied delivery of anti-doping impact, to helping identify the future regulatory challenges, which then finally feedback to drive future research direction. This has been a core component of our success.

The DCC is the first ever human sports analytical laboratory to be established outside of an Olympic Games, delivering practical application of our anti-doping research to provide support and confidence to athletes competing across the world stage. We are internationally recognised leaders in this field - trusted to carry out testing for many of the world's most important sporting organisations and events.

King's research helped identify a systemic culture of doping in Russian sport. The McLaren Report is one of the most important recent events in worldwide anti-doping efforts. Following high-profile allegations of doping at the 2014 Winter Olympics, a WADA Independent Commission was set up to investigate corrupt practices around sample collection and results management, which

implicated the governing body for athletics in Russia (The Russian Athletics Federation), Russian athletes, coaches, trainers, and doctors, the WADA accredited laboratory in Moscow, the Federal Security Service of the Russian Federation, and the Russian Anti-Doping Agency.

The DCC played a key part in this investigation [**A,B,C**], taking responsibility for the management and analysis of athlete samples, co-ordinating a spectrum of forensic approaches from testing organisations in 6 different countries, and recording this process to a legally defensible standard. Highlighted in Chemistry World [**D**], this work required new protocols to detect sample manipulation with salt [**C**], and used our research on short tandem repeat DNA typing to detect urine swapping [**6**]. These findings were ultimately used to suspend 111 Russian athletes from the Rio 2016 Olympics and a ban of Russian participation in the 2016 Paralympics [**E**].

Professor Richard McLaren, who led the investigation, states [**C**] that the DCC "*had in their repertoire of analytical methods or rapidly developed methods that provided me with legally defensible evidence that samples had been manipulated as claimed by Dr. Rodchenkov. This greatly assisted me in proving the involvement of individuals who could then be identified in my formal and public reports of 18 July and 9 December 2016. […] I am very indebted to the DCC for the very significant contributions they made to my work as the Independent Person conducting the WADA investigation of the events that occurred at the Sochi Winter Olympic Games in 2014. The impact of that work is still very much in place as we currently await the Court of Arbitration for Sport (CAS-TAS) ruling on the manipulation of the Moscow Laboratory computer data."*

Overall, the success of this investigation helped strengthen the coordinated global fight against doping; demonstrating that those who seek to subvert the system, no matter how powerful, will be heavily sanctioned. McLaren emphasised that *"without the assistance of the Drug Control Centre, my investigation would at best have been delayed and possibly may not have been able to reach the clear conclusions as published"* [**C**].

King's research has led to the adoption of new national and international standards and policies in anti-doping. A key example lies in work associated with new methodological approach to indirectly test for hGH via insulin-like growth factor-I as a biomarker [**2**]. Following our underpinning research, WADA worked closely with the DCC team to develop an approved test for the use of biomarkers for the detection of hGH doping. We advised during the creation of regulatory documentation, helped implement the laboratory accreditation process, and monitored the performance of these new measures. The testing method arising from our research now forms part of the WADA guidelines that must be followed by all anti-doping laboratories throughout the world [**H**].

The Senior Deputy Director of Science and Medicine at WADA was clear that *"the research output of the DCC was pivotal in the establishment of legally defensible biomarker scores and the implementation of the WADA Guidelines"* [**I**]. As noted by former Chief Executive of UK Anti-Doping (UKAD), *"This culminated in another world first in successfully prosecuting two Paralympians for the use of human growth hormone. It cannot be understated the important of this work, given the increasing prevalence we were seeing in the misuse of this substance around the world"* [**J**].

UKAD is the executive non-departmental public body sponsored by the Department for Digital, Culture, Media & Sport that is responsible for implementing and managing anti-doping policy in the UK. Our long-standing and deep partnership with UKAD has been key to ensuring that our science remains effectively employed in practice within the UK - and has helped secure UKAD's standing as one of the world's leading anti-doping organisations. In 2018, the Department for Digital, Culture, Media and Sport published a 'Tailored Review of UK Anti-Doping' where the DCC's role was highlighted as their *"most impressive example"* of effective partnership [**G**].

The Tailored Review recommended a 50% increase in testing across sport, and in January 2018, the UK Government gave UK anti-doping a GBP6,000,000 funding boost to educate athletes, share intelligence and conduct testing in the fight against drug cheats to keep sport clean [**N**]. As a result, the number of samples analysed by the DCC more than quadrupled, to approximately 13,000 in 2019. The Chief Executive of UKAD, states that, "*The UK's anti-doping programme is recognised internationally, which is only possible with the support of partners and stakeholders. The DCC provides the necessary WADA accredited state of the art laboratory alongside an expert*

contribution to anti-doping science and research. The DCC's support in the fight for clean sport enhances the deterrent to athletes and increases the chances of catching those who cheat" [**K**].

The former Chief Executive of UKAD also corroborates this picture of sustained, longstanding, impact: "*The partnership that UKAD and the DCC had during my time with UKAD was just that and set a benchmark for how National Anti-Doping Organisations and WADA Accredited Laboratories could make a positive impact through working together*" to "*develop new scientific methodologies on real samples"* leading to "*a number of world firsts in relation to new analytical findings which we could not have achieved without the involvement of the DCC."* [**J**].

Our expertise is widely sought and has delivered long-lasting impact in international sporting competition and governance. We play a major, internationally recognised, role in anti-doping efforts at many major international sporting events. This work requires close partnership with both national and international regulatory bodies. For example, we were selected to deliver anti-doping testing for the 2018 European Championships in Glasgow, and for the annual London Marathon [**J**]. We also made key contributions to the planning and delivery of the PyeongChang Olympic Winter Games in 2018 [**L**] and the Rio Olympic Summer Games in 2016 [**M**].

Speaking about the role of the DCC in the 2018 PyeongChang Winter Games, the then head of the South Korean WADA laboratory states that the DCC were *"key in helping us to fulfil our work to the international standard required. I found that their scientific knowledge and experience in the forefront of anti-doping science were essential to my work…. [the DCC] was the best supporter to us in advising and suggesting the technical solutions of the sample analysis for its successful achievement"* [**L**].

The former director of the Brazilian Doping Control Laboratory said, *"this sizeable contribution of Professor Cowan, the DCC and King´s College London surely had an impact on the quality of the doping control analysis performed at the Rio 2016 games"* [**M**]. The Independent observer for the Rio 2016 Olympic Laboratory report had also stated that *"[the laboratory] was superbly equipped, operated very securely and generally very efficiently, and now represents an outstanding legacy from the Games for the anti-doping movement in South America"* [**O, p.5**].

The DCC is the single internationally accredited sports testing laboratory for the UK. Building from our work in providing independent anti-doping facilities for the London 2012 Olympics and Paralympics, we have witnessed a significant expansion of our role to provide new methodology, new standards, and the delivery of widespread sample testing in competitive sport. The DCC is the only WADA-certified laboratory in the UK; one of only 16 laboratories worldwide. Accredited to ISO/IEC 17025 international standards, we now analyse ~15,000 samples each year, a doubling of our capacity since 2014 [**F**].

5. Sources to corroborate the impact (indicative maximum of 10 references)

A. Mclaren, RH. *WADA Investigation of Sochi Allegations.* (2016) part i, part ii

B. Project Report: UK Anti-Doping and the Russian Anti-Doping Agency during Non-Compliance. (2019)

C. Mclaren, RH. Testimonial. (2020).

D. Mehta, A. Anti-doping scientists expose cheating Russian athletes. *Chemistry World* (2016)

E. International Olympic Committee. Decision of the IOC executive board concerning the participation of Russian athletes in the Olympic Games Rio 2016. (2016)

F. WADA. *Annual testing statistics report.* (2020)

G. Department of Digital, Culture Media & Sport. Report of the tailored Review of UK Anti-doping. (2018)

H. WADA. *Guidelines for Human growth hormone biomarkers test for doping control analyses*. (2016)

I. Barroso O. Senior Deputy Director WADA. Testimonial. (2021)

J. Parkinson, A. (Former) Chief Executive of UKAD. Testimonial (2021)

K. Sapstead, N. Chief Executive UKAD. Testimonial (2021)

L. Kwon, O-S. Principal Research Scientist of Doping Control Center. Korea Institute of Science and Technology. Testimonial (2021).

M. Former Director of the Brazilian Doping Control Laboratory and Director of the Laboratory for the Support of Technological Development at Federal University of Rio de Janeiro. Testimonial (2021)

N. UK Anti-Doping receives £6 million funding boost (2018).

O. WADA. Report of the Independent Observers of the Olympic Games at Rio de Janeiro (2016).