Institution: University of Southampton

Unit of Assessment: 01 Clinical Medicine

Title of case study: 01-04 A new anti-doping test to detect Growth Hormone misuse in sport

1. Summary of the impact

High-profile cases of growth hormone misuse by leading international sports stars have made the development of an effective detection test a main priority of global anti-doping organisations. A research team headed by the University of Southampton developed a new test, adopted at the 2012 Olympic Games, which identified two drugs cheats at the London Paralympic Games just weeks after it was first introduced. The subsequent bans serve to act as a powerful deterrent to other athletes and help restore public confidence in fair competition. The World Anti-Doping Agency has announced its commitment to rolling out the test internationally.

2. Underpinning research

The development of a test to detect growth hormone (GH) misuse has long been a major priority of the World Anti-Doping Agency (WADA) to combat cheating in professional sport. Several high-profile athletes including Ben Johnson, Marion Jones and Tim Montgomery have admitted taking GH and a 2007 report by former U.S. Senator George Mitchell exposed the scale of GH misuse in Major League Baseball.

Detecting GH is a significant scientific challenge because, unlike many substances of abuse, GH is a naturally occurring protein, the concentration of which varies widely throughout the day. Traditional antidoping methods are ineffective and although a GH test was introduced in 2004, it only detects GH up to 24 hours after administration, meaning users could stop taking it on the eve of the competition without fear of detection.

The GH-2004 team, based at the University of Southampton and led by Professor Richard Holt (Professor in Diabetes and Endocrinology 2000-current), has developed a method to detect GH misuse up to several weeks after administration by measuring two GH-sensitive serum markers, IGF-I and P-III-NP. The method principle was established by Peter Sönksen (then Professor of Endocrinology, St Thomas's Hospital) who led the multinational GH-2000 project. When this project ended in 1999, several issues remained, most notably the possible effects of injury and ethnicity on test results. The International Olympic Committee requested further validation to identify "beyond reasonable doubt" GH dopers with minimal risk of false accusation.

Sönksen joined Southampton as a Visiting Professor (2002-current) and the GH-2004 project was established by Holt and Sönksen in December 2002 to address these questions. All clinical studies were undertaken at Southampton; other Southampton academics included research fellows Dr Cathy McHugh (2003-2006), Dr Ioulietta Erotokritou-Mulligan (2003-2007) and Dr Nishan Guha (2007-2011). Laboratory analysis was undertaken at the WADA-accredited Drug Control Centre at King's College London and statistical analysis at the Universities of Southampton and Kent. The team has disseminated its research findings. The project was funded by $2.7m in WADA grants from 2003 to 2012 and $1m from the US Anti-Doping Agency (USADA).

The GH-2004 team found small variations in IGF-I and P-III-NP concentrations with ethnicity but these had no effect on the test performance (2003-05) **[3.2, 3.3]**, and they found no significant ethnic effects on peak or maximal responses of IGF-I and P-III-NP to the recombinant human growth hormone (2004-07) **[3.3]**. While injury increases P-III-NP concentration, it does not significantly affect the test performance (2004-06) **[3.1]**. The team determined how adolescence affects marker concentration (2006-08) **[3.6]** and found no significant biological variation of marker concentration within athletes. The team validated the test in two independent data sets **[3.4, 3.5]** (2005, 2012).

Further studies focused on the practical implementation of the test. The GH-2004 team determined

the optimal pre-analytical collection and storage conditions (2006, 2011), determined the definitive decision limits for use by anti-doping laboratories (2010-11), coordinated a successful test pilot in the London and Rome WADA-accredited laboratories (2011) and wrote the approved WADA technical manual for implementing the test (2011) ahead of its first use at the London 2012 Olympics.

3. References to the research

3.1 Erotokritou-Mulligan I, Bassett EE, Bartlett C, Cowan D, McHugh C, Seah R, Curtis B, Wells V, Harrison K, Sönksen PH, Holt RI; GH-2004 Group. The effect of sports injury on insulin-like growth factor-I and type 3 procollagen: implications for detection of growth hormone abuse in athletes. *J Clin Endocrinol Metab*. 2008;93:2760-3.

3.2 Erotokritou-Mulligan I, Bassett EE, Cowan DA, Bartlett C, McHugh C, Sönksen PH, Holt RI; GH-2004 group. Influence of ethnicity on IGF-I and procollagen III peptide (P-III-P) in elite athletes and its effect on the ability to detect GH abuse. *Clin Endocrinol* (Oxf). 2009;70:161-8.

3.3 Holt RI, Erotokritou-Mulligan I, McHugh C, Bassett EE, Bartlett C, Fityan A, Bacon JL, Cowan DA, Sönksen PH. The GH-2004 project: the response of IGF1 and type III pro-collagen to the administration of exogenous GH in non-Caucasian amateur athletes. *Eur J Endocrinol.* 2010 Jul;163(1):45-54. Epub 2010 Apr 26

3.4 Erotokritou-Mulligan I, Guha N, Stow M, Bassett EE, Bartlett C, Cowan DA, Sönksen PH, Holt RI. (2012) The development of decision limits for the implementation of the GH-2000 detection methodology using current commercial insulin-like growth factor-I and amino-terminal pro-peptide of type III collagen assays. *Growth Horm IGF Res*. 2012: 22:53–58

3.5 Erotokritou-Mulligan I, Bassett EE, Kniess A, Sönksen PH, Holt RI. Validation of the growth hormone (GH)-dependent marker method of detecting GH abuse in sport through the use of independent data sets. *Growth Horm IGF Res*. 2007;17:416-23.

3.6 Guha N, Erotokritou-Mulligan I, Burford C, Strobridge G, Brigg J, Drake T, Bassett EE, Cowan D, Bartlett C, Sönksen PH, Holt RI. Serum insulin-like growth factor-I and pro-collagen type III N-terminal peptide in adolescent elite athletes: implications for the detection of growth hormone abuse in sport. *J Clin Endocrinol Metab*. 2010 Jun;95(6):2969-76. Epub 2010 Apr 21.

Grants

US Anti-doping Agency — Jan 03 – July 05 — $1,031,739

The development of a methodology for detecting abuse with growth hormone in sport: GH-2004. Pilot study on ethnic effects 2 ½ years RIG Holt, PH Sonksen

World Anti-Doping Agency grants — Mar 03 – Dec 12 — $2,675,457

The development of a methodology for detecting abuse with growth hormone and IGF-I in sport: GH-2004. Pilot study on ethnic effects RIG Holt, PH Sonksen, EE Bassett, DA Cowan, N Guha

Partnership for Clean Competition — Mar 11 – Dec 13 — $400,000*

GH-2004: Novel biomarkers for the detection of IGF-I abuse. RIG Holt, PH Sonksen, EE Bassett, DA Cowan, N Guha, I Erotokritou-Mulligan. *Further funding up to $200,000 has been agreed subject to results in phases II of the study

4. Details of the impact

Research led by the University of Southampton resulted in the implementation of a more effective test, backed by international anti-doping organisations, to detect GH misuse. The test had an immediate impact. During its first use, at the 2012 London Olympic and Paralympic Games **[5.1]**,

the International Paralympic Committee announced two-year suspensions for two Russian powerlifters found guilty of GH misuse after returning a positive test **[5.2, 5.3]**.

The effectiveness of GH-2004's new test was demonstrated almost immediately as neither of these athletes failed the previously available WADA test for GH misuse; this was introduced in 2004 and has a much shorter window of opportunity of ~12 to 24 hours making in-competition detection of GH misuse difficult.

The successful development of a test for GH has been a major goal for the International Olympic Committee, WADA and national anti-doping agencies for more than a decade in order to preserve the integrity of and restore public confidence in professional sport. WADA President John Fahey said: "We are confident that (the new test) will prove a significant tool in the fight against doping in sport. It will complement the test that has been in use since the 2004 Athens Olympic Games, the major difference being that the anti-doping community now has a much longer detection window to work with." **[5.4]**.

Although exact numbers are confidential, a significant proportion of athletes at the London Games were tested for GH misuse using the Southampton-led test. The implementation of the test will not only lead to better detection of athletes who are taking GH but crucially act as a strong deterrent to other athletes considering taking performance-enhancing drugs.

News of the suspension of the Russian powerlifters through the new testing procedure generated significant global media interest, leading to more than 500 online articles **[5.5, 5.6]**. As well as acting as a deterrent, this blanket coverage serves to demonstrate to the sports-viewing public that cheating athletes are being punished and reassures clean athletes that cheats are not at an unfair advantage.

Andy Parkinson, UK Anti-Doping Agency (UKAD) Chief Executive, said: "Continual improvement in testing science is fundamental to the global anti-doping movement, ensuring that sophisticated dopers are caught and those at a tipping point are deterred. I am delighted that this UK developed test … was used at the 2012 Paralympic Games to such good effect." **[5.3]**. As Parkinson alludes to in his statement, another beneficiary of the research is UK science as a whole. The test, created and refined in the UK, is set to be used around the world.

The successful implementation of the GH-2004 test followed years of close collaboration between Holt's team and international authorities during the impact period. WADA, USADA and UKAD held two-day annual meetings with the academics to review the science. From 2008, Holt established a close working relationship with UK Sport and UKAD through meetings five times a year. A statement from UK Sport said: "Any gap in our testing armoury obviously concerns us as it damages our ability to tackle doping in sport. As such, to be actively involved in a research project in partnership with the GH-2004 team at Southampton University and the WADA-accredited laboratory at King's College … is of real importance and invaluable in continuing the drive to combat doping in sport." **[5.7]**.

Holt has been proactive in disseminating the results. From 2003 and continuing throughout the REF period, he has spoken to a vast range of media outlets about the GH test, including BBC Radio, newspapers and television (e.g. the Richard & Judy Show on Channel 4). He has given lectures at events that have included the 2008 Major League Baseball GH Summit, Los Angeles (reported by the Los Angeles Times **[5.8]** and USA Today **[5.9]** quoting Holt) and the joint USADA and UK Sport anti-doping science symposium, London (2011).

At present WADA undertakes ~5000 tests for GH per annum but this is likely to increase with the introduction of a more effective test. WADA's goal is to roll out the test internationally and laboratories worldwide will apply for approval to administer the test. The test is not confined to athletics. After discussions with Holt, the U.S. National Football League **[5.10]** and Major Baseball League made internal recommendations to commission anti-doping labs in the U.S. to carry out the

test. The test has already been used outside the Olympics in other UK sports although the details remain confidential. WADA intends to include the test in athletes' biological passports, which will ensure GH detection is even more effective.

5. Sources to corroborate the impact

5.1 David Howman, director general of the World Anti-Doping Agency, announces the introduction of the test at the London Olympic Games. This story was picked up by many news agencies including the BBC. London 2012: Selsouli to miss Games after failed drugs test. http://www.bbc.co.uk/sport/0/olympics/18985217. Published 25 July 2012. Accessed 6 June 2013.

5.2 Report of suspension of Nikolay Marfin and Vadim Rakitin by International Paralympic Committee following their positive test at the London Paralympic Games. Latest Testing Methods Result in Suspension of Two Russian Powerlifters for Anti-Doping http://www.paralympic.org/press-release/latest-testing-methods-result-suspension-two-russian-powerlifters-anti-doping. Published 8 Sept 2012. Accessed 6 June 2013.

5.3 Report of suspension of Nikolay Marfin and Vadim Rakitin by International Paralympic Committee by UK Anti-Doping including quote by Andy Pakinson, UK Anti-Doping Agency (UKAD) Chief Executive. UK research leads to new Growth Hormone test and positive findings. http://www.ukad.org.uk/news/article/uk-research-leads-to-new-growth-hormone-test. Published 19 Sept 2012. Accessed 6 June 2013.

5.4 Reported on the European Commission website. New test to catch illegal drug doping in sports including quote by WADA President John Fahey. http://ec.europa.eu/research/headlines/news/article_12_10_08_en.html. Published 8 October 2012. Accessed 6 June 2013.

5.5 Example of media coverage of the positive GH test at the Paralympics. New test detects longer-term growth hormone abuse. http://www.topnews.in/healthcare/content/22939new-test-detects-longer-term-growth-hormone-abuse. Published 17 September 2012. Accessed 6 June 2013.

5.6 Example of media coverage of the positive GH test at the Paralympics. University of Southampton develops better test for banned human growth hormone. http://www.dailyecho.co.uk/news/9932997.Uni_develops_better_test_for_banned_substance/. Published 17 September 2012. Accessed 6 June 2013.

5.7 The UK Sport perspective on detecting growth hormone abuse. Stow MR, Wojek N, Marshall J. Growth Horm IGF Res. 2009 Aug;19(4):375-7

5.8 Report of GH summit in Los Angeles. Researchers cite progress on HGH. http://articles.latimes.com/2008/nov/11/sports/sp-hgh11. Published 11 November 2008. Accessed 6 June 2013.

5.9 Report of GH summit in Los Angeles. MLB won't be testing for HGH any time soon. http://usatoday30.usatoday.com/sports/baseball/2008-11-10-113459931_x.htm?csp=34 Published 11 November 2008. Accessed 6 June 2013.

5.10 Evidence of NFL commitment to testing for GH. NFL wants its players tested for human growth hormone. http://www.nfl.com/news/story/09000d5d81ef2988/article/nfl-wants-its-players-tested-for-human-growth-hormone. Published 25 November 2011. Accessed 6 June 2013.