Institution: University of Kent

Unit of Assessment: 10 (Mathematical Sciences)

Title of case study: Detection of growth hormone abuse in sport

1. Summary of the impact

Statistical research at Kent has made an essential contribution to the development of an effective test to detect growth hormone (GH) abuse in sport. GH is naturally present in the human body, but its exogenous use has been banned in sport for many years. However, it is believed to be widely misused across a broad spectrum of sports and the research attracted a wide range of support from national anti-doping authorities in the UK (UKAD) and USA (USADA), from the EU, via the Biomed 2 Programme, from the International Olympic Committee (IOC) and the World Anti-Doping Agency (WADA), and from industry. The development of a reliable anti-doping test (the "biomarker" test), based on the biological and statistical research, is a breakthrough that benefits the public, by helping to ensure fairness in sporting events. There are also potential health benefits to sportspeople who are discouraged from using exogenous GH, which can have serious side effects. The new test was finalised and approved by WADA in July 2012. The test was used for the first time just prior to the 2012 London Games and led to two Paralympic competitors being convicted of GH doping.

2. Underpinning research

The aim of the research was to develop and validate an anti-doping test to detect use of exogenous GH. The multidisciplinary research team comprised specialists in medicine, statistics and bioassay technology. The statistical work was done at Kent or led by Kent statisticians **[5.1, 5.2, 5.3]**.

Because GH is present naturally in the body, detection of exogenous GH is difficult and inevitably relies on statistical techniques. The concentration of GH in blood varies considerably; it depends on age and it responds to exercise. GH is secreted in a pulsatile manner, and is eliminated quickly from the body. Research to find a marker to detect GH started in 1996 with the GH-2000 project, sponsored by the European Union (EU) and the IOC. The medical work centred on St Thomas' Hospital, London, with partners in Denmark, Sweden and Italy; and all of the statistical work on the project was undertaken at Kent by staff from the University of Kent: **Bassett** (1970-2007; 2007-present, Honorary Senior Lecturer, work done at Kent), **Brown** (1995-present) and **Kenward** (1995-1999) **[5.3, p.7]**. The project was successfully completed in 1999, and a novel statistical approach (the "trajectory" method) which aimed to model the way in which combinations of marker levels varied over time following GH administration was published **[3.1]**.

Four major studies were undertaken during the project: a Washout study, a Double-blind study, a Cross-sectional study and a Longitudinal study. This preliminary research was needed to identify and study hormones which could act as markers of GH abuse. To be suitable, a biomarker had to have a reasonably long half-life in the body, and it had to be responsive to GH administration, but relatively unresponsive to exercise. The research identified 8 possible markers. A key component of the University of Kent contribution to the project was the finding that, for each sex separately, a discriminant function based on only two of these markers, insulin-like growth factor-I (IGF-I) and N-terminal pro-peptide of type III collagen (P-III-NP), could distinguish dopers from subjects given a placebo. These statistical functions, derived during the GH-2000 project, form the basis of the test; without this statistical component of the work, the test would have not been economically viable **[3.2]**.

A follow-up project (GH-2004), involving Southampton University (Medicine, project leader), the University of Kent (Statistics), and Kings College London (assay work), started in 2002, building on the earlier work. The statistical component of the work was done or supervised at Kent by **Bassett [5.1, 5.2]**. Key statistically-based components of the work were the specification of the score function **[3.2]** and the decision limits; that is, the scores above which an athlete would be prosecuted **[3.3]**.

To ensure that the test could withstand legal challenge, the GH-2004 team needed to establish robustness; for example, in respect of ethnicity **[3.5]**, the effects of injury, and differential changes

during adolescence. Validation of the method on independent sets of data was also required, as was confirmation that the test would give consistent results in different laboratories **[3.6]**. Further, because out-of-competition blood samples may need to be obtained far from WADA-accredited laboratories, research has been needed to determine stability of assay results under varied storage and transport conditions **[3.4]**. WADA policy also requires concentrations obtained from assay work to be estimated using two different types of assay. To meet all these requirements, several detailed studies were needed; the planning of these was achieved by collaboration between the chemists and statisticians, and the data analysis was the specific responsibility of the statistical team.

The leader of the GH-2004 project acknowledged the statistical work done at Kent and said that the "statistical analysis of the project, which has been a key part of the work, was led by Dr Eryl Bassett, University of Kent. This work has played a vital part of the development of the test as the test has to stand up to legal scrutiny. Dr Bassett has been involved in the project since its inception and designed the statistical analysis plan for the GH-2004 project and preceding GH-2000 project" **[5.3]**.

To summarise, the statistical research conducted at Kent by **Bassett**, **Brown** and **Kenward** has been crucial in designing the biomarker test and ensuring its viability and validity.

3. References to the research

One paper specifically on statistical methodology was published by the GH-2000 research team:

[3.1]* Brown, P.J., **Kenward, M.G** & **Bassett, E.E.** (2001). Bayesian discrimination with longitudinal data. *Biostatistics*, **2(4)**, 417-432. doi: 10.1093/biostatistics/2.4.417

Papers which deal in detail with the follow up research, and which are crucial to the formal specification of the test are:

[3.2] Powrie J.K., **Bassett E.E.**, Rosen T., Jorgensen J.O., Napoli R., Sacca L., et al. (2007) Detection of growth hormone abuse in sport. *Growth Horm IGF Res*, **17(3)**, 220-226. doi:10.1016/j.ghir.2007.01.011

[3.3] Erotokritou-Mulligan, I.; Guha, N., Stow, M., **Bassett, E.E.**, Bartlett, C., Cowan, D.A., Sönksen, P.H. & Holt, R.I.G. (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,* **22(2)**, 53-58. doi: 10.1016/j.ghir.2011.12.005

The following papers give examples of the work needed to ensure that the test is robust to logistical problems which may occur, and that it remains a fair test for individuals with particular characteristics; there is also a commentary on the use of statistical reasoning in assay work:

[3.4] Holt R.I., Erotokritou-Mulligan I., Ridley S.A., McHugh C.M., **Bassett E.E.**, Cowan D.A., et al. (2009) A determination of the pre-analytical storage conditions for insulin like growth factor-I and type III procollagen peptide. *Growth Horm IGF Res*, **19(1)**, 43-50. doi: 10.1016/j.ghir.2008.06.001

[3.5] Erotokritou-Mulligan I., **Bassett E.E.**, Cowan D.A., Bartlett C., McHugh C., Sonksen P.H., et al. (2009) 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)*, **70(1)**, 161-168. doi: 10.1111/j.1365-2265.2008.03319.x

[3.6] Bassett E.E., Erotokritou-Mulligan I. (2009). Statistical issues in implementing the marker method. *Growth Horm IGF Res*, **19(4)**, 361-365. doi: 10.1016/j.ghir.2009.04.024

(Reference marked with a star best indicates the quality of the underpinning research.)

4. Details of the impact

Drug abuse in sport is a significant global problem. Exogenous GH was banned by the IOC as long ago as 1989, but it has continued to be used because of the lack of a reliable anti-doping test. The 2012 WADA-approved test for exogenous GH is the culmination of many years of multidisciplinary work, in which statistical research conducted at Kent played an essential role, and represents a significant breakthrough in the fight against drug abuse in sport. The impact lies both in improving the integrity of sport, for the benefit of the millions of people who follow it, and in discouraging the

use of exogenous GH, thereby reducing the associated health risks for sportspeople.

The difficulty of devising a sensitive test for exogenous GH administration is evidenced by the range of official bodies which have become involved with or have supported the research, and by the amount of conference time devoted to the topic. One test (the "isoform" test) for GH was approved and has been in use since the Athens Olympics in 2004, but it has had little success in detecting dopers, and it is widely regarded as very easy to evade. This feature has motivated the intense interest in developing a more sensitive test **[5.7]**.

The US Anti-doping Agency (USADA) views this area as sufficiently important and long-lived that after the 2004 Annual Symposium (Dallas, on Detection of Human Growth Hormone Abuse), it was again the topic of the 2011 event (London, on Detection of Growth Factors). Two members of the GH-2004 team gave invited talks at the Dallas meeting and three members gave invited talks at the 2011 London meeting (Holt, on *Overview of the GH-2000 biomarkers method*; Bassett, on *Development and application of the discriminant function in the GH-2000 biomarker test*; Cowan, on *The marker method: Inter-lab study*). These Symposia are "aimed at bringing together anti-doping experts from around the world ... to inform and shape meaningful anti-doping research programs for the future" **[5.9]**. The 2011 London meeting "gathered over 100 scientists, laboratory directors and sports administrators, representing renowned entities such as research institutes, international sport federations, universities, the World Anti-Doping Agency, the International Paralympic Committee, professional sports leagues, and the London Olympic Organizing Committee", with participants from almost 30 countries **[5.9]**.

Interactions between the GH-2004 team and various anti-doping agencies are also evident through their contributions to a special issue of the journal *Growth Hormone and IGF Research* that covered medical, legal and social aspects of GH abuse in sport **[5.10]**.

The UK Anti-Doping Agency (UKAD, then part of UK Sport) expressed interest in the project in late 2006 **[5.5]**, having perceived a need for a more sensitive test of GH administration. UKAD have given practical support (for example, supplying athletes' blood samples when permitted for research purposes) **[5.1]**. The GH-2004 project was funded by WADA and USADA **[5.6]**.

The robustness of the biomarker test in the face of potential legal challenges was established by the end of 2011 and formal approval by the UK Accreditation Service to conduct the test was achieved in early July 2012. The announcement of the introduction of the new test led to much press comment; the Chief Science Officer of USADA, Larry Bowers, described it as "a terrific day for anti-doping when you can put a test like this in place" **[5.8]**. The test was used formally for the first time in the run-up to the Olympic and Paralympic Games, and successfully **detected two cases of GH doping in the Paralympic Games**, leading to the disqualification of the powerlifters involved and their suspension for two years **[5.1, 5.2, 5.4]**.

The leader of the GH-2004 project confirms that the "test has been endorsed by the World Anti-Doping Agency and was introduced for the first time at the 2012 London Olympic Games resulting in two Russian powerlifters being disqualified at the Paralympic games" **[5.3]**.

Summary: The statistical research at Kent has had a significant impact on the 2012 Olympics and on the integrity of sport in general, through the design and validation of a new internationally recognised test to detect exogenous use of GH.

5. Sources to corroborate the impact

Main sources:

[5.1] The basis of the impact case study is summarised in a press release from UK Anti-Doping about the biomarker test. It explains the background to the test, gives detail of the funding, explains the role of the Kent statisticians and gives details of the positive test results for two powerlifters at the London 2012 Paralympics:
http://www.ukad.org.uk/news/article/uk-research-leads-to-new-growth-hormone-test

[5.2] Email from the leader of the GH-2004 team confirming the vital role of the statistical work done at Kent in developing the test, and the disqualification of two athletes at the London 2012 Paralympics Games thanks to this new test. (See Contact 1.)

[5.3] Final report for the GH-2000 project confirming the role of Kent statisticians in this project.

Available at:
http://www.gh2004.soton.ac.uk/GH-2000%20Final%20Report.pdf

[5.4] Announcement of first positive test at the Paralympic Games:
http://www.paralympic.org/press-release/latest-testing-methods-result-suspension-two-russian-powerlifters-anti-doping

Additional sources:

[5.5] A statement from UKSport about the importance of their active involvement with GH-2004:
http://www.gh2004.soton.ac.uk/collaboration_with_uk_sport.htm

[5.6] Results and conclusion for the GH-2004 project available on the WADA webpage confirming in particular sources of funding:
http://www.wada-ama.org/rtecontent/document/A1_2002_results.pdf

[5.7] Criticism of the then-current ("isoform") test, with hint at a better test coming:
http://news.bbc.co.uk/sport1/hi/olympics/7339460.stm

[5.8] Announcement by WADA of the introduction of the biomarker test:
http://sportsillustrated.cnn.com/2012/olympics/2012/writers/david_epstein/07/27/london-olympics-drug-testing/index.html

[5.9] General information about the scope and purpose of USADA Annual Symposia:
http://www.usada.org/symposia/

Details about the USADA Annual Symposium in London 2011:
http://www.usada.org/symposia/london/

[5.10] A special issue of the journal *Growth Hormone & IGF Research* in August 2009 was devoted to "The Abuse of Growth Hormone in Sport and its Detection: a Medical, Legal and Social Framework". Eight of the 24 papers were from the research team; other contributors included scientific staff of WADA and UKAD:
http:/www.sciencedirect.com/science/publication?issn=10966374&volume=19&issue=4

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