Clinical Chemistry 57:7
969–976 (2011)

Reviews

The Athlete Biological Passport

Pierre-Edouard Sottas,[1*] Neil Robinson,[1] Olivier Rabin,[2] and Martial Saugy[1]

BACKGROUND: In elite sports, the growing availability of doping substances identical to those naturally produced by the human body seriously limits the ability of drug-testing regimes to ensure fairness and protection of health.

CONTENT: The Athlete Biological Passport (ABP), the new paradigm in testing based on the personalized monitoring of biomarkers of doping, offers the enormous advantage of being independent of this endless pharmaceutical race. Doping triggers physiological changes that provide physiological enhancements. In the same way that disease-related biomarkers are invaluable tools that assist physicians in the diagnosis of pathology, specifically selected biomarkers can be used to detect doping.

SUMMARY: The ABP is a new testing paradigm with immense potential value in the current climate of rapid advancement in biomarker discovery. In addition to its original aim of providing proof of a doping offense, the ABP can also serve as a platform for a Rule of Sport, with the presentation before competition of the ABP to objectively demonstrate that the athlete will participate in a healthy physiological condition that is unaltered by performance-enhancing drugs. Finally, the decision-support system used today for the biological monitoring of world top-level athletes can also be advantageously transferred to other areas of clinical practice to reach the goal of personalized medicine.

The promotion of ethical values and the protection of health in and throughout sports are the primary objectives of the sport movement. In that context, the abuse of substance doping represents the most serious threat to the integrity of modern sports. The *World Anti-Doping Code*, the reference document that provides the framework for harmonized antidoping rules within sports organizations, has been written to preserve the core values of natural performance, protection of health, and the spirit of the sport *(1)*. Accordingly, a substance or method is considered for prohibition if it violates at least 2 of these 3 values. The primary tool used by sports authorities to ensure a doping-free sport has been the detection of prohibited substances in the biological fluids of athletes, specifically urine and blood. This drug-testing paradigm was introduced in the 1960s (Table 1) and has since been remarkably successful in the detection of substances that are not naturally produced by the body, such as stimulants, narcotics, β2-agonists, and diuretics. This success is largely attributed to the use of chromatography coupled to mass spectrometry techniques that have revolutionized the detection of a large number of compounds *(2)*.

As a result of advances in biotechnology, the pharmaceutical industry continues to market new drugs at a remarkable pace. A substantial number of these new substances are recombinant proteins or peptides that are strikingly similar in structure, and in some instances absolutely identical, to those naturally produced by the human body. The identification of these substances in biological fluids can be difficult or virtually impossible in some cases. In modern sports, doped athletes are in a constant race with antidoping researchers, who must employ great ingenuity to develop toxicology tests capable of distinguishing exogenous substances from their endogenous counterparts. In addition, detection is further complicated by the medical supervision and increased sophistication of doping protocols. Contemporary protocols are shifting towards long cycles of small microdoses taken repeatedly that are difficult to detect by using conventional drug tests. Worse, designer drugs are currently being produced by black-market laboratories to get around existing drug tests. Consequently, the drug-testing paradigm established in the 1960s cannot prevent elite athletes from doping with impunity when using many potent doping substances such as designer recombinant erythropoietin (rEPO)[3] and designer testosterone. For these reasons, alternative strategies that are independent of this endless pharmaceutical race must be developed to maintain fairness in elite sports.

[1] Swiss Laboratory for Anti-Doping Analyses, Chemin des Croisettes, 1066 Lausanne, Switzerland; [2] World Anti-Doping Agency, Montreal, Canada
* Address correspondence to this author at: Swiss Laboratory for Doping Analyses, Croisettes Epalinges, 1066 Lausanne Switzerland. Fax +41-21-3147333; e-mail pesottas@gmail.com.
Received January 23, 2011; accepted April 20, 2011.
Previously published online at DOI: 10.1373/clinchem.2011.162271

[3] Nonstandard abbreviations: rEPO, recombinant erythropoietin; ESA, erythropoiesis-stimulating agents; HGB, hemoglobin concentration; HCT, hematocrit; T/E, testosterone/epitestosterone; ABP, Athlete Biological Passport; WADA, World Anti-Doping Agency.

Table 1. History of anti-doping.

Year	Event
1928	The IAAF becomes the first federation to ban doping
1966	The IAAF, the Union Cycliste Internationale (UCI), and the Fédération Internationale de Football Association (FIFA) introduce urine drug tests in their respective championships
1967	The International Olympic Committee (IOC) institutes its Medical Commission and sets up the first list of prohibited substances
1968	Drug tests introduced at the Olympic Games
1970s	Marked increase in the number of doping-related disqualifications after the introduction by the IOC of anabolic steroids to its list of prohibited substances
1980s	Introduction of out-of-competition testing
1986	blood transfusion banned by IOC
1990	rEPO included in the IOC's list of prohibited substances
1990s	Introduction of blood tests
1999	WADA is established
2004	The World Anti-Doping Code is adopted worldwide
2005	United Nations Educational, Scientific and Cultural Organization (UNESCO) adopts the International Convention against Doping in Sport
2008	The UCI is the first federation to introduce the Athlete Biological Passport

A Paradigm Shift in Testing

The development of erythropoiesis-stimulating agents (ESA) for the treatment of anemia has been a highly active field over the past 2 decades, wherein 6 different rEPOs have been licensed worldwide and more than 90 biosimilar rEPOs or copies have become available in countries with low regulatory controls of pharmaceutical products *(3)*. This frenzied rhythm is expected to continue because new generations of ESAs are expected in the near future, such as the synthetic peptide-based EPO receptor agonist Hematide™; the conjugated EPO-mimetic peptide Sestide™; hypoxia-inducible transcription factor stabilizers, such as FG-2216™; and modified cells that carry the human EPO gene or the EPO protein, such as EpoDure™. In parallel with increasing numbers of prescribed ESAs, some designer rEPOs have been created by black market laboratories to get around existing drug tests.

All ESAs aim to improve oxygen transport by the metalloprotein hemoglobin. Consequently, measurement of hemoglobin concentration (HGB), one of the most common medical tests in a full blood count profile, has been used as a biomarker of blood doping. In the mid-1990s, some sports federations introduced upper limits on HGB and hematocrit (HCT) levels, and athletes with values above these limits were temporarily suspended from competition in an attempt to limit the abuse of rEPO. Interestingly, such doping biomarkers are independent from the marketing of novel doping substances, and although the pharmaceutical industry continues to market new drugs every year, the biology of the human body is relatively stable for general physiological functions. The evolution of the human body takes at least several generations, and owing to this biological stability, a biomarker of doping such as hemoglobin measurement will remain sensitive to any past, present, or future ESA abuse.

As a result, there is an ongoing paradigm shift in testing, from the direct identification of banned substances in the biological fluids of athletes to the detection of abnormalities in biomarkers that potentially indicate that doping has occurred. Although it is difficult to predict which of the new ESAs will be available during the 2016 Olympic Games in Rio de Janeiro and beyond, the biological characteristics of the athletes participating in these games will not differ from the biological characteristics of athletes that are competing today. Consequently, all of the doping biomarkers that have already been developed will remain applicable in the upcoming Olympic Games and for several decades into the future, whereas a toxicology test must be established for almost every newly marketed drug. For example, today's biomarkers of blood doping are already sensitive to gene doping with the human EPO gene.

Biomarkers of Doping

Athletes who abuse doping substances do so to trigger physiological changes that provide physiological enhancements. Therefore, in the same way that disease-related biomarkers are invaluable tools that assist physicians in the diagnosis of pathology, doping can be detected from specifically selected biomarkers. Generally, the effect of the drug remains detectable in the body much longer than the substance itself, which can be quickly excreted and therefore go undetected by toxicology testing.

The use of biomarkers of doping is not new. For example, the testosterone/epitestosterone concentration ratio (T/E) was introduced by several sports organizations in the 1970s to deter the administration of anabolic steroids. Because epitestosterone is only a minor product of testosterone metabolism and does not increase after exogenous testosterone administration, the net effect of the latter is an in-

crease in T/E *(4)*. In 1983, a T/E in excess of 6.0 was considered indicative of steroid doping by the International Olympic Committee. The introduction of this rule was mitigated, however, by the discovery a few years later that some individuals may have naturally increased T/E *(5)*, a phenomenon that has recently been attributed to the discovery of genetic polymorphisms that are associated with the metabolism of anabolic steroids *(6)*. Currently, in addition to the T/E, a urinary steroid profile that includes multiple testosterone metabolites and precursors is used to detect steroid doping (Fig. 3), in addition to doping with other anabolic agents, such as designer steroids, gonadotropins, estrogen antagonists, aromatase inhibitors, androgen precursors, and selective androgen receptor modulators *(7, 8)*.

The development and validation of blood-doping biomarkers have also greatly evolved since the introduction of hematological variables by some international sports federations in the mid-1990s. With the advent of automated blood analyzers, blood variables can be quantitatively measured to yield a complete hemogram, either in an accredited laboratory or directly at the location of the competition, in less than a minute after blood collection *(9)*. Several approaches have contributed in recent years to make the use of biomarkers of altered erythropoiesis an efficient approach to deterring any form of blood doping in sports: (*a*) the introduction of multiparametric blood-doping markers *(10, 11)*; (*b*) the inclusion of heterogeneous factors, such as sex and age, as recommended by the WHO in the diagnosis of anemia *(12)*, as well as other factors specific to sports *(13, 14)*; (*c*) the add-on of potentially confounding factors, such as the athlete's exposure to altitude *(15)*; (*d*) the record of the athlete's own previous measurements *(16–18)*, with the underlying concept being the use the athlete as his or her own reference *(19–21)*; (*e*) the adoption of standardized protocols for sample collection and analysis, in addition to the extensive use of external QC systems to control analytical uncertainty *(22)*; and (*f*) the development and validation of probabilistic inference techniques to evaluate the value of doping evidence *(17, 18)*.

The Athlete Biological Passport

All of the knowledge that has been acquired in recent decades concerning doping biomarkers has been formalized in the ABP program. The term passport was first proposed in the early 2000s when the preservation and tracking of a longitudinal record of hematological variable measurements were planned to be used as a means to define an individual's hematological profile *(19)*. Large disparities between an athlete's historical values and the values obtained in a recent test indicate that either doping has taken place or that the athlete has a potential medical condition that requires closer examination *(20)*. The concept of the ABP has been discussed and then further elaborated for antidoping application by the World Anti Doping Agency (WADA) beginning in 2002. Since the 2006 Torino Winter Olympic Games, several international sports federations have agreed that the WADA should harmonize the development and validation of the ABP program. As a result, in 2009, the WADA published the Athlete Biological Passport Operating Guidelines *(23)*, which can be used as a reference for any antidoping organizations that are interested in developing a concordant biological monitoring program.

Three distinct modules can be distinguished in the ABP: the hematological, steroidal, and endocrinological modules. The hematological module of the ABP aims to detect any form of blood doping *(22)*. As part of a full blood count, 8 hematological variables are considered today in this module. In 2008, the Union Cycliste Internationale was the first sports organization to implement the hematological module of the ABP to deter blood doping in elite cycling (Fig. 1), and subsequently, several riders have been prosecuted and sanctioned on the sole basis of their abnormal hematological profiles. Currently, hematological tracing is performed by several antidoping organizations for several thousand athletes worldwide. The steroidal module of the ABP, which aims to detect direct and indirect forms of doping with anabolic agents *(7)*, is presently being finalized for implementation in the near future. The endocrinological module of the ABP aims to detect doping with growth factors, such as growth hormone and insulin growth factor-1. Despite abundant scientific publications on growth hormone–dependent markers *(24)*, the implementation of the endocrinological module in the ABP in the network of WADA-accredited laboratories requires further validation to fulfill forensic standards.

Biological fluids, such as blood and urine, contain a treasure trove of potential doping markers that can be discovered by today's omics techniques, such as proteomics and metabolomics. The usefulness of this gold mine for diagnostic purposes has been recognized *(25)*, and the same is true for doping biomarkers. By definition, any deviation in a biomarker from what is expected in a healthy physiological condition according to well-defined protocols can be attributable only to doping or a medical condition. Interestingly, these 2 possible causes are the exact targets of any antidoping program; hence, the criteria that are used to introduce new biomarkers into the ABP are the same as those that are used to define a banned substance, more specifi-

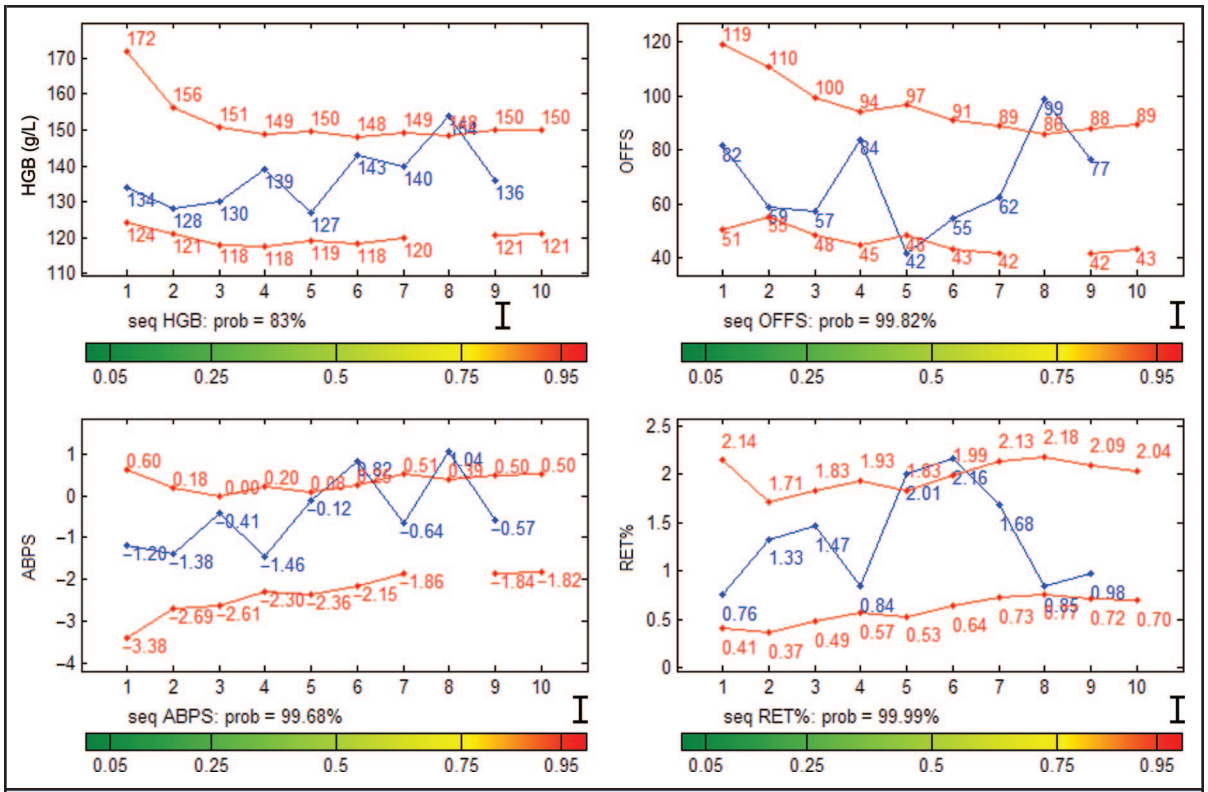

Fig. 1. Hematological passport of an elite rider tested on 9 occasions for 4 markers of blood doping: HGB, the stimulation index OFF-score (OFFS), the Abnormal Blood Profile Score (ABPS), and the percentage of reticulocytes (RET%).

Blue lines represent actual test results. Red lines indicate limits at which the test result is considered abnormal. Initial limits (e.g., 124–172 g/L for HGB) are based on population epidemiology and are adapted in the course of individual data acquisition to produce individual final limits (121–150 g/L for HGB). Color bars indicate sequence (seq) abnormality [Sottas et al. *(22)*]; prob, probability. The numerous abnormalities suggest that it is very unlikely that such a blood profile would not be obtained under normal physiological conditions. The rider was subsequently convicted of doping with the variant of rEPO known as CERA (continuous erythropoiesis receptor activator). How to calculate OFF-score and ABPS can be found in Gore et al. *(10)* and Sottas et al. *(11)*, respectively.

cally, the criteria of performance and health. In addition, an eligibility rule becomes a logical consequence of this assumption, wherein athletes present their passports at the beginning of a competition and individuals are allowed to participate only if their passport indicates that they are in a healthy and unaltered physiological condition. Therefore, in addition to proving a doping offense under the World Anti-Doping Code, the ABP can be a platform for a Rule of Sport enforced by the sport authorities to prevent athletes from manipulating their physiology to an extent that would significantly impact their performance and health. We foresee the implementation of a Rule of Sport in which the athletes who have demonstrated unnatural deviations in physiology would be temporarily withdrawn from competition to allow a period for return to normal physiological levels or initiation of appropriate medical controls or treatments. This short period of debarment could also be used by a panel of experts to determine the cause of the abnormality and may lead to sanctioning the athlete for a longer period if doping is the cause.

Although the ABP had the initial exclusive intent of biological monitoring, today, the ABP contains more than a simple series of individual biomarker values. Heterogeneous factors, such as age, sex, and genotype; confounding factors, such as exposure to higher altitudes for the hematological module; and some information regarding the conditions of sample collection, transport, and analysis are also stored in the passport for improved decision making *(7, 22)*. As such, the ABP becomes a platform for the evaluation of multiple pieces of scientific evidence *(15)*, which is similar to a forensic approach.

Toward a Global Forensic Antidoping Policy

Similarly to forensic identification science *(26)*, the strength of the ABP is that it relies on sound empirical testing in large populations by use of justifiable protocols. The decision support system that is used routinely to interpret the biomarker data stored in an ABP heavily relies on Bayesian inference techniques *(7, 11, 14–15, 17–18, 22)* (Fig. 2). Every element of information that constitutes doping evidence can be incorporated into other elements and/or corroborated by additional evidence. For example, the result of traditional drug tests, such as the detection of rEPO in urine *(27)*; some characteristics of athletes, such as a particular genotype *(28)*; and the longitudinal monitoring of individual performance *(29)* are evidentiary values that can be incorporated into the ABP decision support system for improved detection of doping.

The ABP introduces a new form of doping evidence and, as such, paves the way for a more global and integrated fight against doping. In particular, we foresee a global forensic approach in which multiple pieces of evidence, not restricted to those in the current testing paradigm, are used to demonstrate the culpability of a suspect. For example, the drug enforcement agencies and customs departments of many countries seize large quantities of doping substances with investigations that target illicit drugs, manufacturing companies, and trafficking networks. Until recently, the lack of collaboration between governmental, public, and sports authorities has hindered the combination of analytical and nonanalytical evidence in many countries. In the current fight against doping, a customs agency can learn that a top-level athlete has received some rEPO by mail before an important competition, but this information is not shared with sports authorities, so that the athlete is still permitted to participate in that competition. Interestingly, the methodology developed for the ABP provides the necessary framework to combine evidence gathered by sports-testing organizations with nonanalytical evidence gathered by public law enforcement agencies. For example, knowledge that an athlete received some rEPO by mail can be combined with the information stored in the ABP to evaluate whether the athlete used that substance before competition. As such, we do not foresee any scientific limitation for a global fight against doping that is based on various sources of evidence.

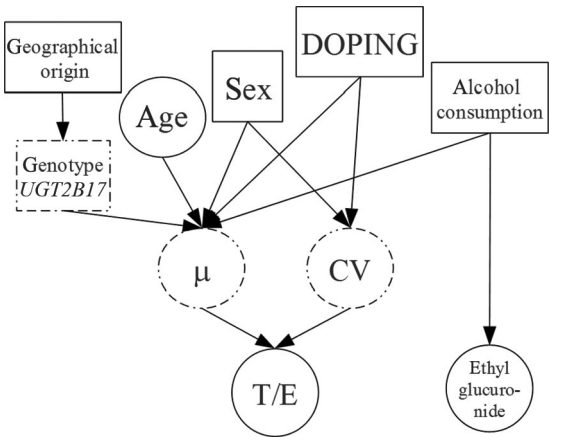

Fig. 2. Hierarchical graphical Bayesian network (BN) [Taroni et al. *(32)*] for the evaluation of the T/E marker of steroid doping [Sottas et al. *(7)*].

The T/E is the ratio of the urinary concentrations of testosterone glucuronide and epitestosterone glucuronide. Each node represents a variable (circle, continuous; rectangle, discrete; solid, observable; dashed, nonobservable). Arcs represent direct relevance relationships between variables, with a conditional probability table associated to each variable. In the BN, probabilities of the states of the variables are updated upon the receipt of new evidence. The hidden variables mean (μ) and CV adaptively integrate information coming from a series of individual T/E values. The heterogeneous factors age and sex are set up to take into account differences in steroid excretion; for example, that females have lower and more variable urinary T concentrations than males. Significant interindividual differences observed in T excretion are associated with a deletion mutation in the UDP glucuronosyltransferase 2 family, polypeptide B17 (*UGT2B17*) gene [Schulze et al. *(6)*]. The introduction of genetic variations in the BN make athletes missing both copies of the gene, a common trait in Asians, equal to those having 1 or 2 copies, a common trait in whites and Africans. Interestingly, the knowledge of the individual's genotype is unnecessary. Only the characterization of the phenotype is necessary, because the genotype can be inferred from the phenotype T/E and from the unusually high degree of geographic variation in the *UGT2B17* gene [Xue et al. *(33)*]. There is no conceptual limitation for the application of such BNs for the evaluation of any biological marker. The incorporation of heterogeneous factors, gene profiles, and longitudinal data allows the elimination of interindividual differences so that the decision can be tailored to the attributes of a single individual.

Perspectives in Medical and Pharmaceutical Applications

Recent medical practice has relied on standards of care that are based on epidemiologic studies of large cohorts. In particular, the interpretation of biomarkers has mostly relied on the use of population-based reference intervals and has largely ignored individual differences. This situation is particularly problematic because most biomarkers present significantly higher

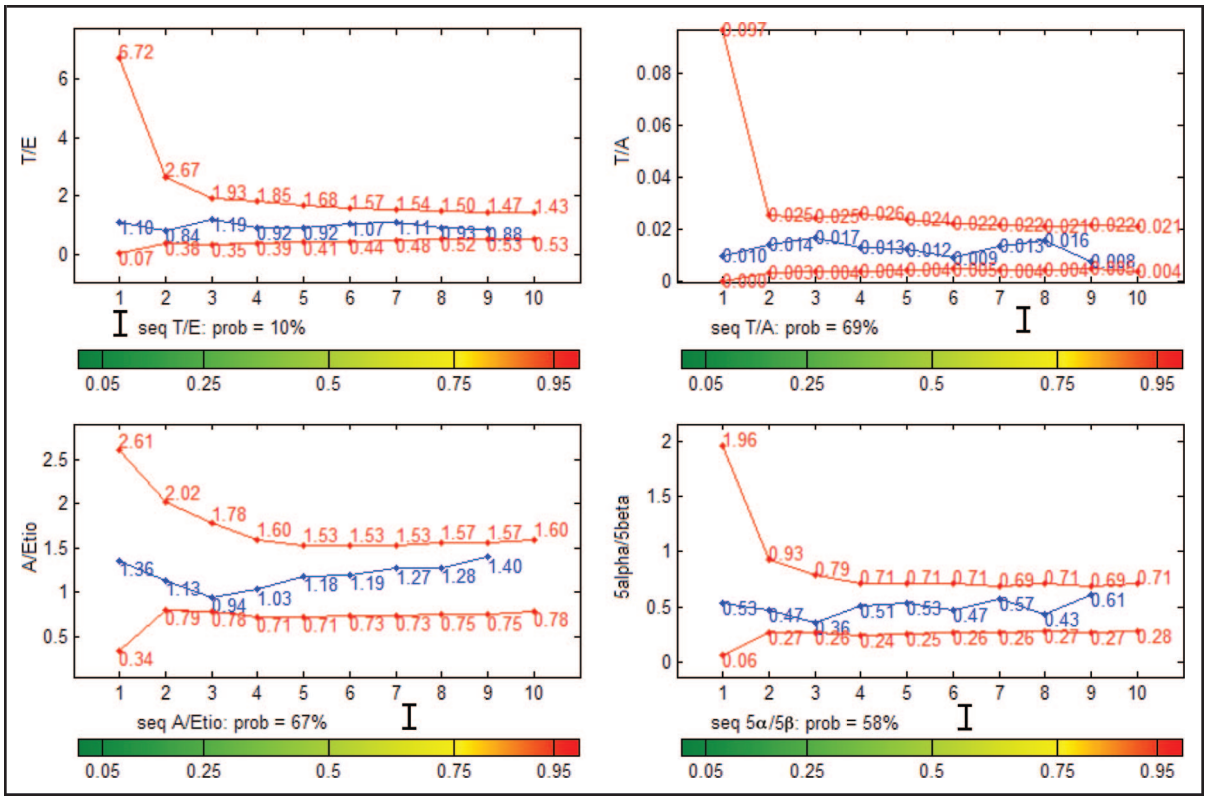

Fig. 3. Steroidal passport of a white male athlete tested on 9 occasions, for 4 markers of steroid doping: T/E, the ratio of testosterone to androsterone (T/A), the ratio of androsterone to etiocholanolone (A/Etio), and the ratio of 5-α-androstane-3-α,17-β-diol to 5-β-androstane-3-α,17-β-diol (5α/5β).

Blue lines represent actual test results. Red lines indicate individual limits. Color bars indicate sequence (seq) abnormality [Sottas et al *(22)*]; prob, probability. The lack of any abnormality indicates that such steroid profile is typical of a normal physiological condition.

inter- than intraindividual variations. In practice, physicians evaluating an individual patient generally take into account heterogeneity macrofactors, such as age and sex. In addition, contemporary advances in omics technologies have permitted information concerning a patient's protein, gene, or metabolite profile to be increasingly used to improve healthcare. A longitudinal record of such profiles is an invaluable tool that can assist physicians in their work, such as in oncology, wherein early diagnosis is critical to patient outcome. The incorporation of heterogeneous factors, use of individual protein or gene profiles, and use of a longitudinal approach have the same goal, which is to eliminate interindividual differences and tailor medical care to an individual's needs. To achieve the goal of personalized medicine, any advances in proteomics and other related fields must be captured by decision support systems to facilitate their use in the clinic *(30)*.

Several pharmaceutical companies have contacted us to evaluate how the knowledge acquired for the ABP in the evaluation of biomarker data can be used in some applications of personalized medicine for improving healthcare. This evaluation was performed for several practical applications in patient monitoring and the assessment of drug safety and efficacy in clinical trials. In patient monitoring, the actual frequency and doses of a treatment are tailored according to a patient's individualized need for medical care, which is often evaluated from biomarker data. For example, the measurement of glycohemoglobin, which is a marker of the degree of glucose metabolism control, is crucial in making treatment decisions in patients with type 1 diabetes. In a second example, cytostatic chemotherapy doses are determined according to various biomarkers and other patient-related factors, such as body surface area. In all of these cases, the decision is complicated by various factors, including: variations in laboratory test results; information that accrues throughout treatment; heterogeneity in factors, such as age, gender, and body size; narrow target ranges that must be refined for

every individual in terms of safety and quality of life; and biological variations among individuals. Similar issues occur in clinical trials, wherein the safety and efficacy of a drug treatment are often evaluated by using longitudinal biomarker data. Adaptive Bayesian clinical trials have been proposed to adapt to information that accrues during a clinical trial *(31)*. Interestingly, the support system developed for the ABP puts all of these concepts into practice and will find a direct application in patient monitoring. In retrospective data provided by pharmaceutical companies, we have found that the knowledge of sources of variations (analytical and biological) is not often taken into account, and the development of an ABP-inspired decision support system improves the decision in all of the aforementioned applications. In clinical trials, we have found that either the number of patients or the sample size to fulfill the requirements of the trial could have been significantly decreased, or that the trial could have been stopped substantially earlier. In both cases, the application of the ABP decision support system could have improved the cost-effectiveness of drug development, resulted in an earlier decision, and helped patients to receive better treatment.

Conclusions

Although drug tests have been remarkably successful in the detection of synthetic doping substances, the recent availability of doping substances identical to those naturally produced by the human body demonstrates the limits of this testing paradigm to ensure fairness and health protection in elite sports. In that context, the ABP represents the new paradigm in detection of doping-triggered physiological changes in elite sports. Doping biomarkers provide a means to deter the athlete from using performance-enhancing drugs that will lead to deviation from natural baseline values. In contrast to a drug test that returns a result for a precise moment in time and does not have any memory or perspective, the presentation at the beginning of competitions of an ABP that demonstrates normal longitudinal profiles will allow athletes to objectively demonstrate that they will participate in an unaltered physiological condition clear of any doping suspicion. Scientists are developing methods that provide an unequalled opportunity to ensure fairness and the protection of health in elite sports; worldwide ABP implementation is now at the discretion of antidoping organizations. The same paradigm can be used in the clinics so that personalized medicine will not only be centered on the deeper molecular makeup of each patient, but also on an interpretation of existing biomarkers tailored to each individual.

Author Contributions: *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.*

Authors' Disclosures or Potential Conflicts of Interest: *No authors declared any potential conflicts of interest.*

References

1. WADA. World anti-doping code 2009. www.wada-ama.org/rtecontent/document/code_v2009_En.pdf (Accessed May 2011).
2. Thevis M, Schänzer W. Mass spectrometry in sports drug testing: structure characterization and analytical assays. Mass Spectrom Rev 2010; 26:79–107.
3. Macdougall IC, Ashenden M. Current and upcoming erythropoiesis-stimulating agents, iron products, and other novel anemia medications. Adv Chronic Kidney Dis 2009;16:117–30.
4. Donike M, Bärwald KR, Klostermann K, Schanzer W, Zimmermann J. Nachweis von exogenem Testosterone. In: Heck H, Hollmann W, Liesen H, Rost R, eds. Sport: Leistung und Gesundheit. Cologne: Deutcher Artze-Verlag; 1983. p 293–8.
5. Oftebro H. Evaluating an abnormal urinary steroid profile. Lancet 1992;339:941–2.
6. Schulze JJ, Rane A, Ekström L. Genetic variation in androgen disposition: implications in clinical medicine including testosterone abuse. Expert Opin Drug Metab Toxicol 2009;5:731–44.
7. Sottas PE, Saugy M, Saudan C. Endogenous steroid profiling in the Athlete Biological Passport. Endocrinol Metab Clin North Am 2010;39:59–73.
8. Handelsman DJ. Indirect androgen doping by oestrogen blockade in sports. Br J Pharmacol 2008; 154:598–605.
9. Robinson N, Schattenberg L, Zorzoli M, Mangin P, Saugy M. Haematological analysis conducted at the departure of the Tour de France 2001. Int J Sports Med 2005;26:200–7.
10. Gore CJ, Parisotto R, Ashenden MJ, Stray-Gundersen J, Sharpe K, Hopkins W, et al. Second-generation blood tests to detect erythropoietin abuse by athletes. Haematologica 2003;88:333–44.
11. Sottas PE, Robinson N, Giraud S, Taroni F, Kamber M, Mangin P, Saugy M. Statistical classification of abnormal blood profiles in athletes Int J Biostatistics 2006;2:3.
12. WHO. Iron deficiency anemia: assessment, prevention and control: a guide for programme managers. Geneva: WHO; 2001. 114 p. Not formally published by WHO.
13. Sharpe K, Hopkins W, Emslie KR, Howe C, Trout GJ, Kazlauskas R,. et al. Development of reference ranges in elite athletes for markers of altered erythropoiesis. Haematologica 2002;87: 1248–57.
14. Robinson N, Sottas PE, Mangin P, Saugy M. Bayesian detection of abnormal hematological values to introduce a no-start rule for heterogeneous populations of athletes. Haematologica 2007;92:1143–4.
15. Sottas PE, Robinson N, Niggli O, Saugy M. A forensic approach to the interpretation of blood doping markers. Law Prob Risk 2008;7:191–210.
16. Sharpe K, Ashenden M, Schumacher YO. A third generation approach to detect erythropoietin abuse in athletes. Haematologica 2006;91: 356–63.
17. Sottas PE, Baume N, Saudan C, Schweizer C, Kamber M, Saugy M. Bayesian detection of abnormal values in longitudinal biomarkers with an application to T/E ratio. Biostatistics 2007;2:285–96.
18. Sottas PE, Saudan C, Schweizer C, Baume N, Mangin P, Saugy M. From population- to subject-based limits of T/E ratio to detect testosterone abuse in elite sports. For Sci Int 2008;174:166–72.
19. Cazzola M. A global strategy for prevention and detection of blood doping with erythropoietin and related drugs. Haematologica 2000;85: 561–3.
20. Ashenden M. A strategy to deter blood doping in sport. Haematologica 2002;87:225–32.

21. Malcovati L, Pascutto C, Cazzola M. Hematologic passport for athletes competing in endurance sports: a feasibility study. Haematologica 2003; 88:570–81.
22. Sottas PE, Robinson N, Saugy M. The athlete's biological passport and indirect markers of blood doping. Handb Exp Pharmacol 2010;195:305–26.
23. WADA. Athlete Biological Passport operating guidelines and compilation of required elements. Montreal: WADA; 2009.
24. Holt RI, Sönksen PH. Growth hormone, IGF-I and insulin and their abuse in sport. Br J Pharmacol 2008;154:542–56.
25. Liotta LA, Ferrari M, Petricoin E. Clinical proteomics: written in blood. Nature 2003;425: 905.
26. Saks MJ, Koehler JJ. The coming paradigm shift in forensic identification science. Science (Wash DC) 2005;309:892–5.
27. Lamon S, Boccard J, Sottas PE, Glatz N, Wuerzner G, Robinson N, Saugy M. IEF pattern classification-derived criteria for the identification of epoetin-delta in urine. Electrophoresis 2010; 31:1918–24.
28. Schulze JJ, Lundmark J, Garle M, Ekström L, Sottas PE, Rane A. Substantial advantage of a combined Bayesian and genotyping approach in testosterone doping tests. Steroids 2009;74: 365–8.
29. Schumacher YO, Pottgiesser T. Performance profiling: a role for sport science in the fight against doping? Int J Sports Physiol Perform 2009;4:129–33.
30. Cantor MN. Enabling personalized medicine through the use of healthcare information technology. Personalized Medicine 2009;6:589–94.
31. Berry DA. Bayesian clinical trials. Nat Rev Drug Discov 2006;5:27–36.
32. Taroni F, Aitken C, Garbolino P, Biedermann A. Bayesian Networks and Probabilistic Inference in Forensic Science. Chichester: Wiley; 2006. 372 p.
33. Xue Y, Sun D, Daly A, Yang F, Zhou X, Zhao M, et al. Adaptive evolution of UGT2B17 copy-number variation. Am J Hum Genet 2008;83: 337–46.