Athletes dope to trigger physiological changes that provide advantages in competition. Doping leaves a biological fingerprint in the athlete’s body. The Athlete Biological Passport (ABP) is the paradigm in testing that aims to detect this biological fingerprint (1, 2). Biomarkers of doping measured or inferred from blood and urine samples are used for that purpose, in the same way that biomarkers of disease are used in medicine as indicators of the presence or severity of a disease. Although both types of biomarkers aim to distinguish a biological fingerprint induced by a specific cause from the usual biological profile expected for a natural physiological condition, biomarkers of doping are collated and evaluated according to standards specific to forensic sciences. Several aspects of the ABP have been developed and validated in recent years. They include strict protocols for the collection, transport, and analysis of samples; a scrupulous chain of custody; an adaptive Bayesian method to evaluate longitudinal biological profiles; and application of forensic standards for the evaluation of doping evidence—with the anonymity of the athlete guaranteed at all steps of the process. The blood passport aims to detect any modification of erythropoiesis, whether by blood transfusion or the use of erythropoiesis-stimulating agents, such as recombinant erythropoietin (rEPO) (1, 3).

The ABP can be used for intelligence, for sanctioning, for health protection, and, in turn, for deterrence. It can be used for intelligence because antidoping organizations (ADOs) can use data from the passport to define suspicious biological profiles and identify athletes who have them. It can be used for sanctioning because the weight of ABP evidence can be sufficiently high in some cases to prove beyond reasonable doubt that an athlete doped. The ABP can be used for health protection because it provides a direct view of the impact of doping on the athlete’s physiology. Finally, it can be used for deterrence because doping leaves a biological fingerprint, so athletes are no longer able to dope with impunity.

In 1996, some sports federations discouraged rEPO doping by introducing upper limits for precompetition hematocrit and hemoglobin measurements. At the time, these analyses were conducted immediately on the field after blood collection, and athletes who tested above these limits were declared unfit for competition. This “no-start rule” was considered a competition rule and not an antidoping rule violation. Each federation had its own internal preanalytical and analytical protocols. The antidoping laboratories conducting these analyses for the federations acquired considerable experience. This experience indicated that most of the preanalytical and analytical conditions set up in hospitals and clinics were not sufficiently exacting to meet the forensic standards required for antidoping analysis. The expertise gained over time by the antidoping community led to the establishment of rigorous protocols. These protocols were submitted over a 2-year period to many experts in the field of laboratory hematology and were officially released by the World Anti-Doping Agency (WADA) in 2009 (4). For the protection of athletes, the criteria are conservative, and the acceptance criteria for blood analyses at the laboratory level are extremely selective. For that reason, 5%–8% of the samples were rejected in the first year the blood passport was implemented, (analytical turnaround time too long, incorrect transport temperature conditions, incomplete documentation, blood samples analyzed only once, and so forth). Currently, many fewer samples are rejected, because all stakeholders have become more experienced, and good couriers have been identified who are capable of delivering refrigerated blood samples collected all over the world within 36 hours.

The blood passport was developed with data derived from many clinical trials and has been validated by scientific publications. Standard cross-validation methods were performed to determine the sensitivity and specificity of the adaptive Bayesian model (3, 5, 6). In 2006, the most discriminating and stable variables were selected. The need for a network of laboratories

### References

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5. Nonstandard abbreviations: ABP, Athlete Biological Passport; rEPO, recombinant erythropoietin; ADO, antidoping organization; WADA, World Anti-Doping Agency; ADAMS, Anti-Doping Administrative Management System.
that could provide services 7 days a week, 24 hours a day soon became obvious. The network of WADA-accredited laboratories was the most suitable solution, although substantial personnel training was necessary to achieve the quality required for the blood passport.

Implementation of the blood passport process is complex, owing to the high number of stakeholders and individuals involved. First, ADOs make the decision of “who, when, what” to test from the available information. Athletes store their whereabouts in WADA’s Anti-Doping Administrative Management System (ADAMS), and ADOs often engage specific companies to collect blood samples. Doping-control officers are responsible for ensuring that preanalytical and sample chain-of-custody guidelines are followed, and blood-control officers are responsible for the phlebotomy. International couriers transport fresh blood samples to the network of laboratories accredited by the International Standards Association and WADA to conduct blood analyses. An independent Athlete Passport Management Unit is responsible for managing the passports from biological data stored on ADAMS and advising the ADOs regarding which athletes have suspicious profiles. A panel of international experts must then review the passports to determine whether abnormal or suspicious passport profiles are the result of a medical condition or doping. When all criteria of an Adverse Passport Finding are fulfilled, the Results Management Authority of the ADO proceeds to a disciplinary hearing, which then initiates the involvement of members of the legal system.

Before the official implementation of the ABP, a retrospective analysis of blood profiles belonging to athletes convicted of blood doping was conducted to demonstrate the efficacy of this approach (7). The ABP enables ADOs to request the right tests at the right time, with a focus on atypical profiles. For example, at the time Roche launched Mircera in 2008, the few athletes who were abusing this new rEPO were immediately identified by the blood passport. The passport was used to augment a traditional analytical antidoping method, albeit with the aid of a new test. In this case, Roche and antidoping authorities together had developed and validated a direct method to detect Mircera in blood. The official WADA statistics also show that the number of rEPO-positive findings increased substantially for those ADOs that implemented the passport program.

Antidoping is a forensic science. Therefore, the burden of proof is on the testing authority, and the risk of false-positive findings must be kept strictly at a minimum. In the ABP, the evaluation of doping evidence follows the logic used in other forensic fields when multiple hypotheses are present. An important feature of the ABP is the presence of potentially confounding factors, such as exposure to altitude and medical conditions. In the presence of one piece of evidence (the passport) and several potential causes (e.g., normal physiological condition with or without exposure to altitude, medical condition, doping), it is important to evaluate all cause-and-effect relationships and the likelihood that each of these potential causes produced the observed passport profile. The adaptive Bayesian model (3, 6, 8) is used to evaluate the likelihood of a given passport profile when assuming a natural physiological condition. The use of this statistical tool is motivated by the excellent scientific knowledge of the expected variations in biomarkers of doping. The adaptive Bayesian model, which was initially built to evaluate biomarkers of doping, also is currently applied by pharmaceutical companies for individualized monitoring of treatments, as well as for evaluating the safety and efficacy of drugs in clinical trials. Owing to the high numbers of tests performed in an antidoping program, multiple testing can be an issue: A high number of tests in a population in which the prevalence of doping is not precisely known may increase the likelihood of finding a match purely by chance. In the absence of adequate precautions, it is erroneous to automatically conclude that an abnormal passport profile is the result of doping; it is also necessary to evaluate how probable a given passport profile would be under the assumption of a doping scenario. Expert evidence is used for the latter.

During the initial implementation of the ABP, several departures from the protocols were expected, because the ABP was a new paradigm that involved many stakeholders, each of which was responsible only in its fields of competence. Although such departures from the protocols can eventually invalidate the corresponding blood results, they certainly do not invalidate the ABP program as a whole. Today, the main limitations of the ABP are not the paradigm per se or its value as an antidoping tool, but rather the sensitivity of the biomarkers of doping. Nowadays, blood markers of doping, such as the hemoglobin concentration and the stimulation index (OFF score), can detect doping with low (20 IU/kg) rEPO doses (but not microdoses), as well as autologous transfusion of 1 or 2 blood bags (but not less) (7, 9). Further investment will be necessary to identify new biomarkers and to improve those currently implemented in the passport. The ABP program is still a young paradigm with enormous potential for improvement. The constant development of new pharmaceuticals with molecules that are identical to endogenous ones and the availability of designer rEPOS that are undetectable by drug tests require new strategies. The ABP is becoming an integral element of the new global fight against doping that includes not only testing but also nonanalytical evidence coming from intelligence agencies. In conclusion, the ABP, an important
tool in the fight against doping, has already shown considerable value in recent years and carries important potential for the future.

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