Expert evaluation of biological data is a key component of the Athlete Biological Passport approach in the fight against doping. The evaluation consists of a longitudinal assessment of biological variables to determine the probability of the data being physiological on the basis of the athlete’s own previous values (performed by an automated software system using a Bayesian model) and a subjective evaluation of the results in view of possible causes (performed by experts). The role of the expert is therefore a key component in the process. Experts should be qualified to evaluate the data regarding possible explanations related to the influence of doping products and methods, analytical issues, and the influence of exercise or pathological conditions. The evaluation provides a scientific basis for the decision taken by a disciplinary panel. This evaluation should therefore encompass and balance all possible causes for a given blood profile and provide a likelihood for potential scenarios (pathology, normal variation, doping) that might have caused the pattern. It should comply with the standards for the evaluation of scientific evidence in forensics.

On the basis of their evaluation of profiles, experts might provide assistance in planning appropriate target testing schemes.

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If the law has made you a witness, remain a man of science—sine ira et studio.

—(A composite quotation from P.C.H. Brouardel and Tacitus)

For many years, expert witnesses have been important contributors to the legal battle following most doping cases. With conventional doping analysis, in which a prohibited substance is detected in a matrix obtained from an athlete, the role of the expert was mostly limited to defending the analytical technique that had led to the adverse analytical finding (prosecution) or in demonstrating that the analysis was flawed or other circumstances had occurred that resulted in the wrongly positive finding (defense). The primary result that led to the opening of the disciplinary procedure (the presence of the forbidden substance in the sample) was an a priori fact independent from the involvement of the expert in the case. With the emergence of the hematological module of the Athlete Biological Passport and the indirect detection of blood doping (1–6), this framework has changed: Unlike a conventional doping test sample that either contains a forbidden substance or not, a raw profile of biological markers does not offer clear-cut information on the use of a prohibited substance or method a priori, because such evidence does not detect the substance itself, but only its effects.

Any assessment of potential doping based upon such evidence is to be provided by experts, which makes their role crucial for the case. The role and the approach of the scientific expert evaluating data for the biological passport is therefore comparable to a forensic scientist who evaluates different pieces of evidence and provides opinions on possible crime scenarios in any criminal case. These opinions form the basis of the decision to be made by the legal panel. For this reason, the same standards that have been established for evaluating scientific evidence in forensics should ideally be applied to expertise in the context of the indirect detection of doping. Forensic reasoning has, however, not yet fully penetrated the realm of antidoping, and for most medical experts involved in doping cases, it is still difficult to assess. Therefore in this report we do not delve deeper into the topic of forensic reasoning. The aim of the present work is rather to describe the experience and challenges encountered by nonforensic medical experts during the first legal cases based on data from the Athlete Biological Passport.

Scientific Evidence in Forensics: Application to the Passport

A body of literature is available that describes the standards by which scientific expertise should be presented...
in a forensic context (7–9). Even for nonforensic experts, these standards are applicable in slightly modified form for expertise in connection with the Athlete Biological Passport and already partly incorporated in the general Athlete Biological Passport procedures (10).

In making an evaluation, the expert should respect 4 principles, which have been defined by the Association of Forensic Service Providers:

- **Balance:** All possible explanations for the evidence should be carefully evaluated.
- **Logic:** It is important to highlight the direction of the assessment of evidence.
- **Robustness:** The opinion provided by the expert should be based on scientific grounds and findings from peer reviewed scientific publications to withstand scrutiny by other experts or aggressive lawyers in cross-examination.
- **Transparency:** The expert should be able to reproduce at any time how he came to his conclusion.

With his expertise, the expert therefore does not provide a decision regarding the case, but rather the scientific ground for the panel to base its decision upon.

For all aspects regarding forensic reasoning, presentation of evidence, and balance of probabilities, we direct the reader to the dedicated literature on this topic, because this matter is beyond the scope of the present article.

**Qualifications of the Expert**

A court might ask for assistance through experts if its own knowledge on specific questions regarding a case is lacking or insufficient. By definition, an expert is a “Person who through education or experience has developed skill or knowledge in a particular subject so that he or she may form an opinion that will assist the fact finder” (11). For the hematological module of the Athlete Biological Passport, this “particular subject” is a vast area that might be called “sports hematology,” comprising physiological, hematological, chronobiological, and many other aspects of the hematological system of an athlete. In fact, the hematological system of an athlete is subject not only to the normal variability visible in the blood readings of a healthy individual, but also to potential changes induced by exercise and unusual environmental conditions such as temperature extremes or the hypoxia of altitude. It could also be affected by the presence of a congenital abnormality or by development of an acquired disease, such as loss of blood from some underlying pathological process, any kind of infection, or the deficiency of iron or vitamins. To suit this complexity, data from the Athlete Biological Passport should be evaluated by a panel of experts from different backgrounds. Ideally, qualified exercise physiologists, hematologists, clinicians, and laboratory experts are part of the expert group. It is important that members of the expert group be familiar with the typical hematological features of blood doping.

Given the complexity of the passport approach and the variety of the challenges in court, the role of the scientific expert is crucial for the outcome of the case, because the legal panel, which usually comprises non-scientists, will base their ruling on the expertise presented by the prosecution and the defense. Unlike normal criminal cases involving professional forensic experts, most scientific experts involved in biological passport cases had to develop in the field a de novo skill to approach the task of testifying. On the basis of the experience that experts have gained in these first years in panel discussions, cooperation with lawyers, and participation in court trials, this issue should be addressed in the near future by teaching seminars for new experts or recommendations issued by the governing bodies that specify expert qualifications.

**The Evaluation Process**

Four years ago, the International Cycling Union in cooperation with the World Anti-Doping Agency (WADA)3 established a routine evaluation system for blood profiles from the Athlete Biological Passport (10, 12). In brief, the Passport is based on a hematologic profile that comprises the results of repeated, random, or targeted blood tests. These tests can be announced or unannounced, in competition or out of competition. The parameters that are taken into consideration for the passport approach are blood hemoglobin concentration, which provides a rough estimate of the capacity of the blood to transport oxygen to tissues, and reticulocyte percentage, which is a quantitative marker of the recent red cell production in the bone marrow. The so-called OFF score is obtained by a formula that correlates these 2 parameters to measure their variation in the same or opposite directions (13). Furthermore, other corroborating variables such as red cell indices are analyzed in each sample. These additional variables might provide information on the presence or absence of pathologies or analytical inaccuracies. After each new test, a new range of expected results for the athlete is determined.

The assessment of the passport data has the main goals of differentiating between normal and

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3 Nonstandard abbreviations: WADA, World Anti-Doping Agency; APMU, Athlete Passport Management Units.
abnormal profiles and assessing the possible causes for abnormalities. The process has 2 aspects, a quantitative evaluation and a qualitative assessment. The latter is aimed at investigating the results of the quantitative assessment in the perspective of doping. The term “quantitative” signifies that the data of the athlete are compared empirically to a large reference group. This quantitative assessment is performed by use of an automated software system that provides a probability for each profile to be normal, i.e., to be found in a healthy, undoped population of athletes (the reference group).

If a profile is flagged by the software, it enters the qualitative assessment, where the focus is on evaluating its abnormality and the potential causes. Once the expert review has excluded preanalytical and analytical errors, potential explanations/hypotheses for an abnormal profile are: (a) the profile displays an extreme of normal variation; (b) the profile points to a potential pathology; (c) the profile is indicative of doping.

The expert should carefully assess all aspects of these explanations and provide an evaluation toward their respective likelihood in view of the profile and the potential explanations. It must be highlighted that the likelihood (or unlikelihood) of one explanation does not affect the likelihood of the other ones. For example, if a pathology appears unlikely from the data, it does not imply that doping (as an alternative explanation) becomes automatically more likely (fallacy of the transposed conditional) (8)

If, at this stage, a limited and predefined number of experts independently state that it is typical to have the blood values found in the profile assuming a doping intervention, the evaluation process enters the next level, at which the profile is discussed with a larger panel of experts and additional information such as the athlete’s whereabouts and competition schedules are scrutinized in connection with the profile. At this stage, the identity of the athlete is still not known to the experts, because all information is anonymized. If all experts of the panel come to the same conclusion, the athlete is contacted by the antidoping organization and asked for explanations for his/her abnormal values. After (s)he has provided explanations, these are forwarded to a designated number of experts of the group, who, again, evaluate the explanations of the athlete. If they consider the explanations of the athlete insufficient to explain the values of his/her profile, the case moves forward and an antidoping rule violation procedure might be opened against the athlete. The evaluation process is illustrated in Figure 1.

**Key Issues in the Evaluation**

**PREANALYTICAL AND ANALYTICAL CONSIDERATIONS**

The first step of the evaluation process of a sample flagged by the adaptive model is careful scrutiny of the analytical and perianalytical aspects of the profile. From a formal point of view, all samples that are included in an Athlete Biological Passport profile have been analyzed by accredited laboratories, which are submitted to a strict internal and external QC system. The technical documents for blood collection, transport, and analysis were written and implemented in 2007, and an independent external QC system was established for all laboratories participating in passport analysis since this time. From 2010 onwards, the standards have been raised further so that only WADA-accredited laboratories are being used for passport analysis, setting the standard of QC at the “forensic” level and thus above the normal “clinical” level of conventional medical laboratories. By approving the report on the sample they have analyzed and including the result in the profile, these laboratories guarantee the conformity of the results and the analytical process with the guidelines issued by WADA for this purpose. The expert could therefore rely on the responsibility of the laboratory for all analytical aspects; however, it is wise to double check certain aspects, such as transport times, results of double analysis, and red cell scattergrams, because these might provide valuable additional information useful in the evaluation of the profile. The key question that should be asked and discussed by the expert in this context is: “Can the abnormal result of the profile be explained by the analytical or preanalytical process?” The answer can be obtained from the documentation of the analytical procedure or from indirect clues derived from experience and knowledge of laboratory procedures and results (e.g. cell volume changes due to inadequate storage).

**ENVIRONMENTAL INFLUENCES ON BIOMARKERS**

As a next step, the environmental conditions to which the athlete was exposed at the time of sampling have to be taken into consideration. Certain variables will be different when measured in the morning compared to the evening. Furthermore, it has been demonstrated in many studies that biomarkers show variations depending on the environmental conditions, e.g., hemoglobin concentration is usually lower in individuals sojourning in warm climates (summer), owing to a temperature-driven increase in plasma volume, which improves thermo-regulation. Altitude is another confounding factor for blood variables, because hypoxia might affect the red blood cell production and the vascular volumes.

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The length of the exposure and the degree of hypoxia (defined by the altitude) are key issues in this context and must be evaluated on an individual basis, considering information regarding the time the sample was taken in relation to the sojourn at high altitude. Thus, any abnormality in a profile should be scrutinized in view of the question “Can the abnormal result of the profile be explained by the environmental conditions to which the athlete was exposed prior to providing the sample?”

**INFLUENCE OF EXERCISE ON BIOMARKERS**

Exercise is an additional preanalytical variable that has a short- and long-term impact on plasma volume. Because most biomarkers used in the Athlete Biological Passport are concentration-based measures, shifts in plasma volume can lead to important variations in the respective markers. Therefore, the Passport guidelines indicate that samples should be taken only at least 2 hours after the last training or competition, to avoid interference related to short-term adaptations to exercise. Although adherence to this principle is usually confirmed on the Doping control form, it is wise, for example, to check the white blood cell count (from the scattergram report in the laboratory documentation package). The white blood cell count will be characteristically altered (increased) if the sample was taken too close in time to the athlete’s last episode of intensive exercise. Another factor that must be considered in the evaluation is that several closely spaced days of heavy
exercise will lead to plasma volume expansion and thus to a decrease in most concentration-based measures. It is of note that reticulocytes are not affected by such plasma volume shifts, because they are measured as a percentage of red cells. The expert should evaluate whether any abnormal value in a profile might be explained by exercise-induced changes.

INFLUENCE OF PATHOLOGICAL CONDITIONS
Many diseases or pathological conditions, such as internal or external blood loss or a congenital, clinically silent red cell abnormality (e.g., hereditary spherocytosis) can modify one or more of the blood parameters used in the passport. Although the prevalence of such conditions is rather low in the population (approximately 1:2500 for hereditary spherocytosis) (14), their possible influence must carefully be considered. This situation applies to other hematological abnormalities that might be even more common in certain subpopulations (for example thalassemia in populations originating from the Mediterranean basin or certain regions of Asia). It is of note that a pathological condition is often claimed by accused athletes as the cause of one or more abnormalities of their blood profile.

DOPING SCENARIO
One of the hypotheses that might explain an abnormal hematological profile is blood doping. Evaluation of the probability of this hypothesis is usually central to the decision the jury has to make, on the basis of the information provided by the expert. It is therefore important, if the expert concludes a given athlete’s profile is typical of doping, that the expert also provides a clear explanation of what doping manipulations the athlete might have carried out to obtain the results seen in the evidence (i.e., the profile). At this stage, the expert evaluation transforms into an “opinion” that comprises a subjective element, i.e., the construction of a scenario. Examples of possible scenarios at the present time include blood withdrawal and reinfusion in particular periods or seasons, the use of erythropoiesis-stimulating agents at different dosages, and the possible combination of both these methods with other substances such as growth factors or anabolic steroids. Such doping behaviors, although heterogeneous and personalized by each cheating athlete, will produce characteristic patterns of change in hemoglobin concentration, reticulocytes, and OFF score over certain periods, which can be attributed to a specific scenario. It is important that each speculation on a scenario be supported by scientific evidence from the literature. Ideally, a doping scenario matching the evidence of the profile should be suggested, but because of the complexity of doping and the ability of a sophisticated cheater to skew a profile, a full explanation of every aberration in a profile may not be possible or necessary.

Experience from Court Cases

GENERAL ASPECTS
The first cases based on information from the Athlete Biological Passport for which rulings have been issued at various levels of the sporting jurisdiction have raised several procedural issues that need to be improved in the future.

THE LEGAL CONSEQUENCES OF THE PASSPORT
For many years, the primary aim in establishing the Athlete Biological Passport as a tool in the fight against doping was to develop valid and powerful scientific methods to identify doping athletes, to standardize analytical procedures, and to implement guidelines and a strict QC system. Accordingly, a multitude of scientific articles have addressed many issues related to the scientific aspects of the Athlete Biological Passport. Today, the passport approach can identify suspect athletes with acceptable specificity and good sensitivity (15).

Now that the scientific side of the passport is solid and many federations are seeking to implement this approach, several problems that had not been considered beforehand have begun to emerge. The main issue that needs attention is the legal handling of passport cases.

QUALIFICATION OF LEGAL PANELS RULING ON ATHLETE BIOLOGICAL PASSPORT CASES
The main problem in the first cases on the Athlete Biological Passport was the fact that most members of the legal panels were, in general, unfamiliar with the approach of indirect detection of doping. In addition, the logic behind the adaptive model and the Bayesian approach of evaluating evidence that provides the quantitative evaluation of the profiles was poorly understood. Therefore, a primary task for all organizations using the Athlete Biological Passport should be to educate its disciplinary panels with regard to this topic. This process should be parallel to the implementation of the Athlete Biological Passport itself. In the meantime, national federations dealing with biological passport cases should be strongly advised to seek legal and scientific help from bodies with more experience in the area, such as WADA or the international federations of their respective sports.

QUALIFICATION OF NEUTRAL EXPERTS IN ATHLETE BIOLOGICAL PASSPORT CASES
For many legal cases dealing with topics requiring expert opinions, the court might decide to hear neutral experts in addition to the experts of the different par-
ties. The role of these experts is extremely important because they are supposed to provide a neutral opinion; thus, their view will heavily influence the decision of the panel, and scientific stances taken by such experts are often accepted as proof by the rules of the Court of Arbitration for Sport (R31, 2). In several recent cases, the neutral experts were mostly qualified and highly skilled clinical hematologists, but lacked specific knowledge in the area of blood doping, exercise physiology, and the adaptation of the hematological system to physical efforts. Thus, the topic they had to evaluate was partly beyond their area of expertise. Therefore, care is strongly advised in the selection of potential neutral experts for Athlete Biological Passport cases. Their areas of expertise should cover most of the topics outlined in the WADA Athlete Biological Passport guidelines (10). For scientists acting as neutral experts for Athlete Biological Passport cases, it should be remembered that the "Standards for the formulation of evaluative forensic science expert opinion" clearly state that "an expert will not give evaluative opinion on matters outside his own area of expertise" (9).

With the emergence of many stakeholders in anti-doping who are implementing their own passport programs, this issue becomes even more important, because any passport program will need qualified experts to evaluate the profiles. As pointed out above, qualified experts are crucial for any step of the process and should be chosen with great care.

SPECIFIC ISSUES
During the first court cases based on the Athlete Biological Passport, the defense teams of the athletes were quite uniform in their tactics. They based their approach primarily on the strategy that has been used for many years in conventional doping cases, in which forbidden substances are detected and the defense usually tries to demonstrate that the sample is not valid owing to improper handling or inconsistencies with the standards in the analysis. Just as in such cases, the first and foremost aim of the defense lawyers in the passport cases was therefore to attack the validity of the samples that had caused the profile to be abnormal. This situation highlights the importance of stringent analytical and preanalytical standards for all passport samples. The attacks aimed furthermore at procedural issues, such as qualification of the experts, admissibility of certain documents and briefs (16), or the definition of abnormality (e.g., the defense tried to demonstrate that the sample flagged at the quantitative level is in fact not abnormal (17)). The latter approach implied critiquing the Bayesian model and the calculation algorithms. Simultaneously, the sample documentation was usually scrutinized in detail and every nonconformity with the standards was highlighted and discussed, from inconsistencies in the signatures in the laboratory reports to QC issues. Interestingly, the panels have, until today, never admitted such criticism mainly because the defense failed to demonstrate how such nonconformities could affect the result of the sample to the disadvantage of the athlete (17).

Outlook

USE OF RESOURCES: TIMING OF PASSPORT TESTING
Aside from the legal and scientific challenges, any passport program relies on a highly organized logistical backbone that will ideally provide conditions under which the right athlete is tested at the right time in view of his/her profile. Large financial resources are used in this context and it is of note that the logistical costs of the passport program (such as those for sample transport) exceed by far the analytical costs in the laboratory. Therefore, it is of crucial importance to use every test to its full potential and to organize dedicated testing schemes. Ideally, a testing scheme will be adapted to potential doping interventions in view of the competition schedule of each athlete and the questions an expert might ask in the context of the profile.

Any expert evaluation is therefore heavily dependent on the right timing of blood tests. Although it is difficult to give general advice on how to organize target testing, several general principles should be respected:

- Every test should be scheduled for a reason.
- Tests should be balanced between unannounced and announced tests (e.g., scheduled precompetition tests, such as in several Nordic disciplines and cycling).
- Tests should be balanced between precompetition, in-competition (where applicable), and out-of-competition tests.
- Athletes should be tested during periods when doping is likely (e.g., preparation for major competitions) and during periods when doping is not likely (e.g., season break, holidays).
- Specific issues with the schedule of each athlete (e.g., altitude exposure) must be considered.

The logic behind this concept is to picture the extremes of the values possibly observed in an athlete in predefined situations. This allows the expert to examine whether variations or changes in the athlete’s values fall into expected physiological patterns or not, e.g., will a cyclist display a drop in his hemoglobin concentration after several days of racing in a stage race (which would be physiological due to plasma volume expansion) or will the hemoglobin
The introduction of the Athlete Biological Passport and the indirect detection of doping has opened new pathways for the fight against doping in sports. For many years, science has made large efforts to provide a solid framework for this new approach. Experts involved in this process should be able to assess hematological profiles regarding possible explanations related to the influence of doping products and methods (doping hematology), analytical issues, the influence of exercise, and pathological conditions. The current challenges in this context are presently found in the legal field, where judges and lawyers have to gain experience on how to present and defend indirect evidence for doping cases in court.

Conclusions

The introduction of the Athlete Biological Passport and the indirect detection of doping has opened new pathways for the fight against doping in sports. For many years, science has made large efforts to provide a solid framework for this new approach. Experts involved in this process should be able to assess hematological profiles regarding possible explanations related to the influence of doping products and methods (doping hematology), analytical issues, the influence of exercise, and pathological conditions. The current challenges in this context are presently found in the legal field, where judges and lawyers have to gain experience on how to present and defend indirect evidence for doping cases in court.

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