



Support of a laboratory-hosted Athlete Biological Passport Management Unit (APMU) to the anti-doping organisations

Introduction to the Athlete Biological Passport (ABP)

Most substances indicated on the prohibited list of World Anti-Doping Agency (WADA) are exogenous substances, for which the analytical approach is to screen and qualitatively identify the adequate target compounds, often metabolites, in the biological sample collected for anti-doping purposes; however, a group of substances, such as testosterone, erythropoietin (EPO) and growth hormone (GH) are model substances of endogenously produced compounds, which are present naturally in the human body but with which there is a potential risk of misuse in sports by exogenously administered, pharmaceutical products for doping purposes.

The fundamental role of an anti-doping laboratory is to identify reliably the prohibited substances or their representative metabolites or markers in biological samples, which are currently urine, serum or whole blood specimens collected from the athletes. Prior to reporting, the objective of the analysis is to study the sample adequately to exclude any other sources of the adverse analytical finding (AAF) than the use of prohibited substances. Due to the successful timing required from the sample collection and often complex and time-consuming methodological set-up, additional tools have been needed to gather orthogonal information on the doping practices. One of these approaches is

the Athlete Biological Passport (ABP). It is a concept to monitor the longitudinal profiles of individual athletes with respect to several selected biological parameters which are altered due to the application of prohibited substances or methods [1] and which may remain altered longer than the direct indicators of the substance/method can be detected in the anti-doping sample. The key element for a representative ABP profile is a frequent collection of samples, which will cover both in and out of competition tests at various degrees of physical stress, taking into account the particular characteristics of the particular sport and discipline.

To date, the routine ABP consists of two modules, hematological and steroidal, in order to discover the use of performance-enhancing substances or methods which are linked particularly to the attempts to enhance oxygen transfer or to the use of testosterone or its precursors. The aim of integration of biological passport profiling into anti-doping programs is to assist the anti-doping organizations (ADOs) in fine-tuning of test distribution plans, i.e. to identify and target athletes for more specific analytical testing. In addition to efficiency of testing, this assessment—in combination with information from investigational and intelligence activities—may provide support to allocate budgetary resources as well; however, in accordance with the World Anti-Doping Code (Article 2.2), the passport

programs might also be used to pursue possible anti-doping rule violations of use or attempted use of a prohibited substance or a prohibited method based on an atypical passport without having to rely on traditional, direct analytical approaches. In this approach, the result evaluation is confronted by very different obstacles in order to consider and to exclude clinical conditions, pathologies, interindividual and intraindividual variation, and various other confounding factors as the reason for atypical behavior observed in the ABP [2–7].

Due to the fundamental difference between the direct identification of an exogenous substance in a biological matrix and indirect interpretation of physiological response to the doping practices, the number of partners required for result management is very different between these two approaches. In the first case, involving the direct measurement for the presence of a prohibited substance and/or its metabolite in an individual biological sample, the analytical work and result interpretation is performed largely by the anti-doping laboratory, which issues an AAF to the ADO responsible of the result management. The case is then evaluated for the potential presence of therapeutic use exemption and for athlete's explanation with the possibility of the B-analysis, and then processed further according to the prevailing rules for adequate result management. Regarding the ABP cases, the complexity of data interpretation emerges from the

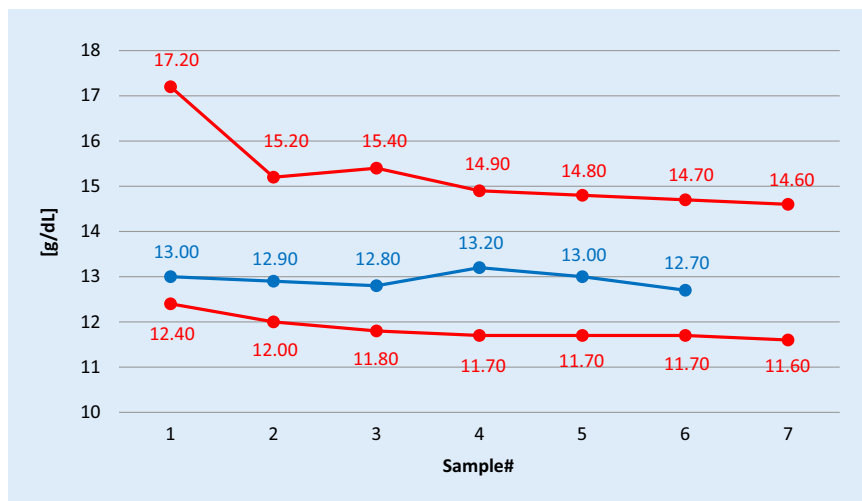


Fig. 1 ▲ Schematic illustration of the athlete biological passport profile. The points in blue represent results obtained from the samples collected from the athlete, whereas the points and lines in red define the upper and lower tolerance ranges established for the normal fluctuation of the parameter by the adaptive model of the ABP

indirect monitoring of modifications in endogenous markers, and from the comparison between multiple samples of the passport profile. For the construction of a passport profile, adequate baseline samples should be collected to establish tolerance ranges set up for the athlete by the adaptive model (■ Fig. 1), an algorithm established for the evaluation of endogenous markers and their natural fluctuation. In the ideal situation, these upper and lower tolerance limits will be used to flag those atypical samples exceeding the amplitude of normal fluctuation, and indicate the need of further passport evaluation, more detailed analytical testing, or collection of further samples.

The ABP concept was introduced by WADA via the hematological module in 2009 and selected parameters are aimed at targeting the physiological response to blood doping, e.g. administration of erythropoietin or practising with blood transfusions. The sample matrix used for the hematological profiling is whole blood, collected in an EDTA tube, and the test menu is very similar to the profiling for clinical purposes (■ Table 1). For an entirely robust process and adequate hematological profile, both preanalytical and analytical conditions are highly harmonized [8], involving e.g. a rest period of a minimum of 2h before sample collection after strenuous stress (to minimize

the impact of a potential variations of plasma volume), refrigerated and temperature-controlled transport to the laboratory, limited time-frame for a valid analysis, and the acceptance criteria for the replicate analyses of the blood sample. The analysis of hematological profiles represents an extremely high degree of a harmonized process, as even the instrument platform is fixed to a specific instrument model to provide harmonized analytical results for blood profiles. Furthermore, the laboratory performance is continuously monitored and scrutinized via a frequent external quality assessment scheme (EQAS) in order to assure the technical performance for the result production and the sensitivity of the hematological profile.

Steroidal profiling is done systematically in each routine urine sample analyzed for either out of competition or in competition test event. The critical points of the analytical procedure are standardized also for ABP steroidal module, involving sample preparation (e.g. enzyme used for hydrolysis and type of derivatization) and analytical aspects (gas chromatographic (GC) - mass spectrometric (MS) analysis) GC-MSⁿ analysis) and performance criteria (e.g. limit of detection; LOD, limit of quantitation; LOQ, maximum combined measurement uncertainty; $u_{c,max}$). The steroid profile consists of six target

compounds and their selected ratios (■ Table 2) as well as of monitoring of some well-known confounding factors (e.g. alcohol and signs of microbial degradation) that may cause an alteration in the steroid profile and invalidate the sample from the profile [9]. The doping scenario targeted by steroid profiling is especially the administration of testosterone or its precursors, although the physiological feedback may also provide information on the administration of exogenous anabolic androgenic steroids (EAAS), which have an impact on the steroid profile by suppressing the production of endogenous steroids. The benefit of the urine matrix is the relatively high volume available as well as long-term stability of the sample, which allows adding new tests on the already available sample, especially to study testosterone and its representative metabolites for endogenous or exogenous origin. This analysis is performed by an extensive sample preparation, gas chromatographic (GC) separation and combustion (C) of the organic material for the mass spectrometry (MS) analysis of ¹³C/¹²C isotopic ratio (IR) of carbon [10]. In brief, the principle of the GC/C/IRMS method is based on the variation of isotopic content between plant-derived pharmaceutical preparations and endogenous steroids, arising from fractionation of ¹³C in photosynthesis [11]. After intake of an exogenous product an alteration can be observed in the ¹³C/¹²C isotopic ratio of testosterone and its downstream metabolites, whereas the isotopic ratio remains intact in the endogenous precursors, such as pregnanediol. Although being still too laborious and time-consuming for routine analysis of all urine samples, GC/C/IRMS analysis provides an efficient and unique tool for the management of steroid profile cases triggered by the review of steroidal passport profiles, as well as the direct analysis of target compounds to support reporting of an AAF.

Operational environment of the Athlete Biological Passport

Common framework for the ABP program is set by the WADA, which is also

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Abstract

The athlete biological passport (ABP) is an established means for longitudinal monitoring of selected individual biomarkers of an athlete to obtain indirect but potentially long-term indications of the use of substances or methods prohibited in sport. Along the change from population-based reference values to individual profiling, the ABP aims at triggering follow-up investigations concerning the potential use of endogenous substances with doping potential, which might be difficult either to identify with the existing analytical methods or to interpret based only on the results of a single biological sample. The ABP program has been on-going within the World Anti-Doping Agency (WADA) management since 2009, when the hematological module

was officially established to discover blood doping practices, such as administration of erythropoietin (EPO) or application of blood transfusion. Since 2014, the ABP has been complemented by the steroid module, with the aim of targeting the prohibited use of testosterone and other endogenous anabolic androgenic steroids with performance enhancing or masking capability. Although the main objective is to guide and assist the anti-doping organizations in their test distribution plans, the ABP may also be used to proceed with a case to an anti-doping rule violation. Evaluation of biological markers, especially in distinguishing between doping from other confounding factors, requires high level and diversity of expertise, which is

coordinated by the athlete biological passport management unit (APMU). Since 2019, the WADA accredited anti-doping laboratories are defined as the host organizations for the APMUs. The benefit of such a structure is to obtain a fully anonymous evaluation process for the passports and an additional level of expertise for the interpretation of analytical results as well as to have a fluent communication line with the analyzing laboratories when further details are needed for the analytical testing and documentation.

Keywords

Athlete biological passport · Anti-doping · Hematological profile · Steroid profile

Unterstützung der Anti-Doping-Organisationen durch eine im Labor angesiedelte Athlete Biological Passport Management Unit (APMU)

Zusammenfassung

Der biologische Athletenpass (ABP) dient der longitudinalen Überwachung ausgewählter, individueller Biomarker eines Athleten, um indirekte, aber potenziell langfristige Hinweise auf den Gebrauch von im Sport verbotenen Substanzen oder Methoden zu erhalten. Entlang des Wechsels von bevölkerungsbasierten Referenzwerten zu einem individuellen Profiling zielt der ABP darauf ab, Folgeuntersuchungen hinsichtlich des möglichen Gebrauchs von endogenen Substanzen mit Dopingpotenzial anzustoßen, die entweder mit den bestehenden Analysemethoden nur schwer zu identifizieren oder auf der Basis der Ergebnisse einer einzigen biologischen Probe zu interpretieren sind. Das ABP-Programm läuft innerhalb des Managements der Welt-Anti-Doping-Agentur (WADA) seit 2009, als das hämatologische

Modul offiziell eingerichtet wurde, um Blutdopingpraktiken wie die Verabreichung von Erythropoietin (EPO) oder die Anwendung von Bluttransfusionen aufzudecken. Seit 2014 wurde das ABP durch das steroidale Modul ergänzt, mit dem Ziel, den verbotenen Gebrauch von Testosteron und anderen endogenen anabolen androgenen Steroiden mit leistungssteigernder oder maskierender Wirkung zu erfassen. Obwohl das Hauptziel darin besteht, die Anti-Doping-Organisationen bei ihren Testverteilungsplänen anzuleiten und zu unterstützen, kann der ABP auch verwendet werden, um einen Fall zu einem Verstoß gegen die Anti-Doping-Bestimmungen zu führen. Die Auswertung biologischer Marker, insbesondere bei der Unterscheidung zwischen Doping und anderen Störfaktoren, erfordert ein hohes Niveau und eine große

Vielfalt an Fachkenntnissen, die von der Athlete Biological Passport Management Unit (APMU) koordiniert werden. Seit 2019 sind die WADA-akkreditierten Anti-Doping-Labore als Trägerorganisationen für die APMUs definiert. Der Vorteil einer solchen Struktur besteht darin, einen vollständig anonymen Bewertungsprozess für die Pässe und eine zusätzliche Ebene der Expertise für die Interpretation der Analyseergebnisse zu erhalten sowie eine fließende Kommunikationslinie mit den analysierenden Laboren zu haben, wenn weitere Details für die analytischen Tests und die Dokumentation erforderlich sind.

Schlüsselwörter

Biologischer Athletenpass · Anti-Doping · Hämatologisches Profil · Steroidprofil

responsible of establishing, revising and following up the implementation of the mandatory procedures (communicated via various international standards and technical documents), as well as assessing the various partners for compliance. Observation points, i.e. analytical results from biological samples, originate from various WADA accredited (full analytical menu) or approved laboratories

(hematological measurements only) and for the sensitivity of the passport, not only the representative number of samples but also the high degree of harmonization of the laboratory performance is required to guarantee the sensitivity of the adaptive model. International standards [12, 13] and previously mentioned technical documents are mandatory WADA regulations with the aim of guiding the com-

plete process, from preanalytical conditions to harmonized reporting, to ensure that the impact of environmental and analytical factors is decreased to a minimum and would have a smaller impact on the fluctuation of the biological passport than the administration of prohibited substances. The WADA also maintains the global data warehouse system, Anti-Doping Administration and Man-

Table 1 Parameters targeted in whole blood for hematological module of the ABP

Parameter	Abbreviation	Units
<i>Analytical indicators</i>		
Hemoglobin	HGB	g/dL
Hematocrit	HCT	%
Immature reticulocyte fraction	IRF	%
Mean corpuscular hemoglobin	MCH	Pg
Mean corpuscular hemoglobin concentration	MCHC	g/dL
Mean corpuscular volume	MCV	fL
Platelets	PLT	10 ³ /μL
Red cell distribution width	RDW-SD	fL
Red blood cell count	RBC	10 ⁶ /μL
Reticulocytes, absolute and percentage	RET	10 ⁶ /μL, %
White blood cells	WBC	10 ³ /μL
<i>Calculated indicators</i>		
OFF score	OFF score [16]	–
Abnormal blood passport score	ABPS [17]	–

Table 2 Parameters targeted in urine sample for steroidal module of the ABP

Parameter	Abbreviation
<i>Analytical indicators</i>	
5α-androstanediol	5a-diol
5β-androstanediol	5b-diol
Androsterone	Andro
Epitestosterone	E
Etiocholanolone	Etio
Testosterone	T
<i>Calculated indicators</i>	
T/E	–
A/T	–
A/Etio	–
5a-diol/5b-diol	–
5a-diol/E	–

agement System (ADAMS), which is established to combine information originating from various operators of anti-doping activities, to allow for matching between the athlete and samples with the laboratory results for the longitudinal profiling of individual steroidal and hematological passport profiles (■ Fig. 2).

For a sensitive individual ABP profile, there is a fundamental need for frequent and representative collection of anti-doping samples, as well as harmonized analytical processes. The first requirement is managed by the anti-doping organizations (ADOs), who assess the risk of doping for the pool of athletes, establishes the strategies for efficient testing, requests the first analysis carried out in the sample, and collaborates with the sample collection authority (SCA) to ensure that the details of the test and sample code can be linked to the athlete's biological passport profile as soon as the laboratory has submitted the results. In practice, the testing authority (TA) decides which athlete to test, when and with which test menu. The TA is also the owner of the sample and, among other responsibilities, defines also the strategies, e.g. for long-term storage of the samples.

Each individual athlete is assigned to one ADO, which possesses thus the passport custodianship of this athlete and depending, e.g. on the sport, country, and level of competing, the passport custodian (PC) could be a national anti-doping

organization, regional or international sport federation. In order to enhance the efficiency of testing, ADOs may have mutual agreements on the transfer or share of passport custodianship and via these sharing agreements, as many samples as possible collected from a given athlete can be incorporated to strengthen individual ABP profiles. As the owner of the passport the PC is responsible of the follow-up of the athlete, further actions for testing, as well as of case management that may take place from the atypicalities observed in the biological passports.

The role of an anti-doping laboratory is straightforward regarding the ABP, i.e. to provide compliant analyses of anti-doping samples upon the request of the TA and to upload the results into ADAMS. Two types of laboratories are involved in this activity, namely the WADA accredited laboratories, which are authorized to perform full menu of analysis of all matrices of anti-doping samples, and the WADA approved laboratories, which operate with limited test menu regarding anti-doping samples and allow for a globally wider network available for the analysis of logistically demanding whole blood samples for the purposes of hematological module of the ABP.

As soon as the laboratory result is matched with the passport of the athlete, the first evaluation of the sample and the updated profile is made automatically by the adaptive model in ADAMS and a no-

tification of the update is submitted to the PC and to the APMU, which is contracted by the PC to this task. The APMU provides independent expertise on the individual samples and longitudinal profile to recommend adding other tests or to guide testing strategies. The review is done anonymously, as the individual biological samples are indicated by a unique external code throughout the sample collection, laboratory analysis and reporting, and assigned to the profiles of the athletes for which the identification is made by the biological passport identifier (#BPID). Furthermore, via ADAMS configuration, the access to athlete data is restricted to the minimum necessary for result interpretation. The analyzing laboratories have the access only to those analytical data that are produced by themselves whereas the TAs are authorized to manage only those samples that are collected within their test missions. In contrast to that, the complete passport profiles are open only to the PC, APMU of that particular PC, and to those TAs with which an agreement is made for sharing of the passport review right.

APMU tasks and services

The PC mandates the APMU for the timely management of the passport within their custody. In practise, the routine work consists mainly of the review of passport notifications received

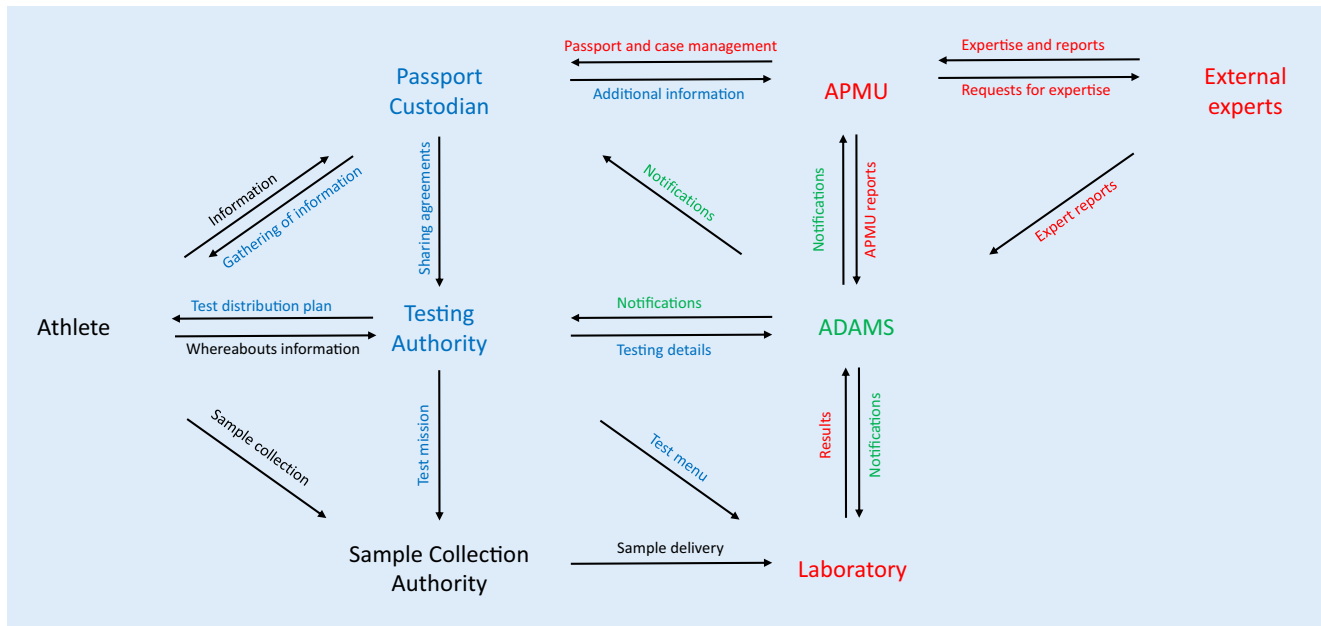


Fig. 2 ▲ Operational framework of the athlete biological passport program. *APMU* athlete biological passport management unit, *ADAMS* Anti-Doping Administration and Management System

from the ADAMS, evaluation of the profiles and provision of recommendations for further testing (■ Fig. 3). Regarding the atypical passport profiles, the APMU liaises with internal and/or external experts, according to prevailing WADA regulations [9, 10, 13, 14]. The APMU is responsible for maintaining a pool of external experts who represent various fields of medical, physiological and pathological competence to the evaluation of atypical profiles and who provide their opinion on the likelihood of the profile to be due to doping practices or any other reason. The evaluation takes place at two stages, the first being performed by a single expert, whereas for the declaration of an adverse passport finding (APF, i.e. positive passport case), a unanimous decision of three experts is needed. For comprehensive review, the experts should be selected to represent the various areas of specialization, for example clinical and laboratory hematology, sports medicine and exercise physiology, in cases if an atypical hematological passport profile is concerned.

In order to interpret atypical results of the biological profiles, the experts may request APMU to coordinate with the PC to gather more detailed data for pass-

port evaluation, e.g. whereabouts information, competition schedules, medical records, or other explanations. Within these communications, the anonymity of an athlete is maintained. One of the APMU tasks is to assure the security and traceability of the expert reports, as well as to compile the documentation necessary for the passport review and case management. In practice, this involves collecting analysis certificates and more detailed laboratory documentation packages from the analyzing laboratories, with the aim of providing solid documentation in the form of ABP documentation package for the external experts to evaluate the validity of each point (sample) in the atypical profile, as well as to consider the global context of the sample collection and confounding factors that may have an impact on the observed parameters of the biological profile.

As soon as the panel of three external experts has completed its evaluation regarding the validity of the samples in the profile, reached a unanimous opinion that it is highly likely that the passport is the result of the use of a prohibited substance or prohibited method and that it is unlikely that it is the result of a normal physiological or pathological condition, and provided a joint evaluation report,

the final task for the APMU is to declare the adverse passport finding to the PC and WADA. From this point on, the disciplinary process is initiated, led by the PC and the support of the APMU involves mainly interfacing between the PC and the experts in the process of evaluation of the athlete's explanations and other evidence provided for the case management.

Assistance provided by the APMU related to the anti-doping laboratory

Since March 2019 and the publication of the WADA technical document for the requirements and procedures regarding the APMUs, the hosting (facilities and resources) shall be provided by an anti-doping laboratory [15]. It should be noted that even if the APMU is hosted by an anti-doping laboratory, it is not a mandatory activity of a WADA accredited laboratory and not every laboratory is involved in APMU expertise. Some confusion also seems to arise regarding the origin of data to be managed, but it should be clarified that the anti-doping laboratory is involved only with the analytical data provided by themselves, whereas the APMU has the access to

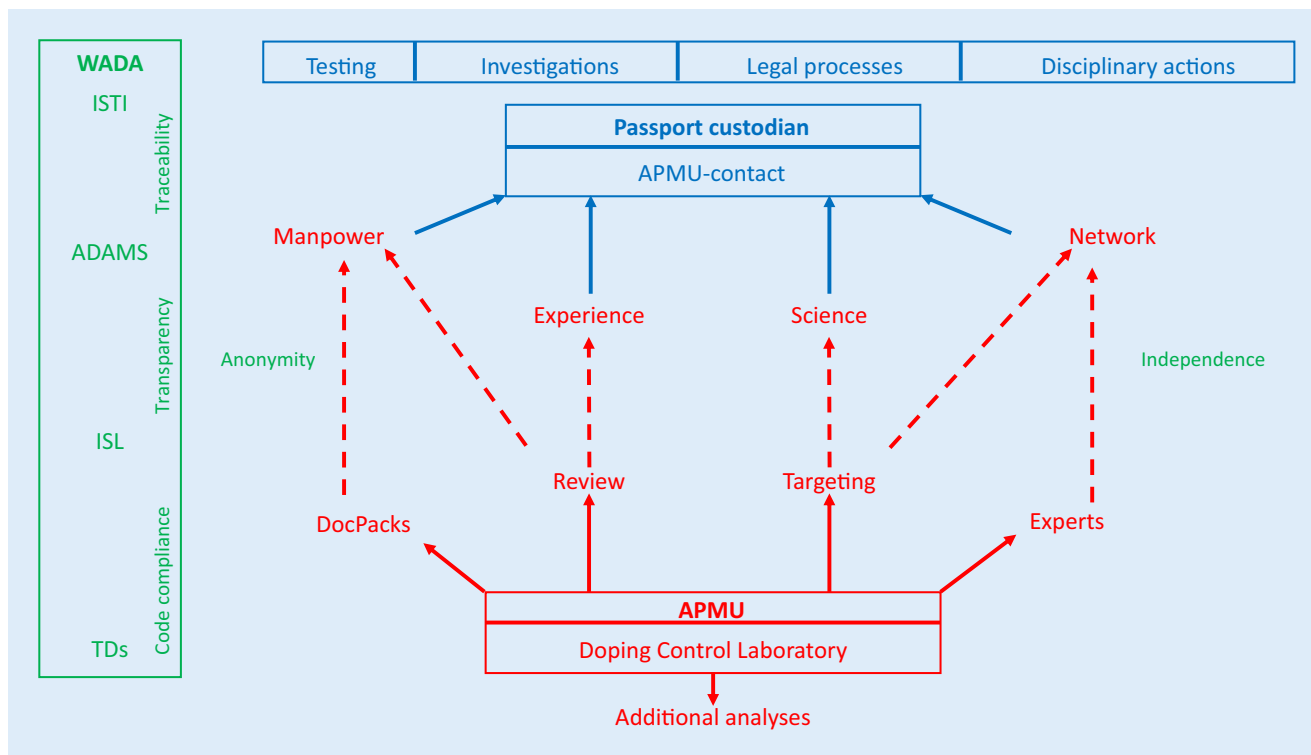


Fig. 3 ▲ Collaboration between the passport custodian (PC) and an athlete biological passport management unit (APMU) related to an anti-doping laboratory. *ISTI* International Standard for Testing and Investigations, *ADAMS* Anti-Doping Administration and Management System, *ISL* International Standard for Laboratories, *TD* Technical Documents

ABP data provided by other laboratories and incorporated to the biological profiles within their management. For these reasons, the two branches of activities, anti-doping laboratory and APMU, shall be well separated processes within the hosting laboratory in order to guarantee the operational independence regarding budget and human resources, as well as the confidentiality between the laboratory and APMU functions. To date, there are 16 WADA approved APMUs associated with WADA accredited laboratories.

The evident benefit of a laboratory-related APMU is the awareness and direct connection with the methodological details related to the analysis of the samples and specificities of instrument characteristics. This is especially important with respect to chromatography-mass spectrometry methods used for the initial testing and confirmation procedure of steroid profiling, which could be of assistance in requesting (or abandoning) further analysis on the sample or revisions to the testing strategy. Despite of highly harmonized procedures for steroid profiling,

the analytical processes for targeting exogenous prohibited substances may be arranged in various ways, depending on the set-up and capacity of available instrumentation, staff and sample numbers, still complying with the WADA criteria for the sensitivity and performance. For the evaluation of the coverage, possibilities and limitations of chromatographic-mass spectrometric analyses of the routine and extended analytical menus, the good comprehension over the arrangements of analytical processes of an anti-doping laboratory is an obvious asset for the APMU staff. One of the criteria for the WADA compliance of an APMU is the sharing of knowledge, which aims at improving the ABP program (e.g. research on the biomarkers and confounding factors) and assuring the adequate distribution of expertise and information obtained from the routine work and daily operations and dialog with the partners. In the one hand, the proximity with the analytical laboratory provides an easy access to the knowledge on scientific advances to the APMU personnel and on the other hand, the practical needs and

cases of the APMU may provide viable feedback to the laboratory on the areas of improvement and objectives for further scientific research projects.

For the compilation of documents for ABP case, the communication between the analyzing laboratory and the laboratory-related APMU has the potential for effortless dialog, as both parties operate within similar contexts and often use the same terminology. A fundamental element of the material provided by the ABP documentation package is to assess solid scientific base of the analytical result, as well as the validity and complete chain of custody of the biological sample, laboratory-related APMUs have also the required competence and/or immediate access to the expertise required for these tasks.

The advantage of a laboratory-related APMU, or of evaluation outside the ADO framework is the management of anonymous samples and profiles and consequently provision of the passport evaluation, which is fully independent from the risk assessment of the ADOs, and may provide an additional dimension for the

routine testing strategies. For the good interpretation of the APMU recommendations and smooth operations, however, it is important that the PC has assigned a contact person to correspond with the APMU, adequately trained to operate as an interface between the APMU expertise and additional information received from other domains of activities of the ADO. In the ideal situation, the internal information originating e.g. from testing, result management, APMU, investigations, and intelligence gathering are all put together in order to assess the pool of athletes and recognize the potential individual athletes or groups with elevated risk for doping for target testing, and to achieve an efficient anti-doping program.

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Compliance with ethical guidelines

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For this article no studies with human participants or animals were performed by any of the authors. All studies performed were in accordance with the ethical standards indicated in each case.

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