Hecksteden A[1], Meyer T[1]

Personalized Sports Medicine – Principles and Tailored Implementations in Preventive and Competitive Sports

Personalisierte Sportmedizin – Prinzipien und maßgeschneiderte Umsetzungen in Gesundheits- und Leistungssport

REVIEW

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1. UNIVERSITÄT DES SAARLANDES, *Institut für Sport- und Präventivmedizin, Saarbrücken*

Summary

- **Optimizing precision and efficacy** of measures on the individual level beyond what is achievable based on group means is the characterizing aim of personalized medicine. Sports medicine is a promising field of application for this concept and some aspects of individualization are already integral part of "standard care" e.g. relative exercise intensities based on reference values measured in the respective individual.
- **To provide the evidence base** for further advancement, the gap between medical practice focused on the individual and experimental research focused on the (true/mean) effect of an independent variable has to be bridged. To this end, methodological specifics of analyses on the individual level need to be taken into account. The resulting "toolbox" contains two main aspects: intraindividual repetition of measurements including the systematic combination of group-based and individual information and the joint consideration of multiple explanatory variables.
- **These two features** – individualization and the consideration of multiple, possibly interacting determinants – set personalized sports medicine apart from standard care. While these fundamental considerations are deducibly based on statistical principles, their full implementation is beset with many practical difficulties. Therefore, from the applied perspective, the ways of implementing personalized sports medicine will differ considerably depending on the specific task and the framework conditions in the field of application (e.g. preventive or elite sports).

Zusammenfassung

- **Kennzeichnender Anspruch** der personalisierten Medizin ist die Optimierung von Präzision und Effektivität von medizinischer Maßnahmen auf Ebene der Einzelperson über die auf Gruppenmittelwerten basierenden Rahmenempfehlungen hinaus. Die internistisch-leistungsphysiologische Sportmedizin ist in vielfältiger Hinsicht ein vielversprechendes Anwendungsgebiet dieses Konzepts. Entsprechend sind Elemente der Personalisierung, wie etwa auf individuellen Referenzwerten basierende relative Trainingsintensitäten, bereits heute selbstverständlicher Bestandteil der „Regelversorgung".
- **Um sich einer personalisierten Sportmedizin** weiter anzunähern ist es notwendig, die Diskrepanz zwischen einer auf die Einzelperson fokusierten medizinischen Praxis und einer auf die mittleren Effekte der unabhängigen Variable zentrierten Forschung zumindest teilweise aufzulösen. Das hierfür notwendige spezifische methodische Arsenal beinhaltet in erster Linie die intraindividuelle Messwiederholung, die systematische Verknüpfung gruppenbasierter und individueller Information sowie die gleichzeitige Berücksichtigung mehrerer erklärender Variablen einschließlich eventueller Interaktionen.
- **Die methodischen Spezifika** von Analysen auf individueller Ebene beruhen auf statistischen Grundprinzipien und sind weitgehend unstrittig. Allerdings ergeben sich bei idealtypischer Umsetzung hieraus teilweise Studiendesigns deren Umsetzung mit kaum überwindlichen Schwierigkeiten verknüpft ist. Schlüssel zu einer personalisierten Sportmedizin ist daher ein für jeden Anwendungsfall zu findender Kompromiss zwischen methodischen Voraussetzungen, konkreter Fragestellung und den Rahmenbedingungen des Anwendungsfeldes im Sinne einer „Maßkonfektion".

KEY WORDS:
Individualization, Precision Medicine, Study Design, Variance Components, Variability

SCHLÜSSELWÖRTER:
Individualisierung, Personalisierung, Studiendesign, Varianzkomponenten, Variabilität

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CORRESPONDING ADDRESS:
PD Dr. med. Anne Hecksteden
Akademische Rätin
Universität des Saarlandes
Institut für Sport- und Präventivmedizin,
Campus, Geb. B8 2, 66123 Saarbrücken
: a.hecksteden@mx.uni-saarland.de

Introduction

Clinical reasoning usually concerns a specific individual person or patient. Its aims at accurate diagnostics or interventions which are effective, safe and well-tolerated while maintaining a favorable cost/benefit ratio. In addition to well-founded medical knowledge, consideration of individual factors is always necessary. If this individual optimization of medical measures is conducted beyond the general, group-based recommendations is conducted in a structured, conscious way based on scientific evidence, it can be considered "individualization" or "personalization".

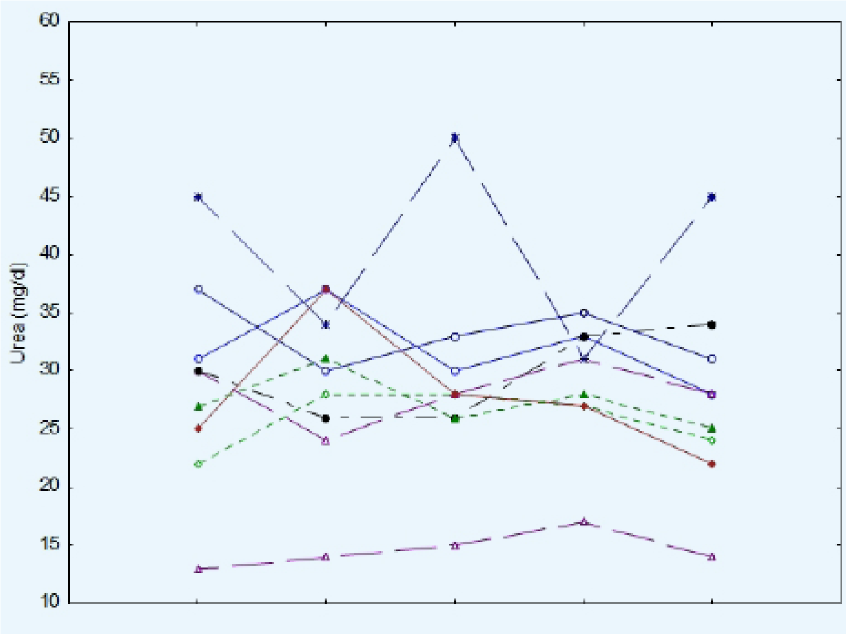

Figure 1

Urea concentration of adolescent swimmers over five consecutive microcycles of the general preparation period (each taken in recovered condition in the morning after the weekly day of rest). Details of the method are described in (15).

(by means of a combination of standardization and randomization) to isolate a single independent variable as the potential systematic influencing factor, whose effects are then investigated in a group-based analysis.

This corresponds to the randomized, controlled (prospective) study as a paradigmatic study design. This approach has definitely enabled great scientific and clinical advances, and the knowledge won thereby forms the indispensable basis of all attempts at optimization.

However, looking at the optimal care of individual patients or athletes, the limitation can be observed that the aim of such studies is to obtain knowledge of the mean ("true") effect of the independent variables under defined conditions, but not to precisely characterize individual study participants and their response to a specific intervention (26). Differences between various persons, but also the complex, multifactorial nature of cellular and systemic adaptation processes are not depicted but are considered random error. For analyses on the group level, this makes sense and is legitimate. In this context, inter-individual differences and randomly-distributed moderator variables only result in a reduction of standardized effect sizes, which can be compensated by a corresponding increase in the number of cases examined. In the context of single-case analysis or individual medical care (Number of cases=1), this is clearly not possible. Therefore, a discrepancy arises between research centered on a single independent variable and a clinical and sports-practical application directed to the optimal supervision and treatment/care of the individual. In order to resolve this discrepancy, at least in part, it is necessary to further differentiate the variation considered thus far as a random error. In other words: an attempt must be made to more precisely and reliably characterize the individual person than is possible with a group-based estimator of central tendency (such as the mean).

For a variety of reasons, sports medicine appears to be a suitable field of application for "personalized medicine" (9). To begin with, both inter-individual differences in the adaptation to physical training ("talent", "trainability") and also numerous influencing factors of training effectiveness (such as nutrition) have been known since antiquity and have been documented by scientific studies (4, 25) as well as by direct everyday experience. From a modern point of view, genetic polymorphisms are the basis on the one hand (2, 24), and on the other the large number of metabolic and signaling pathways involved in physical performance and training adaptation (5, 20). These factors form the mechanistic background for the influence of the numerous non-genetic moderators of training effectiveness.

Examples of such influencing factors are the availability of nutrients, age and epigenetics. An overview is provided in (20) and (13). In addition to these physiological considerations, the preventive and thus also economic importance of regular physical training and last but not least the tradition of individualized and multimodal approaches in high-performance and elite sports – even if they are not always evidence-based –underline the suitability of sports medicine as a field of application for personalized medicine.

Accordingly, current standard care in sports medicine already includes elements of personalization, such as relative training intensities based on individually-measured reference values (19) or the consideration of factors which limit bearable training load (such as cardiovascular diseases (22, 32) or recovery deficits (21)).

Unlike this clinical focus on the individual person, scientific evidence, on which this practice is founded, consists primarily of group-based experimental studies in which the intervention in question is typically the only independent variable, along with epidemiological recordings. In accordance with the experimental-paradigm, the attempt is made

Two possibilities are salient in order to obtain the required additional information on the individual person: on the one hand, repeated assessment of the parameters of interest on the individual level, on the other, taking more explanatory variables into account. On the level of data analysis, these options are paralleled by a separation of inter- and intra-individual variance components and modelling based on multiple, possibly interacting explanatory variables.

These specific methodical and statistical elements, which can also be applied in combination, go beyond the typical characteristics of group-based work. Building on the paradigmatic methodical principles of group-based studies and supplemented by the structured combination of group-based and individual information, they form the "toolbox" of personalized (sports) medicine (9).

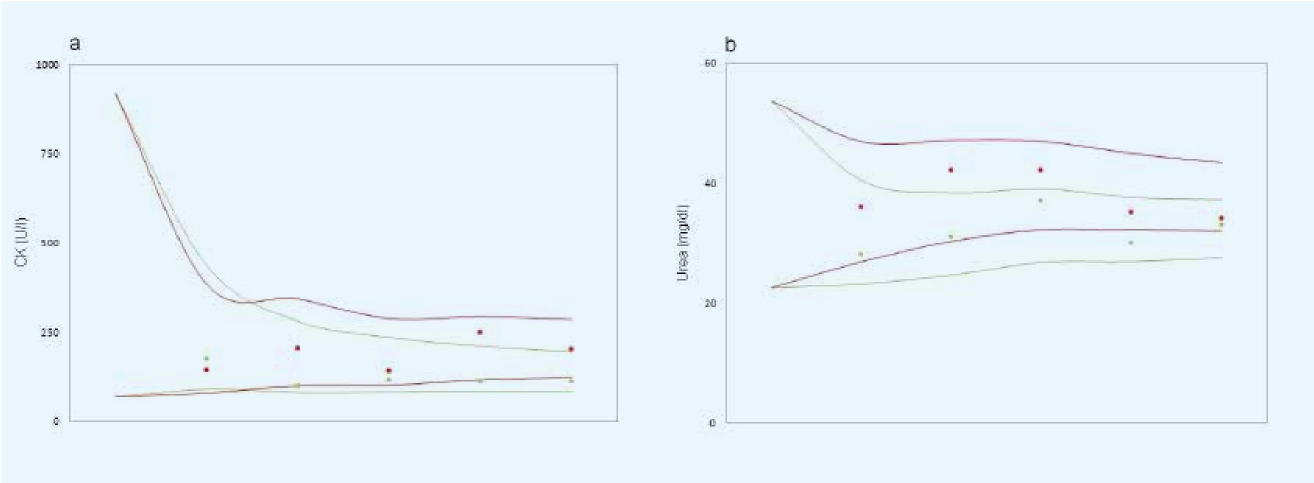

Figure 2

Gradual individualization of the 95% confidence interval for the serum concentration of creatinkinase (CK) in the recovered and fatigues state for one exemplary male athlete (Figure 1 from (15) with permission) Green: Recovered (after day of rest), Red: Fatigued (after 4 consecutive training days); Dots: Measured values.

Basic Methodical Principles of a Personalized Sports Medicine

Repeated Measures as the Key to Differentiation of Inter- and Intra-Individual Variability

There are considerable inter-individual differences in most parameters important in sports medicine. Striking examples are physical performance capacity and anthropometry. But large inter-individual differences are also observed for diverse blood values (15, 29), individual patterns of strain (7) and fatigue markers (17) or the efficacy of interventions ("Individual Response") (6, 13, 27). Consequently, inter- and intra-individual variance components are always confounded in the usual group-based reference ranges, whereby these become "broader" than would be appropriate for a single person (only intra-individual variation caused bytechnical measurement errors and biological variability). Figure 1 illustrates this consideration based on urea concentration in the serum of adolescent swimmers over 5 microcycles. In these individual courses, the different "levels" of the individual athletes as well as the intra-individual variability can be recognized.

Regarding the diagnostic value of a parameter, it is important that broad reference ranges reduce the sensitivity for deviations from the norm. Values which are remarkable for a certain individual can thus still be well in the broader, group-based reference range. Repeated measurement of the parameter of interest in each individual person is prerequisite to creating an individual reference range (only intra-individual variation) and thus to obtain a more precise characterization of the individual. Moreover, the outstanding importance of the reliability of the applied measuring instruments arises from the goal of characterizing the individual person and eliminating avoidable variability.

The principle of the individual baseline can be implemented at various levels of complexity: from the intuitive consideration of previous values by experienced (team) physicians and trainers, over the calculation of individual means and standard deviations and on to the application of explicit bayesian procedures (15). The latter procedure additionally offers the possibility of coupling the advantages of group-based (large number of observations) and individual estimate ranges (only intra-individual variation) by systematically combining group-based prior information with observations at the individual level. This principle, which originated in forensics, is also the basis for the Athlete Biological Passport implemented by the WADA (1, 29, 30). Our group published the first application to fatigue monitoring in elite sports. Figure 2 (with permission from (15)) illustrates the principle of the individual "corridors". A more detailed presentation is found below in the section on the practical implementation possibilities of personalized sports medicine.

Accounting for Several, Possibly Interacting Determinants

Improvement in the predictive and/or diagnostic accuracy is possible in many cases by means of multivariate data recording and analysis. However, the possibility for more precise depiction of complex physiological circumstances is faced with considerable demands on research methods and study design. Important thereby is particularly whether interactions are permitted within the determinant variables (13). In most cases relevant to exercise physiology, an interactive model probably reflects the physiological situation most closely, considering the multiple connections of the determinants (13, 20) and mechanisms (5) involved in training effects. However, the requirements for a completely valid analysis of these interactions corresponds nearly to a factorial design with a high number of cases, so that trading off methodical stringency and feasibility can hardly be avoided (13, 26).

In addition, the selection of the explanatory parameters takes on decisive importance. In this, "personalized medicine" is in no way simply the application of genetic polymorphisms and/or "-omics"-based biomarkers (3, 26). Rather, the scope of potentially informative factors ranges from the genetic (3) and molecular (14) levels via easily measurable predictors (4, 10, 11) and on to personal goals and preferences (8). Which "source of information" should be used within a concrete query should therefore not be defined by the measuring method or parameter type, but by the evidence available for each set of explanatory ›

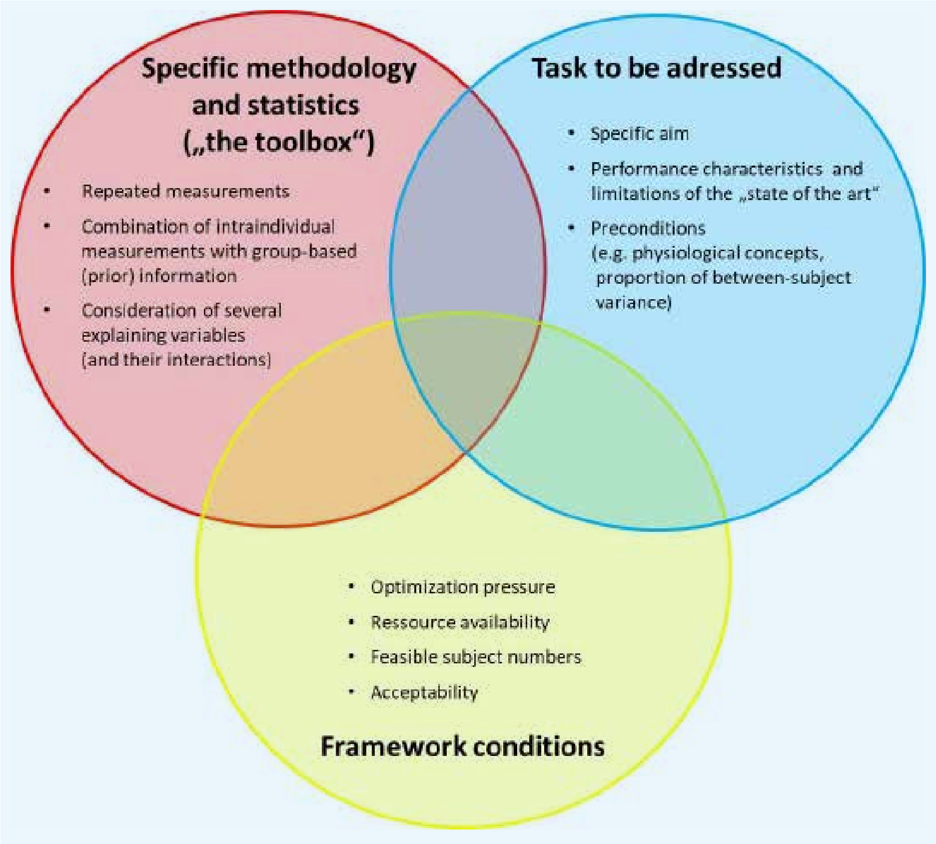

Figure 3

Development of concrete individualization approaches by balancing the methodical arsenal, query and framework conditions in the field of application.

and explained variables. A hypothesis-deduced procedure based on explicit physiological concepts ("white box") appears particularly meaningful in questions of training adaptation.

Tailored Implementations

The fundamental considerations discussed above are based on largely accepted methodological and statistical principles (13, 26) and are valid beyond the design of training programs for other types of intervention and in the diagnostic context. By contrast, their practical importance and also their adequate experimental as well as clinical implementation depend in many ways on the framework conditions in the specific field of application. To begin with this concerns the performance characteristics of standard care: the effect size of common interventions or the inter- and intra-individual variability of diagnostic markers defines the frame within which individual optimization is possible.

On the other side are optimization pressure and resource availability in the particular field of application (health, performance, elite sports) and finally – with a view to the methodical requirements – realizable sample sizes and acceptance of experimental manipulation, repeated examinations and possibly invasive sample collection. Figure 3 illustrates this field of tension which is the decisive interface for practical implementation of personalized sports medicine (from (9)). The necessity of compromises becomes exemplary in the conflict between highest optimization demands and the smallest number of available cases in elite sports.

Since a typically perfect implementation of the above characterized "toolbox"is thus only rarely feasible (and usually also not necessary), the development of pragmatic alternatives and targeted combinations of sub-aspects gains great importance from the application perspective. This is met by the methodical range of "tailored" procedures for specific applications. Their complexity may extend from informal consideration of the possibility of relevant individual deviations from the mean (12) through easy-to-determine (10, 11), molecular-biological (14) and genomic (3, 31) predictors and on up to personalized regression models (7) and deduction of individualized reference ranges based on bayesian procedures (15) (9).

In light of the multidimensional gradualist development of practical individualization approaches, a single procedure which is superior in every respect will exist only in very rare cases. Rather, the performance capacity of the "tailored" procedure must be critically verified in each case and confirmed for the specific application (3, 7, 10, 11, 14, 15, 31). Two applications are given as examples below to demonstrate the diversity in form of possible implementations of a personalized sports medicine.

Implementation Example 1

Prediction of Health-Related Training Effectiveness in Preventive Sport

Task: The effectiveness of preventive training to improve physical performance capacity and state of health is beyond doubt. However, the extent of training-induced changes varies considerably. This gives rise to great uncertainty in the specific "dosing" of exercise as medicine. In addition, estimation of the individual training effect would be helpful the coordination of exercise with therapeutic drug measures. A frequent example in clinical practice is the question whether a pure life-style intervention has a good chance of success in hypertension, or whether concurrent medication should be directly recommended for the particular patient (in the case that only little training effectiveness is anticipated). However, reliable and practice-relevant predictors are needed for this.

Procedure: For several cardiovascular risk factors (e.g. blood pressure), acute changes after a single bout of physical exercise (e.g. exercise-EKG) are similar to the longer-lasting, adaptive changes which result from a longer-lasting training program. If a relationship exists between the two phenomena, the acute changes (e.g. post-exercise hypotension) could be suitable as predictors of the training effectiveness, and can even be determined with no great expense during the exercise EKG.

Results: A relationship between acute and chronic changes could be shown in two independent pilot studies for blood pressure and insulin sensitivity (but not for the blood lipid values) (10, 11, 18). Figure 4 (with permission from (10)) illustrates the relationship for resting systolic blood pressure. This finding was recently reproduced in a broad randomized controlled training study (33).

Perspective: Acute changes in blood pressure and insulin sensitivity appear to be suitable for the prediction of corresponding training effects in the practice of sports and preventive medicine. Determination of reference values and predictive precision in relevant groups of people is still lacking.

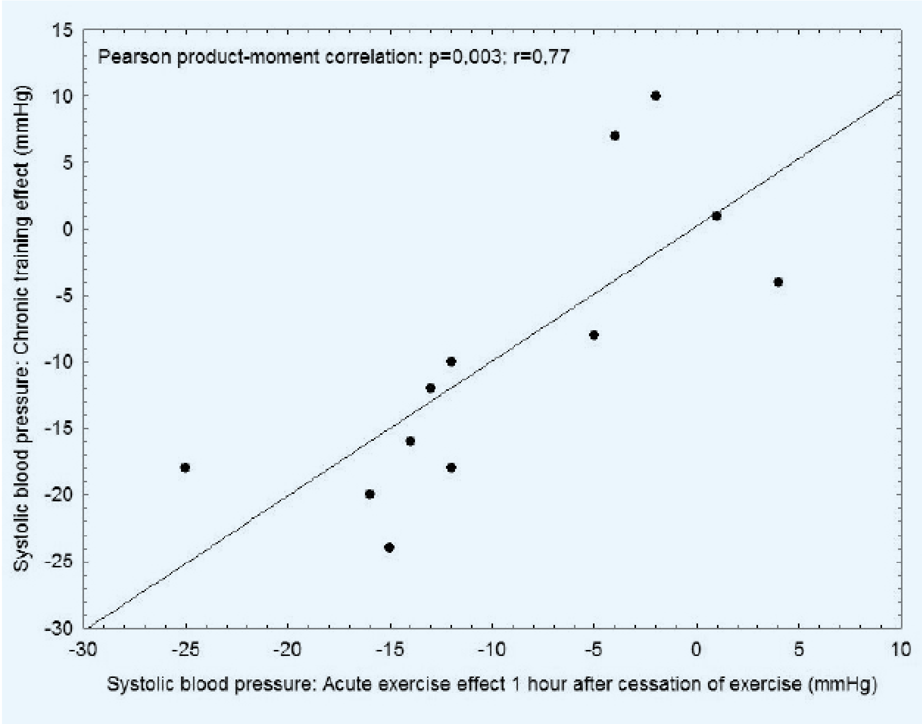

Figure 4

Relationship between acute changes in resting systolic blood pressure after an exercise EKG during the preliminary test with the training-related change resulting from an 8-week endurance training program (48 hours after the final training session) in previously untrained persons (Figure 3a in (10)).

Implementation Example 2

Individualization of the Reference Range of Fatigue Markers

Task: The assessment of the fatigue status of athletes is the basis for the daily fine-tuning of training. The goal is a maximization of training effects while avoiding longer-lasting regeneration deficits. Numerous fatigue markers are known, some have been used for decades, but they all bring the problem of broad variability. The correspondingly broad reference ranges impede on accuracy in the assessment of the individual athlete's fatigue status.

Procedure: Differences between individual athletes explain a considerable part of the overall variability (Fig. 1). In other words, each athlete has an individual "level" (or a personal reference range) for the individual fatigue markers. Accordingly, the meaning of a measured value differs between athletes; it may be above the personal normal range of one athlete, below that of another athlete and at the same time lie within the broader group-based reference range. For this reason, it makes sense to individualize the reference range to increase the certainty of assessment in the individual case. In principle, the mean and standard deviation of the measured individual values could be used. But since the width of the reference range depends largely on the number of measured values, it makes sense to begin with a group-based reference range and individualize this step-by-step with an increasing number of individual measurements. A similar bayesian strategy is also the basis for the Biological Athlete's Pass. Since unlike in the anti-doping campaign, two physiological situations are to be delineated (recovered and fatigued), two reference ranges are formed (Fig. 2). A detailed presentation of the method and an Excel spreadsheet for further use are found in (15).

Results: The error rates in the assessment of fatigue status in 14 elite athletes in swimming and triathlon based on the parameters urea and CK were significantly lower using individualized reference ranges compared to an optimal group-based threshold value (15).

Perspective: A better diagnostic validity of fatigue markers using individualized reference ranges has meanwhile be confirmed in other types of sports (28). At the moment, an application observation is being performed in several types of sports. Moreover, the procedure is being expanded for multivariate distribution in light of the multi-dimensional character of training-related fatigue. This has resulted in further improvement in the diagnostic validity (23). Work is in progress to refine the algorithm and account for additional parameters.

Summary

The field of sports medicine and in particular its subdisciplines overlapping with internal medicine and exercise physiology offer favorable conditions for a successful personalization of diagnostics and intervention. On the one hand, relevant inter-individual differences concern not only the training effectiveness ("individual response") (3, 4) but also, for example, the habitual values of relevant laboratory parameters (15, 17) and characteristics of training-related stress (7).

On the other hand, multifactorial processes (e.g. training adaptation (13)) and multivariate, complex phenomena (such as training-related fatigue (15, 16, 21)) play a conspicuous in the field. For this reason, precision and effectiveness can be optimized by means of individualized and/or multivariate procedures beyond the possibilities offered by a univariate procedure based on group means (10, 11, 15, 31). This corresponds to the goal of personalized sports medicine as formulated at the beginning of this article. From the scientific perspective, it is of decisive importance to take into account the specific requirements of analyses at the individual level and, with this in mind, to develop a specific research-methodical arsenal (13).

Practical individualization procedures can be developed for individual tasks in research or sports practice from balancing this specific methodical "toolbox" with requirements, prior knowledge and framework conditions in the particular application (Figure 3). The last step is then evaluation of the performance capacity compared to an optimal group-based procedure. A single procedure which is superior in every way will only be achieved in very rare cases under the circumstances.

Conflict of Interest
The authors have no conflict of interest.

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