Editorial

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**Personalized (laboratory) medicine: a bridge to the future**

**Keywords:** gender; laboratory medicine; personalized medicine; reference range; reference values.

Rapid advances in genomics and related technologies are promising a new era of personalized healthcare and disease prevention, not limited to new drugs, but also involving diagnostic and screening biomarkers. Although scientists have put forward the hypothesis that the time of personalized medicine has come (or will soon arrive), the chasm between new discoveries and the clinical use of new insights is wide. The gap between discovery and clinical implementation of diagnostic testing has made it necessary close cooperation between different stakeholders to accelerate and streamline the effective translation of validated knowledge into daily medical practice [1, 2]. Several lines of evidence suggest, however, that translation of new insights gathered from basic research studies as well as from clinical research per se is substantially biased. As provocatively highlighted by Redberg in a recent Editorial “...although there is a growing interest in personalized medicine, we still lack high-quality data on the largest group of patients in practice – women” [3]. The design of both research and clinical studies is affected by several drawbacks and, in particular, gender difference appears to be an often neglected dimension of medicine.

As brilliantly emphasized by Giovannella Baggio and colleagues in an article that we publish in this issue of *Clinical Chemistry and Laboratory Medicine* [4], the vast majority of epidemiological and clinical trials in the past 30 years have reported results only in one gender, nor have outcomes been adequately stratified for genders. Even more importantly, there is poor evidence that a gender approach has been incorporated into evidence-based medicine for developing practice clinical guidelines, recommendations or best practices throughout most areas of healthcare. As a result, we are facing a real paradox, lying between a major emphasis placed on personalized medicine and the still poor appreciation of gender, which is the most relevant variable in a personalized approach. This article, therefore, represents a valuable source for updating our knowledge on gender medicine and its relevance for laboratory medicine (Figure 1).

It is undeniable that laboratory medicine has been subjected to a paradigmatic (r)evolution over the past century, evolving from a classical clinical discipline focused on providing reliable diagnostic information to a broader enterprise aimed at exploring biochemical pathways in health and disease, discovering innovative biomarkers, and developing innovative and more efficient technologies. Regardless of emerging goals and future perspectives, laboratory diagnostics remains, however, a vital part of clinical and therapeutic decision-making, wherein test results are essential components of screening strategies (e.g., cardiovascular risk prediction and cancer screening), diagnosis of most – if not all – human disorders, as well as prognostication and therapeutic monitoring of patients with acute and chronic conditions. With growing diffusion of personalized medicine throughout several areas of healthcare, it is not surprising that the face of laboratory diagnostics is also undergoing a paradigm shift in the outline test results that are being – or should be – delivered to the stakeholders [5].

The intuition of using reference ranges (also known as “reference intervals”) for interpreting whatever type of measure is probably as old as mankind. In laboratory diagnostics, this concept has gradually evolved from – and has now virtually overcome – the former notion of “normal value”, because it now describes the variation of measurements or values in a population of “presumably” healthy individuals, which should conventionally include not <120 subjects [6]. The so-called cross-sectional assessment in respect of a predetermined reference range, along with the increasing but still limited diffusion of longitudinal comparison of patient’s data, is virtually unavoidable, because this prevents misinterpretation of test results, and thereby misdiagnosis or mistreatment [7]. Given these definitions for granted, the process that leads to generation of a reliable reference range is nothing but simple, and requires that several fundamentals are fulfilled, as

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currently specified by the official (joint) recommendations of foremost organizations such as the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) [8] or the Clinical and Laboratory Standards Institute (CLSI) [9]. Here, two leading drawbacks emerge: the influence of demographic variables and/or comorbidities on the calculation of accurate reference ranges, as well as the appropriate significance of the adjective “healthy”, accredited to the reference population.

The partitioning of reference ranges in separate subclasses according to age, gender, ethnicity or “other” is advisable when a clinical foundation or a logical physiological basis exists. Although we would all agree that some degree of difference will always emerge when reference subjects are clustered according to main demographic parameters, the final partitioning should be a reasonable compromise between the importance to explain clinically meaningful variations and the potential generation of a virtually infinite number of patient subclasses, which are supposed to represent all potential biological diversities. The ideal approach may be indeed the definition of a “personal” reference range, wherein laboratory data are longitudinally interpreted according to a personal database, which can be progressively enriched with values that dynamically contribute to generate a sort of “biological passport”, characterized by personalized thresholds [10]. This approach seems, however, unsuitable as yet, owing to problems of practicability (i.e., the need to obtain a considerable number of values to define reliable thresholds of interindividual variation) and related costs, so that the concept of identifying a representative selection of reference values appears the most favorable choice at this point in time.

A paradigmatic case here is that of reference ranges for the novel highly sensitive (HS) troponin immunoassays. The use of the former “contemporary sensitive” methods (i.e., those allowing to obtain measurable values in 1%–35% of presumably healthy subjects) [11] did not typically require a redefinition of the diagnostic threshold (i.e., the 99th percentile value) according to demographic variables, such as age and gender, or potential comorbidities, because the values of analytical sensitivity (i.e., the limits of blank and detection) were nearly overlapping with the diagnostic cut-off value. The widespread introduction of novel HS immunoassays has however revolutionized this approach, wherein measurable concentration of HS troponin(s) can now be obtained in more than 80% of presumably healthy individuals, so that the 99th percentile value may differ across genders (i.e., nearly double in males than in females) and, even more importantly, increases with ageing (i.e., nearly four times higher in subjects aged 81 years or older than in those younger than 31 years) [12].

The latter issue, that is, the appropriate definition of “healthy”, is nothing but ancillary, and requires the acquisition of a number of preclinical and clinical information by means of short medical examination and/or questionnaires for each candidate reference subject [8]. There are some examples of how a heterogeneous selection of different populations of “presumably” healthy individuals may generate different statistical outputs. Again, one of the most representative cases is that of HS troponins, wherein the virtually physiological release of proteins after moderate physical exercise was almost undetectable with contemporary sensitive methods [13], but is now clearly detectable and often exceeds the 99th percentile value with the novel HS immunoassays [14], thus requiring a more accurate clinical interpretation and hypothetical partitioning according to physical status. The concentration of HS troponin(s) has also been found to be significantly increased in patients with stable coronary artery disease [15]. Therefore, an ideal reference population for the diagnosis of acute myocardial infarction (AMI) should include a representative
subset of clinically healthy subjects (both males and females, with broad age distribution), in whom coronary angiogram is negative. Another valuable example here is that of cancer biomarkers such as prostate specific antigen (PSA) and related measures [16], wherein the diagnostic cut-off values should be calculated using a reference population where the presence of benign disorders or small malignancies (e.g., in situ carcinomas) has been accurately ruled out by means of prostatic biopsy [17]. Anyone would know, however, that invasive testing is not routine practice for excluding individuals from reference range calculation.

Although the review by Baggio and colleagues underlines current limitations in knowledge and clinical application of knowledge of gender differences [4], it is noteworthy that laboratory medicine has been the forerunner in supporting the view that male and female biology presents several diversities, and that such differences should be clearly emphasized by using separate reference ranges for several laboratory parameters, at least when a reasonably clinical basis for partitioning subsists. The list here is nearly unlimited and includes most hematological variables (e.g., hemoglobin, leukocyte count and differential), a variety of clinical chemistry tests (e.g., creatinine, aminotransferases and other enzymes), several cardiovascular (e.g., brain natriuretic peptide and HS troponin) and cancer biomarkers (e.g., carcinoembryonic antigen). The continuous efforts of laboratory medicine in this field are mirrored, for example, by ongoing research for identifying creatinine-based equations to help harmonize (or standardize, at best) the expression of estimated glomerular filtration rate (GFR) across different ages and genders [18, 19]. An additional key issue is that several drugs may exert their desired and undesirable effects differently in women than in men [20]. Gender medicine has thereby the invaluable potential to dissect therapeutic needs between men and women.

In conclusion, research into differences between male and female biology is continuously adding new pieces to the puzzle about health and disease from a gender perspective. We hope that the broad readership of Clinical Chemistry and Laboratory Medicine will also enjoy the valuable contribution by Giovannella Baggio and colleagues.

Conflict of interest statement

Authors’ conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article.

Research funding: None declared.

Employment or leadership: None declared.

Honorarium: None declared.

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