

Opinion Paper

Abdurrahman Coskun*, Sverre Sandberg, Ibrahim Unsal, Fulya G. Yavuz, Coskun Cavusoglu, Mustafa Serteser, Meltem Kilercik and Aasne K. Aarsand

Personalized reference intervals – statistical approaches and considerations

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Abstract: For many measurands, physicians depend on population-based reference intervals (popRI), when assessing laboratory test results. The availability of personalized reference intervals (prRI) may provide a means to improve the interpretation of laboratory test results for an individual. prRI can be calculated using estimates of biological and analytical variation and previous test results obtained in a steady-state situation. In this study, we aim to outline statistical approaches and considerations required when establishing and implementing prRI in clinical practice.

Data quality assessment, including analysis for outliers and trends, is required prior to using previous test results to estimate the homeostatic set point. To calculate

the prRI limits, two different statistical models based on ‘prediction intervals’ can be applied. The first model utilizes estimates of ‘within-person biological variation’ which are based on an individual’s own data. This model requires a minimum of five previous test results to generate the prRI. The second model is based on estimates of ‘within-subject biological variation’, which represents an average estimate for a population and can be found, for most measurands, in the EFLM Biological Variation Database. This model can be applied also when there are lower numbers of previous test results available. The prRI offers physicians the opportunity to improve interpretation of individuals’ test results, though studies are required to demonstrate if using prRI leads to better clinical outcomes. We recommend that both popRIs and prRIs are included in laboratory reports to aid in evaluating laboratory test results in the follow-up of patients.

Keywords: biological variation; personalized medicine; reference intervals.

***Corresponding author: Abdurrahman Coskun, MD,** Department of Medical Biochemistry, School of Medicine, Acibadem Mehmet Ali Aydinlar University, Istanbul, Turkey; and Acibadem Labmed Clinical Laboratories, Istanbul, Turkey, Phone: +90 532 744 66 83, Fax: +90 216 576 51 20, E-mail: Coskun2002@gmail.com

Sverre Sandberg, Norwegian Organization for Quality Improvement of Laboratory Examinations (Noklus), Haraldsplass Deaconess Hospital, Bergen, Norway; Norwegian Porphyria Centre and Department of Medical Biochemistry and Pharmacology, Haukeland University Hospital, Bergen, Norway; and Department of Global Health and Primary Care, Faculty of Medicine and Dentistry, University of Bergen, Bergen, Norway

Ibrahim Unsal and Coskun Cavusoglu, Acibadem Labmed Clinical Laboratories, Istanbul, Turkey

Fulya G. Yavuz, Department of Statistics, Faculty of Arts and Sciences, Middle East Technical University, Ankara, Turkey

Mustafa Serteser and Meltem Kilercik, Acibadem Labmed Clinical Laboratories, Istanbul, Turkey; and Department of Medical Biochemistry, School of Medicine, Acibadem Mehmet Ali Aydinlar University, Istanbul, Turkey

Aasne K. Aarsand, Norwegian Organization for Quality Improvement of Laboratory Examinations (Noklus), Haraldsplass Deaconess Hospital, Bergen, Norway; and Norwegian Porphyria Centre and Department of Medical Biochemistry and Pharmacology, Haukeland University Hospital, Bergen, Norway

Introduction

Using laboratory test results in the diagnosis and monitoring of an individual requires a reliable and relevant “reference” to which the test results can be compared. In most settings, population-based reference intervals (popRI) are used for this purpose, but there are many limitations to the generalizability of popRIs to an individual [1]. We have, therefore, recently proposed a model to calculate a reference interval (RI) for an individual, termed the personalized reference interval (prRI) [2]. The original idea of RIs for individuals goes back to the 1960s. In their seminal paper Grasback and Saris [3] wrote that ‘it would be helpful to establish the range of variation for every healthy individual’, and later Harris [4] proposed a complex model to derive intraindividual variations for blood constituents. The model we have proposed [2] is simple and allows for a patient’s current test result to be compared to that person’s prRI, established based on previous test results obtained in a steady-state situation.

Following the developments of IT technology in the last half century, it has become possible to store and process the data of large numbers of patients and to set up algorithms including statistical evaluations in the laboratory information system to aid in the interpretation test results. Additionally, reliable biological variation data of the numerous measurands can be found easily [5]. Therefore, now we have the bases for the practical implementation of prRIs in medical laboratories.

The theory of prRI is based on a homeostatic model [2]. In this model, we assume that the concentration of each analyte fluctuates around its true homeostatic set point (HSP), where this variation is termed inherent biological variation (BV). To determine the width of the prRI, we must estimate the total variation around the HSP (TV_{set}), which can be calculated using the following equation (Eq.):

$$TV_{set} = k \times \sqrt{\frac{(n+1)}{n} (SD_B^2 + SD_A^2)} \quad (1)$$

where SD_B is the within-subject (representing the “average” within-subject BV, as standard deviations (SD_I) in a population) or the within-person (representing the within-subject BV of the person (SD_P) in question) BV component of total variation, SD_A is an estimate of the analytical variation, n is the number of observations used to estimate the HSP and k is a constant depending on the probability and the type of distribution used to determine the limits of the prRI. In this equation, the factor $((n+1)/n)$ represents the uncertainty, which is mainly related to the determination of the HSP.

The prRI can then, as previously described, be determined using the following equation:

$$prRI = HSP \pm TV_{set} \quad (2)$$

This equation defines the prRI and has two critical parameters, HSP and TV_{set} , and can, as seen from Eqs. (1) and (2), also be written as given below:

$$prRI = HSP \pm k \times \sqrt{\frac{(n+1)}{n} (SD_B^2 + SD_A^2)} \quad (3)$$

Thus, calculating prRI requires relevant BV estimates, estimates of analytical variation and previous test results obtained in a steady-state situation. In this study, we expand on our model [2] and outline how to calculate prRI from a practical point of view, describing a two-step approach consisting of (a) data quality assessment prior to using previous test results to estimate the HSP and (b) different options for calculating the HSP and TV_{set} , including parametric and non-parametric approaches. Furthermore, the minimum number of test results required for prRI

calculations and other requirements for implementing prRI in laboratory reports are discussed.

Data quality assessment

In order to establish the prRI, we must calculate the HSP for the individual, using previous test results, which may either have been obtained specifically for this purpose or as part of routine assessments. A prerequisite for using these data for the calculation of the HSP is that these results have been obtained when the patient was healthy and in a steady-state situation. Results outside the popRI or clinical decision limits should, therefore, in principle not be used. In addition, outliers or extreme data can change the HSP significantly and, therefore, the data must be assessed for outliers before using previous test results to calculate the HSP. Various statistical tests can be used to detect outliers, and we recommend the Dixon q test [6, 7]. Alternatively, Grubb’s test can also be applied when data are considered likely normally distributed.

After excluding outliers, the data should be analyzed for the presence of a positive or negative trend. The presence and significance of a trend can be evaluated by linear regression analysis. If the confidence interval (CI, 95%) of the slope of the regression line includes 0, the trend can be considered not statistically significant and the individual is at steady-state [8]; see examples in the Appendix. Otherwise, if the trend is statistically significant i.e., the 95% CI of the slope of the regression line does not include 0, the data cannot be used to determine the HSP. Although trend correction can allow for the calculation of the variation, it may cause a dramatic shift in the HSP. Thus, prRI would no longer be valid and we, therefore, recommend discarding the data if a significant trend is identified.

Calculation of the homeostatic set point

After quality assessment has shown that the data can be used, the HSP can be calculated by taking the mean of the previous test results as given below:

$$\bar{X} = \frac{X_1 + X_2 + X_3 + \dots + X_n}{n} \quad (4)$$

where \bar{X} is the average HSP, x_i , $i=1, \dots, n$ is the measurement result(s) of the measurand and n is the number of observations included in calculation. The standard error (SE) of \bar{X} is calculated using the following equation:

$$SE_{\text{HSP}} = \sqrt{\frac{V}{n}} \quad (5)$$

where V is the variance of the distribution. V is represented by σ^2 and SD^2 for the population and sample, respectively. From Eq. (5), it can be seen that increasing n , will decrease the uncertainty of the HSP inversely proportional to the square root of n .

However, if the number of previous measurements is low, the median, instead of the mean, can be used as a measure of the HSP. In this case, a non-parametric approach should be used to derive the prRI.

Establishing the limits of the personalized reference interval

Previous measurement results can be used to predict future observations with a certain probability. In statistical terms, the interval for the future observation i.e., the prRI, is the ‘prediction interval’ derived from previous measurement results [9].

In statistics, the prediction interval is often used in regression analysis, and it also has great potential for laboratory medicine applications. It can be estimated using the variance and the HSP of the measurands. In a broad perspective, prediction intervals can be calculated using parametric [9] or non-parametric approaches [10]. A parametric approach can be considered under four different conditions using data with:

- Known mean and known variance.
- Known mean and unknown variance.
- Unknown mean and known variance.
- Unknown mean and unknown variance.

Practically, the known mean and known variance can be represented by the mean and variance of the population, while the unknown mean and unknown variance can be considered the mean and variance of a sample. In the prRI setting, the HSP represents the mean of the individual’s previous measurement results. Since the number of previous measurement results is limited, the population mean does not represent the HSPs of all different individuals and therefore the prediction interval calculated using model a and b cannot be applied to prRIs. The variance, though preferably derived from the individual, can also be derived from the population, assuming that this is representative and relevant for the individual to whom it will be applied. Consequently, the availability of estimates of the variance

is the decisive factor for choosing the method of prRI calculation.

Personalized reference interval based on estimates of within-subject biological variation

The within-subject BV, the CV_I , represents the “average” fluctuation of the concentration of a measurand around the HSPs of a group of individuals. It is considered random variation and statistically has the characteristics of normal distribution.

The limits of the prRIs are the upper (UL) and lower limits (LL) of the TV_{set} and can be calculated using Eq. (1). If an SD_I (or CV_I) estimate is used to represent the biological component of Eq. (1), then Eqs. (1) and (3) can be rearranged as given below [2]:

$$TV_{\text{set}} = z \times \sqrt{\frac{(n+1)}{n} (SD_B^2 + SD_A^2)} \quad (6)$$

$$\text{prRI} = \text{HSP} \pm z \times \sqrt{\frac{(n+1)}{n} (SD_I^2 + SD_A^2)} \quad (7)$$

where SD_I is the within-subject BV and z is a table value that can be set from the normal distribution as 1.96 for 95% probability (two-sided change). The SD_A estimate represents here the relevant long-term estimates of analytical variation from the laboratory reporting the prRI. Since the SD_I is considered to be normally distributed, we used the z -score in Eq. (6). Depending on how we prefer to use the prRI, z -values can be applied either for a two-sided or one-sided setting.

It should be noted that despite the term ‘within-subject BV’, here represented as SD_I , is derived from the data of a study population. Since the HSP is derived from the individual and the SD_I from the population data, the prRI can be calculated using the model of prediction interval based on unknown mean and known variance. It is therefore essential when using SD_I estimates to deliver prRI, that these must be assessed as to whether they are reliable and representative of the individual to which they will be applied. For a high number of measurands, global CV_I based on meta-analyses of suitable studies can be obtained from EFLM Biological Variation Database and used for prRI calculation [5]. Since the limits of prRI are based on absolute numbers, the SD_I for HSP should be calculated from CV_I . There may be differences in CV_I estimates between population groups such as genders that must be taken into account, but for most measurands, no

apparent differences related to methodological, geographical, sampling intervals have been demonstrated [11].

Personalized reference interval based on within-person biological variation

The numerical SD_I represents the “average” BV of the studied population. It is thus associated with an uncertainty that reflects the variation in the studied population and is not specific for each individual. Therefore, principally, using a BV estimate for the individual, i.e., the within-person estimate, the SD_P , would be preferable for prRI calculation. In comparison to the SD_I , the SD_P is a new concept and reflects the BV of a single individual. To derive such estimates for each individual is resource-demanding, requiring a relatively high number of results, limiting its applicability. In this approach, both the HSP and the SD_P are calculated based on the individual’s own data and the prRI can thus be derived using the model of prediction interval based on unknown mean and unknown variance. Therefore, it is accepted that all observations (measurement results) used to calculate both HSP and variance belong to t distribution rather than normal distribution.

In a similar approach to when using SD_I , the limits of the prRIs (UL, LL) of the TV_{set} can be derived from the SD_P as given below:

$$TV_{set} = T_{(1-\alpha/2)} \times \sqrt{\frac{(n+1)}{n} (SD_P^2 + SD_A^2)} \quad (8)$$

where SD_P is the within-person biological variation, the SD_A represents the analytical variation and $T_{(1-\alpha/2)}$ is the t-table value with $n-1$ freedom. T -values for either two-sided $(1-\alpha/2)$ or one-sided $(1-\alpha)$ settings, can be applied, depending on how we intend to use the prRI. For prRI calculations, the estimates of the SD_P and the SD_A should both be based on analysis from the same laboratory. In this setting, the SD_A is a component of total variation (SD_{TV}). It is thus not rational to separate SD_A and SD_P since they together represent the SD_{TV} . In this setting, Eq. (8) can be rearranged as:

$$SD_{TV} = \sqrt{SD_P^2 + SD_A^2} \quad (9)$$

$$TV_{set} = T_{(1-\alpha/2)} \times SD_{TV} \times \sqrt{\frac{(n+1)}{n}} \quad (10)$$

$$prRI = HSP \pm T_{(1-\alpha/2)} \times SD_{TV} \times \sqrt{\frac{(n+1)}{n}} \quad (11)$$

Equations (7) and (11) give the prediction intervals for single observation. However, statistically these equations can be rearranged for the next m measurement results (observations) as given below [12].

$$prRI = HSP \pm k \times SD_{TV} \quad (12)$$

Calculation of k factor is complex and beyond the scope of this paper. However, the Tables contain k value for different combinations of n (number of previous measurement results) and m (number of future measurement results) values can be found in Refs. [12, 13].

It should be noted that in clinical practice we compare the single measurement result to the RIs and therefore Eqs. (7) and (11) should be used to interpret patients’ tests results.

Nonparametric (distribution-free) prediction interval

In addition to the parametric approaches as described above, the prediction interval can be estimated using a non-parametric approach. When the number of observations is small or when there is no information about the distribution of the data, applying a non-parametric method may be preferable. The prediction interval is in this setting based on order statistics, such as the smallest and largest observations in the basic nonparametric prediction interval approach. However, in comparison to parametric approach, non-parametric PI may not produce a robust prRI estimate. Since it is not always possible to get the desired confidence levels for small data and additionally, prediction interval may be wider than distribution-dependent ones [13]. Different approaches may be used to establish non-parametric prediction interval and the detailed information can be found in Refs. [10, 13].

Minimum number of data required for the calculation of the personalized reference intervals for the different models

When calculating prRI, it is also important to consider the number of available previous test results derived in a steady state situation. There is no strict limitation for the minimum

number of data for the calculation of the prRI. However, increasing the number of measurement results decreases the TV_{set} and estimates the HSP better [2]. The required number of measurement results also varies depending on the biological component of TV_{set} .

If using SD_I estimates, only three measurement result may be sufficient to calculate the HSP, as previously shown [2]. However, trend analysis cannot reliably be performed on only three data points and the TV_{set} will be 15% wider than the actual level. Therefore, we propose to include at least five measurement results for the model based on SD_I .

Though principally the model based on SD_P estimates may be preferred, a greater number of measurements is needed to deliver reliable prRI, as the SD_P is derived using the individual’s own data. If the available number of measurement results is 5–30, then t statistics or a nonparametric approach can be used to derive the prRI. If the number of available test results is higher than 30, statistics based on the normal distribution can be applied, which is unlikely to be present for a steady-state situation for many patients.

Personalized reference intervals and reference change value

Due to the limitations of single diagnostic tests, physicians often request repeated tests to reduce the diagnostic uncertainty. Different approaches have been suggested for interpretation of multiple tests results [14]. Galen et al. [15] introduced the concept of parallel and serial testing for more than one measurand. They proposed that in parallel testing all samples are measured twice, whereas in serial testing only positive results are repeated. Using repeated measurements, the significance of difference between consecutive test results becomes crucial for objective decision making. This difference can be compared with the reference change value (RCV) which is the difference between two single measurements results that can be explained by pre-analytical, analytical and biological variation of the measurand. Assuming the preanalytical variation is negligible; the classical RCV can be calculated by using the following equation:

$$RCV = z \times \sqrt{2} \times \sqrt{(SD_B^2 + SD_A^2)} \tag{13}$$

PrRI and RCV complement each other in the interpretation of patients’ test results. While prRI is mainly used for diagnosis, RCV is used to evaluate the difference between serial measurements and therefore mainly used in monitoring.

Mathematically the equation of RCV (Eq. (13)) is a special form of the equation of TV_{set} (Eq. (6)). For Eq. (6) if $n=1$ then $TV_{set}=RCV$. However, it should be noted that a single measurement result is not recommended used to calculate the TV_{set} around the HSP, because in this case, the uncertainty around HSP will be 41% higher than the actual level [2].

Implementation of personalized reference intervals into the laboratory test report

The prRI offers an opportunity for improved evaluation of laboratory test results. However, further studies are required to demonstrate whether this will lead to better clinical outcomes. Prior to implementation into clinical practice, procedures related to data analysis and calculation of the prRI must be set up as suggested here, preferably in the laboratory information system, so that prRI can automatically be included laboratory reports for each specific patient. Though the SD_P approach likely provides prRI more suited for each individual, to estimate the SD_P requires a relatively high number of measurement results. Thus, as of yet, implementing prRI based on the SD_I approach may be a more pragmatic solution (particularly if $n<5$). We

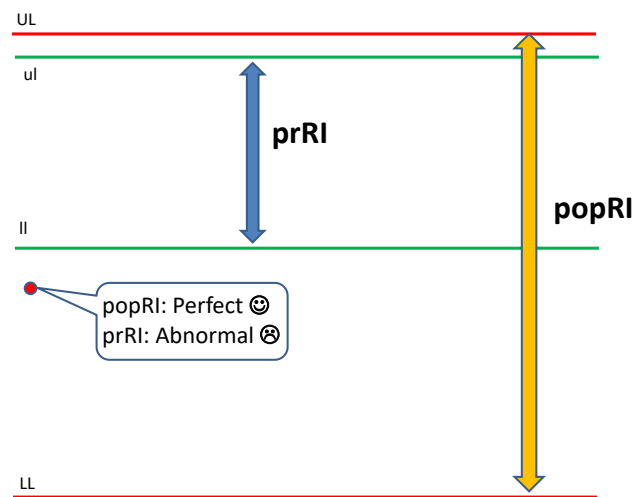


Figure 1: Personalized reference interval (RI) should be assessed in combination with population based reference interval. Using both RIs on the same report will facilitate the interpretation of patients’ test results. According to the population based reference interval a test result (red point) appears normal, but the same result may be abnormal according to the personalized reference interval. LL: lower limit of popRI; UL: upper limit of popRI; ll: lower limit of prRI; ul: upper limit of prRI.

recommend that both popRI and prRI are included in laboratory reports for all relevant measurands (Figure 1), and that clinicians are educated on how these can be best used in the evaluation and follow-up of patients.

Conclusions

The prRI concept is derived from the ‘homeostatic model’, where it is assumed that the concentration of each analyte fluctuates around its HSP. If the individual is at a steady-state, the mean or the median of an individual’s previous test results will represent the HSP. Before using previous test results to establish the HSP, data quality assessment including testing for outliers and trend must be performed. The limits of the prRI can be derived from the prediction interval. In this, we infer the result from a subject based on their own information. We have established two different approaches to deliver the prRI, either by using an SD_1 estimate, representing the average within-subject BV in a population, or an SD_p estimate, representing the within-person BV. If an acceptable number of previous test results is available for an individual, the SD_p can be used to deliver the prediction interval based on unknown mean and unknown variance. The SD_1 estimate can be used with a prediction interval for unknown mean and known variance to derive the limits of the prRI, if in principle, only three previous test results are available, though the minimum recommended number is five. The prRI can, in combination with popRI, be used to aid in the interpretation of patients’ laboratory test results and offers a more personalized approach for patient follow-up.

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Appendix

Numerical examples of how to derive the prRI for different data sets

The measurand is serum creatinine. Two patients; patient A and B, have 5 and 10 previous test results, analyzed in a routine setting, respectively (data derived from ref. [2]).

Table 1: Serum creatinine ($\mu\text{mol/L}$) concentrations of patients A and B.

Patient A	Patient B
58.3	80.4
57.5	76.9
60.1	84.9
61.0	83.1
51.3	79.6
	84.0
	84.0
	81.3
	84.0
	76.9

Calculation of prRI of creatinine for patient A

Step 1. Data quality assessment

The data of patient A were analyzed for possible outliers and the presence of trend.

No outliers were detected by Dixon q test ($p > 0.05$), and there was no significant trend (slope (95% CI) of -1.05 (-5.03 to 2.93)).

Step 2. Calculation of the homeostatic set point and the limits of personalized reference intervals

HSP was calculated by taking the mean of the previous measurements of creatinine.

$$\text{HSP}_A = \frac{58.3 + 57.7 + 60.1 + 61.0 + 51.3}{5} = 57.6 \mu\text{mol/L}$$

Only five measurements are available to calculate the total variation around the HSP. The t table value with $n-1$ freedom for 5 is 2.78. Therefore, the model based on estimates of within-subject BV (CV_1) was selected.

The EFLM Biological Variation Database reports a CV_1 for creatinine of 4.5% and SD_1 for HSP was calculated.

$$SD_{1(57.6)} = 2.59 \mu\text{mol/L}$$

$CV_{A(\text{pooled})} = 2.21\%$ (obtained from routine quality control)

$$SD_{A(57.6)} = 1.27 \mu\text{mol/L}$$

The prRI of creatinine for patient A can thus be calculated using Eqs. (2) and (6) as given below:

$$\text{prRI} = \text{HSP} \pm TV_{\text{set}}$$

$$TV_{\text{set}} = z \times \sqrt{\frac{(n+1)}{n} \times (SD_1^2 + SD_A^2)}$$

$$\text{prRI} = 57.6 \pm 1.96 \times \sqrt{\frac{(5+1)}{5} \times (2.59^2 + 1.27^2)}$$

$$\text{prRI} = 57.6 \pm 6.2 = 51.4 - 63.8 \mu\text{mol/L}$$

Calculation of prRI of creatinine for patient B

Step 1. Data quality assessment

The data of patient B was analyzed for possible outliers and the presence of trend.

No outliers were detected by Dixon q test ($p > 0.05$), and the trend was not significant (slope (95% CI) of 0.044 (−0.758 to 0.846)).

Step 2. Calculation of the homeostatic set point and the limits of personalized reference intervals

HSP was calculated by taking the mean of the previous measurements of creatinine.

$$\text{HSP}_B = \frac{80.4 + 76.9 + 84.9 + \dots + 76.9}{10} = 81.5 \mu\text{mol/L}$$

The number of previous measurements ($n=10$) is acceptable for calculating the total variation. The t table value with $n-1$ freedom for 10 is 2.26. Therefore, we used the model based on within-person BV (CV_P).

When all samples have been analyzed in the same laboratory, it is not necessary to separate and then combine the biological and analytical variations. Therefore, the total variation (including analytical and within-person BV) can be taken as the SD of the previous measurement results (SD_{TV}).

The prRI of creatinine for patient B can thus be calculated using Eqs. (2) and (10) as given below:

$$\text{SD}_{TV} = 2.97$$

$$\text{prRI} = \text{HSP} \pm \text{TV}_{\text{set}}$$

$$\text{TV}_{\text{set}} = T_{(1-\alpha/2)} \times \text{SD}_{TV} \times \sqrt{\frac{(n+1)}{n}}$$

$$\text{prRI} = 81.5 \pm 2.26 \times 2.97 \times \sqrt{\frac{11}{10}}$$

$$\text{prRI} = 81.5 \pm 7.0 = 74.5 - 88.5$$

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