Letter to the Editor

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No mathematical shortcuts for standardization or harmonization of laboratory measurements

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To the Editor,

The upcoming introduction of the new German healthcare telematics infrastructure (https://www.gematik.de) has led to several publications in recent issues of the *Journal of Laboratory Medicine* [1, 2]. The electronic health card is the most visible part of this new infrastructure. It contains very limited storage space for patient data such as administrative details (e.g. insurance status), e-prescriptions and emergency information. However, this new card can also act as an electronic key to secure an electronic health record on dedicated servers integrated into the telematics infrastructure. Additionally, the telematics infrastructure creates a health information exchange system that allows secure transmission of medical data between all actors of the German health system. In the context of the German Federal Medical Informatics Initiative (http://www.medizininformatik-initiative.de/) and similar international projects [3], the secondary use of routine clinical data, including laboratory findings, for scientific purposes is also gaining relevance.

Hoffmann et al. [1] and Haeckel et al. [2] observed that in electronic health records laboratory measurements that are assay-specific and thus not very comparable might be difficult to interpret. Both groups proposed mathematical calculations that employ reference intervals [LL, UL] of lower (LL) and upper reference limits (UL) to adjust the results from different laboratories. Hoffmann et al. suggested to calculate a so-called *z*log value of a measured laboratory result *x* using the equation

$$z\log(x, \mathrm{LL}, \mathrm{UL}) = \left(\log(x) - \frac{\log(\mathrm{LL}) + \log(\mathrm{UL})}{2}\right) * \frac{3.92}{\log(\mathrm{UL}) - \log(\mathrm{LL})}$$

In this equation, the logarithm transforms an often right-skewed distribution of results to approximate Gaussian form. The *z*log value projects values within the reference interval onto a common interval between –1.96 and 1.96. Haeckel et al. introduced a quantity quotient (QQ) with similarities to the well-known intelligence quotient:

$$\mathrm{QQ}(x, \mathrm{LL}, \mathrm{UL}) = 100 + 40 * \left(\sqrt{x} - \frac{\sqrt{\mathrm{LL}} + \sqrt{\mathrm{UL}}}{2}\right) \Big/ \left(\sqrt{\mathrm{UL}} - \sqrt{\mathrm{LL}}\right)$$

The QQ projects values within the reference interval onto a common interval between 80 and 120.

As already noted [1], because of regulatory requirements from Rili-BÄK or ISO 15189, these new standardized values can only supplement and not replace the traditional data set containing the (untransformed) laboratory results and the reference intervals. However, storing a new value that can be unambiguously and effortlessly inferred from already available information is considered bad software design. Instead, every piece of knowledge should have a single representation within a system to ensure consistency when data is modified [4], also allowing to compute *z*log or QQ representations at runtime.

Although the telematics infrastructure is new in Germany and the scale of this project is impressive, medical informatics has already gained significant experience with similar projects in other countries. The Integrating the Healthcare Enterprise (IHE) initiative, for example, promotes interoperability among health information technology systems worldwide. In the laboratory medicine domain, work has progressed with the support of the College of American Pathologists since 2003 (https://www.ihe.net/IHE_Pathology_and_Laboratory_Medicine/). A key concept is to reuse existing standards (e.g.

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terminologies such as LOINC or SNOMED-CT, messaging standards of the HL7 family). On this basis, health information exchange proved beneficial even though the issue of non-standardized laboratory results have not been specifically addressed. When exchanging laboratory data, Germany should build on experiences from other countries. Changes to long-established standards (e.g. the introduction of new LOINC codes to represent transformed values) need to be well justified.

From the perspective of laboratory medicine, mathematically transformed values relying on reference intervals have severe drawbacks. As reference intervals themselves are not well standardized, the calculated result contains the uncertainty from the reference interval determination as well [5, 6]. Different protocols exist to determine the reference interval from a sample of a reference population or from past measurements stored in a laboratory information system. Factors such as the method employed, the composition of the reference population, or the construction of subgroups all influence the reference interval. Indeed, a study in Australian and New Zealand laboratories found that reference intervals do not compensate for method differences and have a variability unrelated to the measurement [7]. Therefore, the transformed values of exactly the same laboratory result obtained by exactly the same analysis can differ only because of different reference intervals (Figure 1). Common reference intervals are assay independent and therefore cannot contain information for normalization.

Both the proposed equations ensure that laboratory results within the reference interval are projected onto a predefined interval. Consequently, it is easier to distinguish normal from abnormal values. Medical interpretation of laboratory results, however, is more complex. Medical guidelines often recommend actions based on a fine grading of untransformed laboratory values. For some analytes, the reference interval is not very meaningful, because of high interindividual variation. Instead, a longitudinal analysis over time is recommended using concepts such as reference change values to detect changes in medical conditions [8]. Fraser and Harris have developed the index of individuality metric to determine for which analytes population-based reference values are useful. Other approaches aggregate several measurements into key figures such as variability to assess patients [9]. Although the proposed mathematically transformed results facilitate interpretations based on reference intervals, they impede all other methods.

It has been rightfully noted that the interpretation of results measured by multiple laboratories can be challenging. With the advent of health information exchange it becomes even more important that measurements of the same sample lead to the same result. Therefore, laboratory medicine should focus on the standardization of measurements using certified reference materials and reference measurement procedures. If non-commutability or other problems impede this approach, but measurements nevertheless correlate sufficiently, harmonization should be attempted. To this end, a panel of multiple samples is measured with different assays. Observed differences can then be mathematically evaluated to recalibrate each assay. After recalibration, the agreement between assays is higher, so that analysis of one sample produces comparable results on all assays [10]. For some laboratory analyses, assays are so heterogeneous that harmonization has not yet been possible [11] (Table 1). Very often more research and a better understanding of the underlying disease is needed to advance these analyses. These

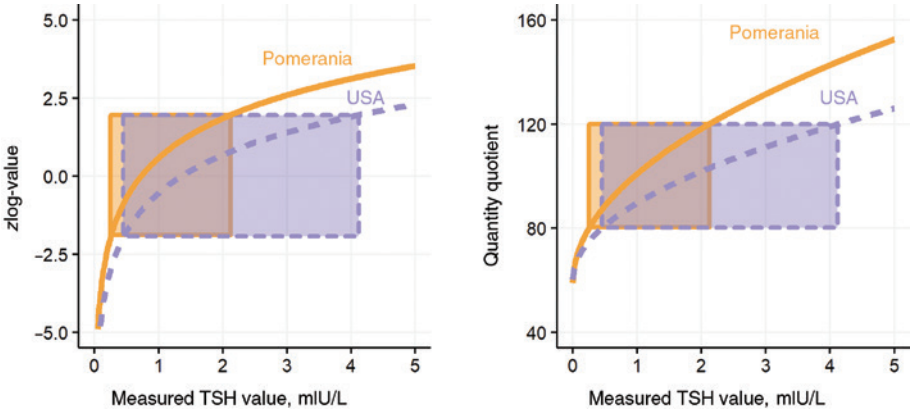

Figure 1: The same measured value leads to different *z*log values or quantity quotients when different reference intervals are used. For TSH measurements, reference intervals were determined in Pomerania, a region in Germany and Poland (0.25–2.12 mIU/L) and in the USA (0.45–4.12 mIU/L) (depicted as colored boxes). Differences in the extent of iodine supply in both populations are the most plausible reason for the diverging reference intervals [5, 6].

Table 1: Anti-cardiolipin IgG measured with three different assays [10].

	Assay 1 Anti-cardiolipin IgG, U/mL	Assay 2 Anti-cardiolipin IgG, U/mL	Assay 3 Anti-cardiolipin IgG, U/mL
Recommended evaluation regarding antiphospholipid syndrome	Negative <10 Positive ≥10	Negative ≤20 Positive >20	Negative <7 Intermediate 7–10 Positive >10
Sample 1	34.4	215.1	159
Sample 2	63.0	674.8	51
Sample 3	34.6	84.9	80
Sample 4	21.7	9.4	5.8
Sample 5	177.0	899.7	77

Assays are so heterogeneous that neither mathematical adjustment nor harmonization is likely to lead to comparable results.

strategies are difficult and time-consuming, but unfortunately there is no mathematical shortcut.

In modern healthcare systems, multimorbid patients are often treated by several specialists in a variety of ambulatory and stationary settings. During this fragmented course of treatment, laboratory analyses are increasingly performed by more than one laboratory. With a health information exchange system, results can be distributed quickly and free of transmission errors and have all information readily available at the place of need. When the results are encoded in a structured way (e.g. by using LOINC and UCUM), different units (creatinine μmol/L and mg/dL) can easily be converted into each other to facilitate interpretation. These benefits likely outweigh the danger of misinterpretation of assay-specific laboratory results for patient treatment. Laboratory medicine should, therefore, embrace the introduction of a telematics infrastructure and act as a steward of laboratory information [12]. As already stated by Hoffmann et al., specialists in laboratory medicine need to ensure that, even when stored electronically, the full laboratory report and not only disjointed results remains accessible. Comments by the laboratory specialist should be clearly visible and their assignments to laboratory request, sample, or analysis must be preserved. Reference intervals and analytical methods employed in the past must be kept in the electronic health record, even if they have later been updated.

While the authors of this letter argue against *storing* mathematically transformed results, the equations are still beneficial. Laboratory reports in an electronic system are not bound by the limitations of a paper-based report. Different electronic views can be adjusted to the needs and health literacy of different user groups. Professionals very likely prefer laboratory results on the traditional scale. Especially laypersons can distinguish between urgent and non-urgent deviations when laboratory results are presented graphically [13]. The proposed equations and standardized color scales can improve these graphical displays. Adoption of LOINC and UCUM to explicitly characterize laboratory analyses, results and units will be crucial to allow pooling of results across sites in the context of scientific reuse in the Medical Informatics Initiative. The applicability of *z*log or QQ representations, and standardized reference intervals for secondary use should be further investigated.

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