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Application of Statistical Features of the Gaussian Distribution Hidden in Sets of Unselected Medical Laboratory Results

JERZY M. JANECKI

Institute of Biocybernetics and Biomedical Engineering,
Polish Academy of Sciences, Warsaw, Poland

The aim of the work was to animate billions of biochemical data obtained from unselected patients and sunk in computer memories of large laboratories. The original method, a software package JEG, allows isolating of the subset of Gaussian distributed values from the low and high values contained in the original data set. In a main parcel of 1455 data sets (1 148 008 results) there were results of systematical analyses of 18 major serum parameters from 6 laboratories. Trueness and reproducibility of the results were examined. The own, indirect laboratory reference limits as well as age and gender dependency of any serum constituent were determined, all without additional blood collection. Statistical comparison with up to 16 sources from the literature showed a significant accordance of 33 from 36 mean and maximal values. The method is fast, fully automatic and simple.

K e y w o r d s: indirect reference distribution; normal distribution; laboratories; inpatients

List of Abbreviations
GRI – Gaussian Reference Intervals, HC – Histographical Curve = smoothed histogram
IQC – Internal Quality Control, JEG – name of the program
MP – main parcel

1. Introduction

IQC verifies only correctness of the preparation of a laboratory to its work. But there are methods that allow controlling the correctness of the laboratory results. Visualizing the distributions of sets of routine, unselected laboratory tests results we found, that they are mostly skew, but "Gaussian-like". Using the own "JEG"-method it is possible to extract reasonable "Gaussian part" from any laboratory data distribution. Archival data sets from many medical laboratories were systematical and comprehensive investigated. Moreover, the averaged statistical features of these Gaussian parts correlated significantly with the general admitted reference ranges.

* Correspondence to: Jerzy M. Janecki, Institute of Biocybernetics and Biomedical Engineering, Polish Academy of Sciences, ul. Ks. Trojdena 4, 02-109 Warsaw, Poland, e-mail: jejan@ibib.waw.pl
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The method enables not only the internal quality control, other than IQC, but also very simple settlement of the own indirect laboratory references, best fitting to the own patients' population. Moreover, any seasonal variation may be determined, any dependency on age or gender easy proved, all without any additional collecting of blood.

2. Material and Method

In the last 10 years great sets (>200) of unselected results obtained from more than 25 Polish and foreign laboratories (USA, Austria, Luxembourg) were investigated. Correlation of the test results with respective clinical diagnoses or patients personal data other than sex and age could not be attempted, because that information is not registered in polish laboratories. The Main Parcel (MP) is made of the 2 to 5 years results from 6 different laboratories [1] (Table 1, A – F). Two of them (C, D) were connected with great general hospitals, two other (A, F) with smaller hospitals with outpatient units, one belonged to a children's hospital (E) and one was located at an outpatient clinic for secondary school (B). Eighteen analytes (listed in the first column in Table 3) were systematically examined. More than 1-year results of some analytes from three great commercial laboratories and many smaller laboratories were also investigated. The quality of work in all these laboratories was kept under constant internal (IQC) and national (by the National Center for Quality Assessment in Laboratory Medicine, Łódź) as well as international control.

Table 1. Overview of the data sets in the Main Parcel

Laboratory	A	B	C	D	E	F
Number of data used	**42** 282	**180** 647	**287** 072	**291** 091	**212** 867	**134** 049
Period from – to	01/Jun/**00** 13/Mar/**02**	13/Jan/**99** 27/Mar/**02**	03/Jan/**00** 01/Jul/**02**	01/Jan/**00** 30/Nov/**01**	02/Jan/**96** 18/Apr/**02**	29/Jun/**00** 19/Aug/**02**
Months	22	39	30	23	75	26
1000 of data/month	**1**.9	**4**.6	**9**.6	**12**.7	**2**.8	**5**.2

Reference values averaged from the data found in up to 16 publications [Table 2 and list at the end of the References] were used for the trueness valuation.

2.1. Program JEG

The JEG computer program [1] enables: 1) constructing of a histogram from a dataset, 2) smoothing this histogram with the kernel density estimation method [2], 3) generating of a scaled Histographic Curve (HC, Fig. 1 left-hand) finally 4) approximating of an appropriate Gaussian curve to the HC (Fig. 1, right-hand). Statistical features of this Gaussian Curve (MV-2SD=min, MV=opt, MV+2SD=max) are called Gaussian Reference Interval (GRI). The height of any HC (its median point) is standardized to a common, fixed level.

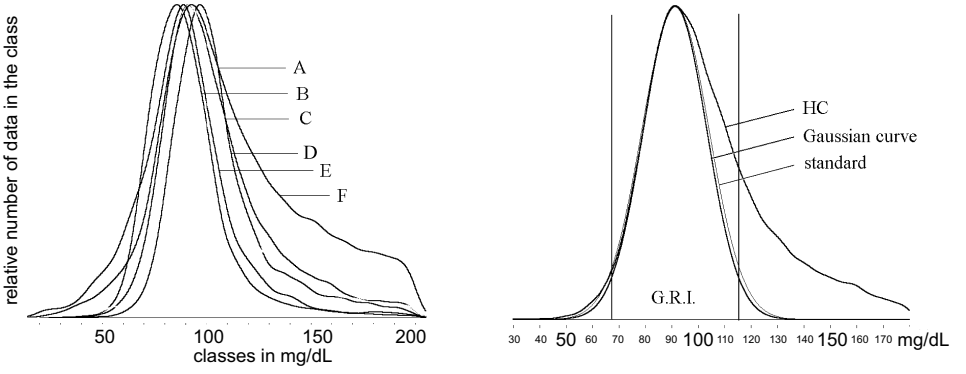

Fig. 1. Standardized histographic curves (HCs) of glucose result distributions from 6 different laboratories (left); (in the original GRI figures horizontal axis means always classes in adequate units, the vertical one always the relative numbers of data in classes). Right: one HC with the full JEG analysis, HC, Gaussian curve (inner curve), Gaussian Reference Interval (GRI) and own laboratory standard (thin line)

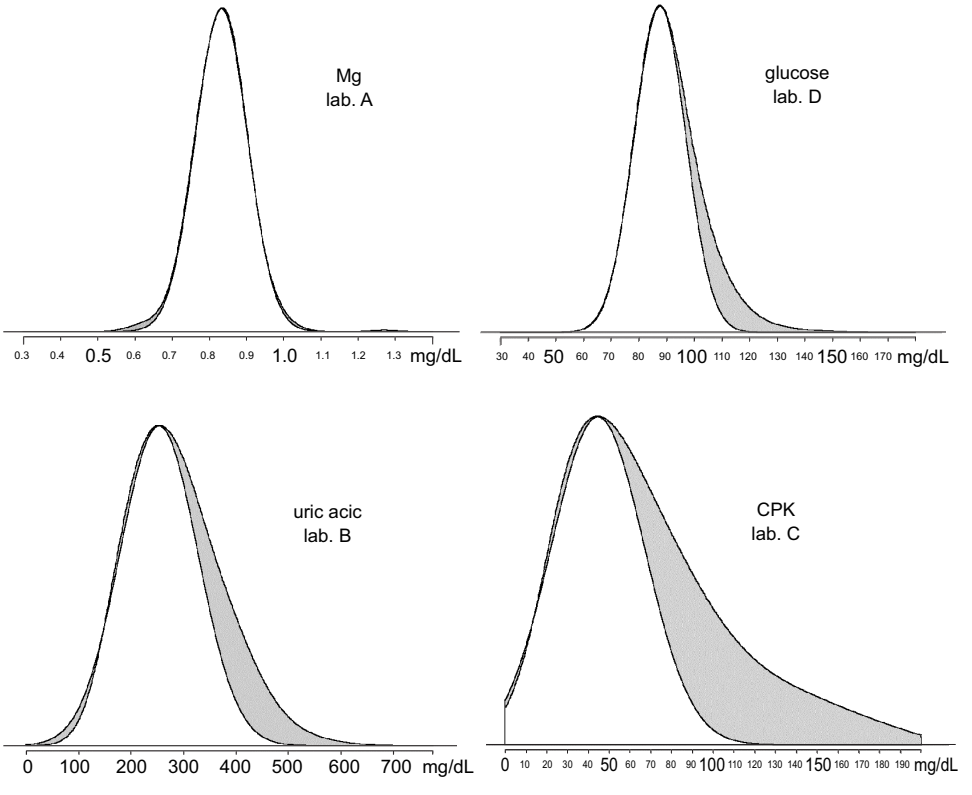

Fig. 2. Examples of the smoothed distributions (HCs) of results of analytes in one of 6 laboratories with the approximated Gaussian curves (shaded – the difference HC-Gauss)

Table 2. List of sources of used reference values. Numbers = upper limits of serum constituents

	Na	K	Cl	glu	krea	UN	ALT	chol	AST	bili	Ca	TG	TP	Mg	UA	ALP	CPK	GGT
	mmol/L				µmol/L	mmol/L	IU/L	mmol/L	IU/L	µmol/L	mmol/L				µmol/L	IU/L		
Amador				6.51		7.88		7.39	25.20									
Back	147	4.8	108	7.20	127	9.4	60	9.40	42	24	2.60	3.80		1	508			25
Boyd	146	5.1	108	6.22	124	8.67	55	7.47	29	24	2.51	2.95	7.9		541	100	374	
Brigden	145	5.1	104	5.94	115		40	5.17	40	20.5	2.50	2.83		0.95		100	200	
Brzezinski	145	5.5	105	6.16	115	9.2	37	5.20	40	21	2.75	1.92	8.3	1.25	327			
Burrit		4.8	108		106	8.5			31		2.50				476			
Burtis	145	5.1	107	5.88	115	7.0	35		40	17.2	2.55		8.3		476			5
Ferre 97	147	4.96			97	7.5	35		27	17	2.49		7.9		337	78		26
Ferre 99	146	5.05			96	7.8	31		29	18	2.48		8.1		345	102		29
Jagarinec	146	5.6	109	6.30	120	8.1	36	6.80	27	23	2.60	3.10	8.1	1.5	400	199	130	29
Kaplan	145	5	111	6.10	92	6.08	55		34	26	2.65		8.14	1.5	458	190	160	37
Reed				7.17		8.66		8.40	55	17.1	2.75		8.3		452	120		
Sibille90	147	4.6	112	6.10	116	8.8	40	7.10	27	26		1.81	8.1		497	106		26
Sibille99	146	4.9	108	5.90	113	8.0	58	6.59	43	31	2.52	1.91	8		462	117	599	47
Solnica	145	5.5	105	6.10	120	6.7	40	5.20	37	17	2.60	2	8	1.2	420	260	180	5
Tomaszewski	145	5	108	5.50	106	6.7	24	6.20	17	20.5	2.70	2	8.7	1.1	475	170	80	35
№ ref	13	14	12	13	14	15	13	11	16	14	14	9	12	7	14	11	7	10
MV ref	146	5.07	108	6.24	112	7.93	42.00	6.81	39.95	21.6	2.59	2.48	8.15	1.09	441.0	140.2	246	35.4
SD ref	0.83	0.29	2.3	0.48	10.7	0.98	15.62	1.36	9.22	4.3	0.09	0.71	0.22	0.11	66.35	56.4	181	10.2

Table 3. Mean values of the optimal (MV) and maximal (MV+2SD). GRI values of the analytes in the main parcel (MP) compared (t test) with the mean values of up to 16 (n ref.) references (ref.)

analyte	n MP	mean MP	SD MP	n ref.	mean ref.	SD ref.	diff. MP-ref	t test
Na opt	6	141.69	2.22	12	140.90	0.88	0.79	1.098
mmol/L max	6	146.91	2.68	13	146.00	0.83	0.91	1.144
K opt	6	4.34	0.15	13	4.33	0.22	0.01	0.131
mmol/L max	6	5.15	0.17	14	5.070	0.29	0.08	0.655
Cl opt	6	104.31	1.30	12	103.00	1.90	1.31	1.510
mmol/L max	6	111.26	2.11	12	108.00	2.30	3.27	2.916
glu opt	6	5.08	0.20	13	5.08	0.33	−0.001	0.007
mmol/L max	6	6.50	0.22	13	6.240	0.48	0.26	1.232
Kre opt	6	75.06	6.79	12	88.70	7.99	−13.64	3.573
µmol/L max	6	108.17	8.16	14	112.00	10.70	−3.83	0.780
UN opt	5	4.80	0.62	13	5.17	0.61	−0.37	1.161
mmol/L max	5	8.22	0.90	15	7.93	0.98	0.29	0.586
ALT opt	6	27.07	5.22	6	23.83	5.14	3.24	1.083
IU/L max	6	44.78	10.08	13	42.00	15.62	2.78	0.396
Cho opt	6	5.38	0.37	9	5.34	0.70	0.04	0.128
mmol/L max	6	7.71	0.41	11	6.81	1.36	0.90	1.565
AST opt	6	21.69	3.85	11	21.13	6.16	0.56	0.199
mmol/L max	6	33.97	6.18	16	39.96	9.22	-5.99	1.462
Bil opt	6	10.28	1.83	11	11.60	1.60	-1.32	1.544
µmol/L max	6	17.88	2.89	14	21.60	4.30	-3.72	1.927
Ca opt	5	2.39	0.07	12	2.40	0.07	-0.01	0.320
mmol/L max	5	2.65	0.08	15	2.59	0.09	0.06	1.275
TG opt	6	1.13	0.11	7	1.35	0.48	−0.22	1.090
mmol/L max	6	1.94	0.22	9	2.48	0.71	−0.54	1.775
TP opt	6	6.96	0.30	11	7.29	0.20	−0.33	2.748
mmol/L max	6	8.26	0.42	12	8.15	0.22	0.11	0.717
Mg opt	6	0.85	0.05	7	0.89	0.075	−0.04	1.239
mmol/L max	6	1.02	0.04	7	1.09	0.11	−0.07	1.483
UA opt	6	263.60	48.90	12	308.20	40.85	−44.60	2.049
µmol/L max	6	428.79	73.66	14	441.00	66.35	−12.21	0.366
ALP opt	6	77.58	18.38	9	106.00	34.70	−28.42	1.827
IU/L max	6	134.43	37.32	11	140.20	56.40	−5.77	0.224
CPK opt	4	134.38	22.90	4	154.00	87.96	−19.60	0.432
IU/L max	4	245.99	44.84	7	246.00	181.00	−0.01	0.000
GGTP opt	6	22.06	4.12	5	19.90	4.29	2.16	0.849
IU/L max	6	43.82	9.68	10	35.40	10.20	8.42	1.628

2.2. Procedure of the Investigation

On the basis of all results of an analyte in a specific laboratory a HC that gives a view on the general type of the distribution is constructed (Fig. 1). A comparison of all HCs from different laboratories enables the visual assessment of the trueness (relative correctness) of each of the HCs. For the examination of the reproducibility

all results of an analyte in a laboratory are divided sequentially into 3–10 (mostly 6) successive equal parts, if possible not smaller than 350 results, and investigated in the same way. A comparison with the averaged references from literature (Table 2 and 3) enables a numerical assessment of the trueness.

3. Results

3.1. Histographical Curve (qualitative and semi-quantitative estimation)

The general shape of a HC is to some extent characteristic for each analyte (Fig. 2). The HCs of some analytes depend more or less distinctly on the gender or/and age of patients (Fig. 3). In a certain but smaller degree it may be typical for a given laboratory (Fig. 1 left-hand), depending on the number and size of pathological results.

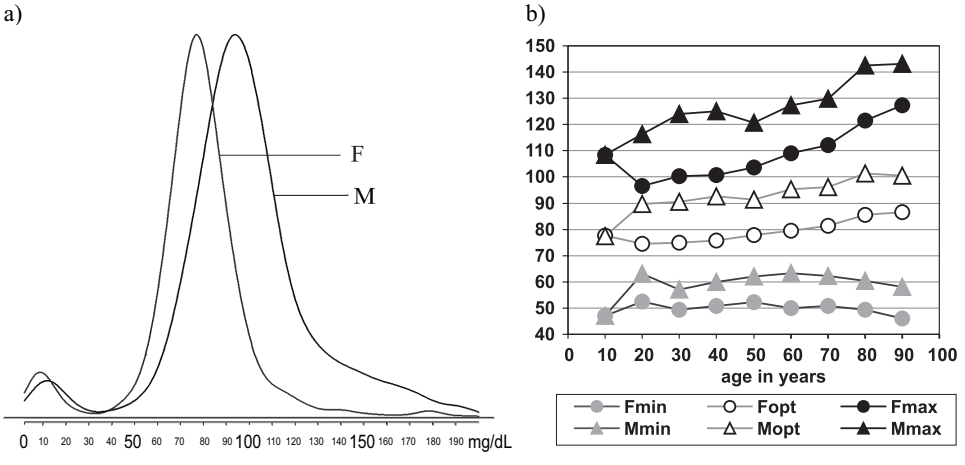

Fig. 3. Differences in creatinine levels depending on sex and age

The examination of the reproducibility is very sensitive and shows always more or less distinct shifts of the successive HCs. Additionally, investigations and experiments show that some untypical HCs result mostly from overlapping of a number of different regular HCs. The greatest part of them results from differences in distributions depending on patient sex and age.

3.2. Gaussian Reference Intervals (Quantitative Measurement)

There is always possible to approximate the Gaussian curve to a nondeformed HC, mostly to one of its arms ("physiological one" [3]) or to the top of the HC (Fig. 2). The JEG program realizes these approximations automatically. At first JEG searches

for the highest point of the HC (the modal). In the second step an appropriate Gaussian curve is approximated to the steeper arm of the HC. Sometimes untypical distributions appear, therefore the shape of the HC and the result of the approximation made automatically by JEG should be visually controlled by any analysis.

In the main picture of the JEG-program the reference bell-curve (which features were previously estimated individually by the user) is shown and compared with the analyzed HC (Fig. 1 right-hand) as the verification of trueness. Finally the JEG program returns a table with the features of all GRIs analyzed in this session. In the present paper standard statistical methods (t test [4, 5]) are used for the comparative calculations.

4. Discussion

The importance and specificity of the described method lies in the fact, that it verifies not the preparation of the laboratory for its work but the results of them.

As early as in 1960 Pryce [6] presented a simple method for defining "normality". He took modal value of unselected samples in a general hospital as the point of reference and superimposed the Gaussian curve on it. We believed that Pryce's original statement: "this statistic simply describes the bulk of the observed population, and does not connote optimum or ideal" very well described the problems in question. In the present study we describe a very similar method which is, however, much simplified and improved, partially due to the use of the specialized JEG computer program. The method is simple and fast, it automatically extracts a Gaussian curve from the smoothed histographic curve (HC). Such an extraction is also possible with use of some mathematical calculations, e.g. [7]. This, however, would not be easy for a physician. Our method lets one to extract the "Gaussian core" from the total distribution, and has several other advantages, especially when compared with numerical calculations reported previously [7, 8].

In spite of numerous discussions published in the literature, the conformity of data obtained from patients to a normal (Gaussian) distribution is still believed to be of fundamental importance [8–14]. At the beginning of our investigation we did not assume that the distributions fitted the Gaussian curve. The problems related to utilization of inpatients' data for determining the reference intervals have been extensively discussed in the literature [3, 7, 15–21], and this inspired us to develop the approach described in this communication. "Absolute health does not exist" said Solberg [21]; we believe that absolute pathology does not exist either. The same author wrote also that "it is possible to be ill in one respect and well in another". An average inpatient has usually a well defined pathology, but this does not exclude the possibility that the values of many parameters of his serum are within the reference ranges. One of the advantages of our method is that it eliminates the high and low (probably pathological) results from the data obtained from unselected patients.

The values obtained with the demonstrated method came surprisingly close to the reference values published previously (Table 2 and 3), and obtained by using much more complicated and time consuming approaches. In any case the method fulfils in a rough, easy and quick way the recommendation concerning the verification of reference values in any laboratory [22] and offers the Patients (Population-) Reference Values [23], useful for solving many diagnostic problems. It is also much easier, more accessible, and cheaper than the big studies cited by Cembrowski et al. [24]

The pictures in Fig. 2 and 3 show, that there is possible to approximate (automatically) a Gaussian curve to a part of the smoothed histogram of any analyte. On the basis of our experience we would conclude that in the major biochemical serum constituents, also in hospital population, the Gaussian distribution may be shown.

The averaged optimal (MV) and maximal (MV+2SD) 33 values of automatically generated GRI in our 4–6 laboratories do not differ significantly from the reference values averaged from 4–16 papers. It seems, that there is advisable to compare the GRI values with the reference ones, to accept GRIs as Laboratory Reference Ranges and that the JEG method renders good services in solving this problem.

Interestingly, for two serum constituents we obtained the GRI values significantly different from the reference ranges published by others. In creatinine and total protein data set optimal data (MV) are significantly lower. We suppose, that this phenomenon is related to the specifity of the investigated population [25]**.**

The exact examination of many thousands of distributions of different analytes from different laboratories enables identification of difficulties in interpretation of some HCs what should not surprise in biological material.

The practical usefulness of similar method was confirmed also by other authors, like Henny at al. [26], Ichihara [27] and some Polish colleagues [e.g. 28] familiar with the JEG-method.

5. Conclusions

1. A JEG method is described, which enables verification of trueness and reproducibility of results obtained in any large laboratory by computerized analysis of archival data sets.

2. Any additional collecting of blood is not necessary.

3. All investigations are done on the basis of the laboratory's own unselected patients' results, independently, but under control of IQC.

4. Results called Gaussian Reference Intervals (GRI) correlate mostly (33/36) with reference limits averaged from the literature and may be used as a Laboratory Reference Range.

5. With the JEG method the sex and age dependence of all serum constituents may be easily determined.

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References

1. Janecki J.: Analysis of the distribution of laboratory results. The statement of Gaussian Reference Intervals. 2004, IBIB PAN, 1–209 (in Polish).
2. Hoser P.: Density estimation of probability distribution with smoothing transformations. Application of mathematics in biology and medicine. Zawoja, 2001, 55–61.
3. Hoffmann R.G.: Statistics in the practice of medicine. J. Am. Med. Assoc. 1963, 185(11), 864–873.
4. Richterich R.: Klinische Chemie. S.Karger, Basel – New York, 1968.
5. Tadeusiewicz R., Izworski A., Majewski J.: Biometria AGH, Kraków 1993 (in Polish).
6. Pryce J.D.: Level of haemoglobin in whole blood and red blood-cells, and proposed convention for defining normality. Lancet, 1960, 2, 333–336.
7. Baadenhuijsen H., Smit J.C.: Indirect estimation of clinical chemical reference intervals from total hospital patient data. Application of a modified Bhattacharya procedure. J. Clin. Chem. Clin. Biochem. 1985, 23, 829–839.
8. Solberg H.E.: Statistical treatment of reference values in laboratory medicine: testing the goodness-of-fit of an observed distribution to the Gaussian distribution. Scand. J. Clin. Lab. Invest. 1986, 46, Suppl. 184, 125–132.
9. Albert A., Harris E.K.: Multivariate Interpretation of Clinical Laboratory Data. Marcel Dekker Inc. New York 1987.
10. Altman D.G.: Statistics notes: the normal distribution. BMJ 1995, 310(6975), 298.
11. Armitage P., Berry G.: Statistical Methods in Medical Research. Blackwell Scientific Publications, Oxford 1994, 66–71.
12. Bhattacharya C.G.: A simple method of resolution of a distribution into Gaussian components. Biometrics 1967, 115–135.
13. Feng Z., McLerran D., Grizzle J.: A comparison of statistical methods for clustered data analysis with Gaussian error. Statistics in Medicine 1996, 15, 1793–1806.
14. Harris E.K., Boyd J.C.: Statistical Bases of Reference Values in Laboratory Medicine. Marcel Dekker Inc., New York, 1995.
15. Zender R.: Study of critical values of plasma concentration of cholesterol in hospitalised patients by an enzymatic method (in French). Ann. Biol. Clin. (Paris) 1977, 35, 57–66.
16. Djurhuus M.S., Rohold A., Vadstrup S., Petersen P.H., Uldall A.: Reference intervals based on hospitalized 'healthy' patients and medical students in relation to analytical bias for serum potassium. Scand. J. Clin. Lab. Invest. 1992, 52, 305–312.
17. Young D.S.: Determination and validation of reference intervals. Arch. Pathol. Lab. Med. 1992, 116, 704–709.
18. Spiekerman A.M., Rudolph R.A., Bernstein L.H.: Determination of malnutrition in hospitalized patients with the use of a group-based reference. Arch. Pathol. Lab. Med. 1993, 117(2), 184–186.

19. Kairisto V., Virtanen A., Uusipaikka E., Viopio-Pulkki L.M., Peltola O., Irjala K.: Method for determining reference changes from patients' serial data: example of cardiac enzymes. Clin. Chem. 1993, 39, 11Pt1, 2298–2304.
20. Kouri T., Kairisto V., Virtanen A., Uusipaikka E., Rajamaki A., Finneman H et al.: Reference intervals developed from data for hospitalized patients: Computerized method based on combination of laboratory and diagnostic data. Clin. Chem. 1994, 40, 2209–2215.
21. Solberg H.E.: Using a hospitalized population to establish reference intervals: pros and cons. Clin. Chem. 1994, 40, 2205–2206.
22. Westgard J.O., Clee G.G.: Quality management. Verification of reference intervals. Tietz Textbook of Clinical Chemistry. WB Saunders Comp., Philadelphia 1994, 559.
23. Gräsbeck R., Saris N-E.: Establishment and use of normal values. Scand. J. Clin. Lab. Invest., 1969, Suppl 110, 62–63.
24. Cembrowski G.S., Fairbanks V.F.: Can hematology reference intervals be derived from hospitalized patient's data? Clin. Chem., 1995, 41 (7), 1048–1050.
25. Janecki J.: Low level of total protein and their metabolits in serum of polish population. Investigation with the analytical JEG method. (in Polish, abstract in English). „Żywienie Człowieka i Metabolizm", 2006**,** 33 (2),123–133.
26. Henny J., Petitclerc C., Fuentes-Arderiu X., Petersen P.H., Queralto J.M., Schiele F., Siest G.: Need for revisiting the concept of reference values. Clin. Chem. Lab. Med. 2000, 38(7), 589–595.
27. Ichihara K., Matsuda N.: Derivation of latent reference intervals from routine laboratory database: its principle, validity and methodological implications for laboratory informatics. Rinsho Byori 1996 March, 44(3), 245–259.
28. Brzeziński A.: Intralaboratory analytical control of the reliability of laboratory results (IQC). Recommended standards (in Polish) Diagn. Lab., 2003, 39, suppl 1, 1–119.
29. Janecki J., Buga B.: Use of the JEG metod in a great commercial laboratory (in Polish) Diagn.Lab. 2004, 40, 519.
30. Janecki J., Urbaniak A.: Statement of the own reference limits on the basis of the own routine examinations Diagn. Lab. 2006, 42, 63–73 (in Polish, abstract in English).

List of sources of used reference values

Amador E., Bartholomew P.: Indirect methods for estimating the normal range Am. J. Clin. Pathol. 1969, 52(5), 538–546.

Bäck S-E., Nilsson J-E., Fex G., Jappson J-O., Rosen U.,Tryding N., von Schenck H., Norlund L.: Towards common reference intervals in clinical chemistry. Clin. Chem. Lab. Med. 1999, 37(5), 573-592.

Boyd J.C., Lacher D.A.: A multi-stage Gaussian transformation algorithm for clinical laboratory data. Clin. Chem. 1982, 28(8), 1735–1741.

Brigden M.L., Heathcote J.C.: Problems in interpreting laboratory tests. Postgraduate Medicine, 2000, 107 (7), 145–162.

Burritt M.F., Slockbower J.M., Forsman R.W., Offord K.P., Bergstralh E.J., Smithson W.A.: Pediatric reference intervals for 19 biologic variables in healthy children. Mayo Clin. Proc. 1990, 65, 329–336.

Burtis C.A., Ashwood E.R.: Tietz Textbook of Clinical Chemistry. WB Saunders Comp., Philadelphia 1994, Appendix: 2176–2211.

Ferre-Masferrer M., Fuentes-Arderiu X., Alvarez-Funes V., Guell-Miro R., Castineiras-Lacambra M.J.: Multicentric reference values: shared reference limits. Eur. J. Clin. Chem. Clin. Biochem. 1997, 35(9), 715–718.

Ferre-Masferrer M., Fuentes-Arderiu X., Puchal-Ane R.: Indirect reference limits estimated from patients' results by the three mathematical procedures. Clin. Chim. Acta 1999, 279 (1–2), 97–105.

Jagarinec N., Flegar-Mestric Z., Surina B., Vrhowski-Hebrang D., Preden-Kereković V.: Pediatric reference intervals for 34 biochemical analysis in urban school children and adolescents Clin. Chem. Lab. Med. 1998, 36(5), 327–337.

Kaplan L.A., Pesce A.J.: Clinical chemistry. CVMosby Co., St Louis, 1989, 864–873.

Reed A.H., Cannon D.C., Winkelman J.W., Bhasin Y.P., Henry R.J.: Pileggi Estimation of normal ranges from a controlled sample survey. I Sex- and age-related influence on the SMA 12/60 screening group of tests. Clin. Chem. 1972, 18 (1), 57–66.

Sibille M., Durand D.Vital.: Laboratory screening method for selection of healthy volunteers. Eur. J. Clin. Pharmacol. 1990, 39, 475–479.

Sibille M., Deigat N., Durieu I., Guillaumont M., Morel D., Bienvenu J., Massignon D., Durand D.V.: Laboratory data in healthy volunteers: reference values, reference changes, screening and laboratory adverse event limits in Phase I clinical trials. Eur. J. Clin. Pharmacol. 1999, 55, 13–19.

Solnica B.: Kalendarz Medycyny Praktycznej 2002, Wybrane badania laboratoryjne. Medycyna Praktyczna, Kraków, 2003, 120–122.

Tomaszewski J.: Diagnostyka laboratoryjna, PZWL, Warszawa 1997.