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# Traceability as a means to obtain worldwide useful reference intervals


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**IFCC,** The Committee on Reference Intervals and Decision Limits (**C-RIDL**), **Chair**

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UNIVERSITÀ DEGLI STUDI DI MILANO

Centre for Metrological Traceability in Laboratory Medicine (CIRME)

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***10th International Scientific Meeting. November 17-18, 2016***


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# Uludag University, Medical Faculty, Teaching and Research Hospital, Bursa, Turkey

# Contents

- Reliable reference intervals (RIs) and Common RIs
- Muticenter studies (C-RIDL)
- Traceability
- Comparability
- Conclusions

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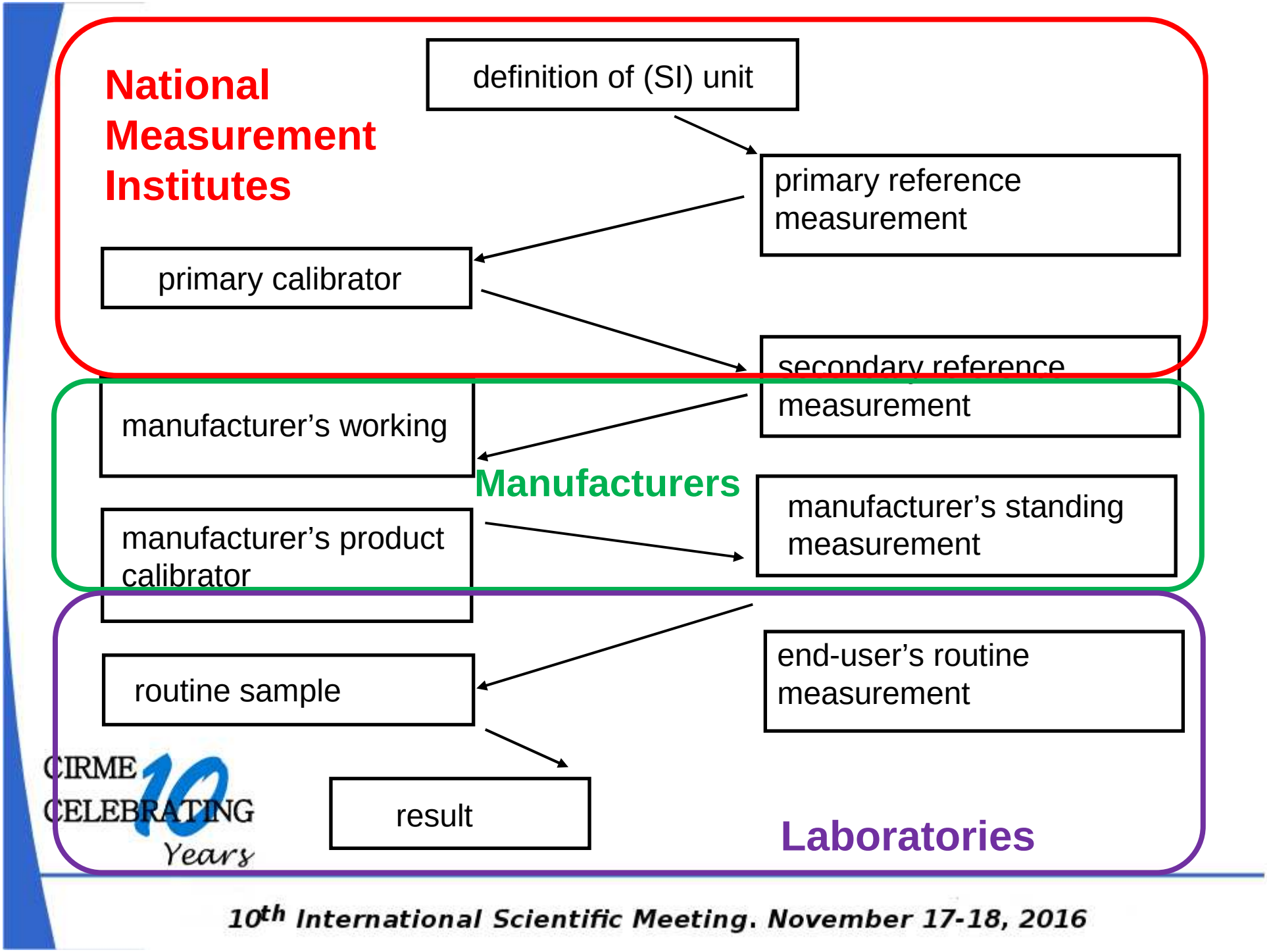
National Measurement Institutes
definition of (SI) unit
primary reference measurement
primary calibrator
secondary reference measurement
manufacturer's working
Manufacturers
manufacturer's standing measurement
manufacturer's product calibrator
routine sample
end-user's routine measurement
result
Laboratories

# How to obtain reliable RIs?

- A reference measurement system for the analyte
  - reference materials
  - reference methods
  - reference laboratory network

reduce the measurement uncertainty

implement measurement traceability

# How to obtain reliable common RIs?

- A reference measurement system for the analyte
  - reference materials
  - reference methods
  - reference laboratory network
- To produce common RIs, the trueness of laboratoies verified

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NORIP Reference Material; NFKK Reference Serum X

RV recalculated according to the target values of Serum X

- AST, ALT, GGT measured in three centers
- Trueness control materials at three different concentrations
- Aligned to the expected values assigned by the reference labs

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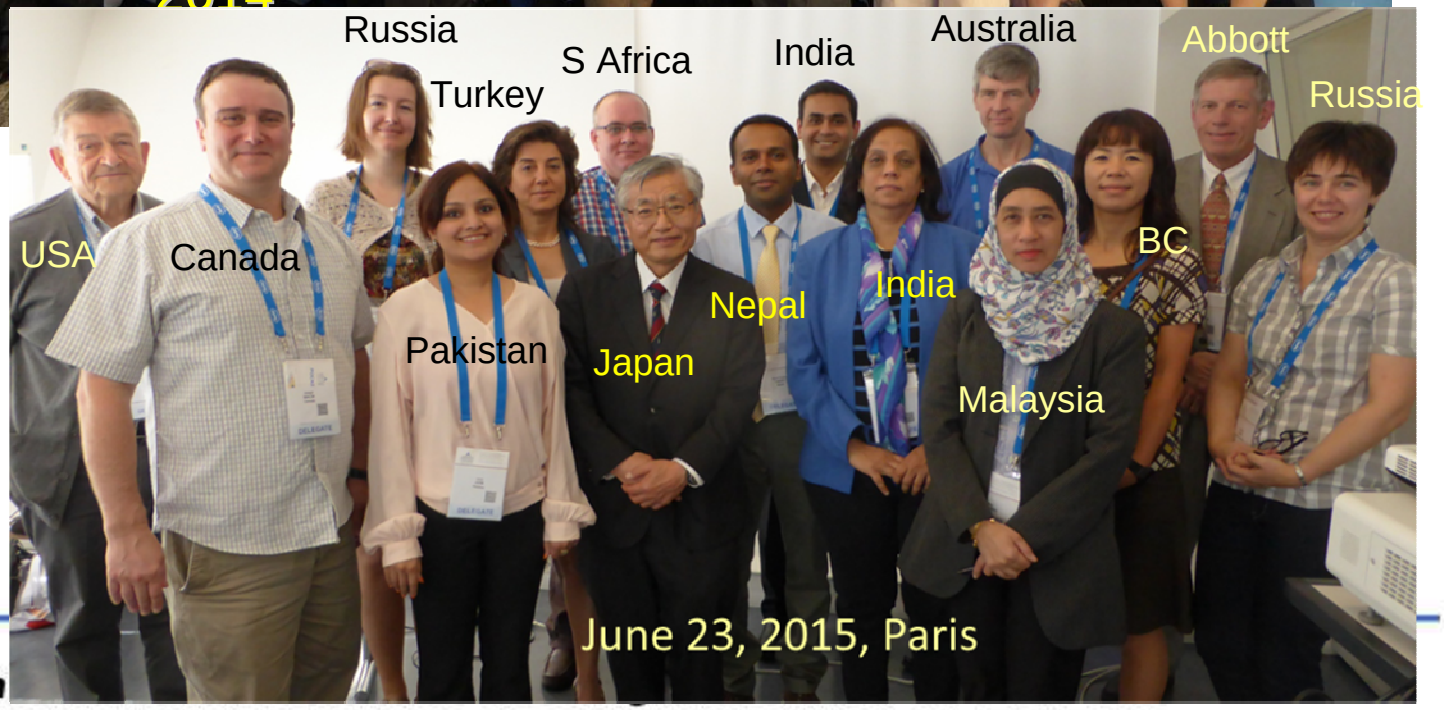
# The IFCC, C-RIDL global multicenter study, 2011


USA
China
Saudi A.
S. Africa
Canada
Nepal
Russia
Australia
China
Bangladesh
Japan
Turkey
Russia
USA
BC
C-RIDL in Istanbul, June22-24, 2014


UK, SD
Chair


Russia
Turkey
S Africa
India
Australia
Abbott
Russia
USA
Canada
Pakistan
Japan
Nepal
India
BC
Malaysia
June 23, 2015, Paris

# Objectives of the IFCC global study-1

- Standardisation of the multicenter study

(1)To obtain test results traceable to the reference measurement procedure

(2)To allow each country to run a multicenter study using the common protocol

DE GRUYTER DOI 10.1515/cclm-2013-0249 — Clin Chem Lab Med 2013; aop

Yesim Ozarda, Kiyoshi Ichihara*, Julian H. Barth, George Klee and on behalf of the Committee on Reference Intervals and Decision Limits (C-RIDL), International Federation for Clinical Chemistry and Laboratory Medicine

# Protocol and standard operating procedures for common use in a worldwide multicenter study on reference values

## Abstract

The reference intervals (RIs) given in laboratory reports have an important role in aiding clinicians in interpreting test results in reference to values of healthy populations. In this report, we present a proposed protocol and standard operating procedures (SOPs) for common use in conducting multicenter RI studies on a national or international scale. The protocols and consensus on their contents were refined through discussions in recent C-RIDL meetings. The protocol describes in detail (1) the scheme and organi-

**George Klee,** MD, PhD: Laboratory Medicine and Pathology, Mayo Clinic College of Medicine, Rochester, MN, USA

## 1 Introduction

The interpretation of data in laboratory medicine is a comparative decision-making process, and reference intervals (RIs) given in laboratory reports have an important role in aiding the clinician in interpreting test results in reference to values for healthy populations. Careful determina-

# Objectives of the IFCC global study-2

- Worldwide comparison of reference values

(1) To make test results comparable across countries through measurement of a panel of sera

(2) To explore sources of variations*on a global scale from the aligned results

* Race, region, gender, age, BMI, lifestyle-related factors

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# Requirements of the Central Laboratory

- **Standardization of the assay**

  Standard Reference Materials and Trueness Control Materials

- **Quality Control**

  Panel of Sera–5 healthy individuals, each measurement day

- **Cross Comparison between centres**

  Panel of sera–80 healthy individuals, divided into 4, tested on 4 separate days

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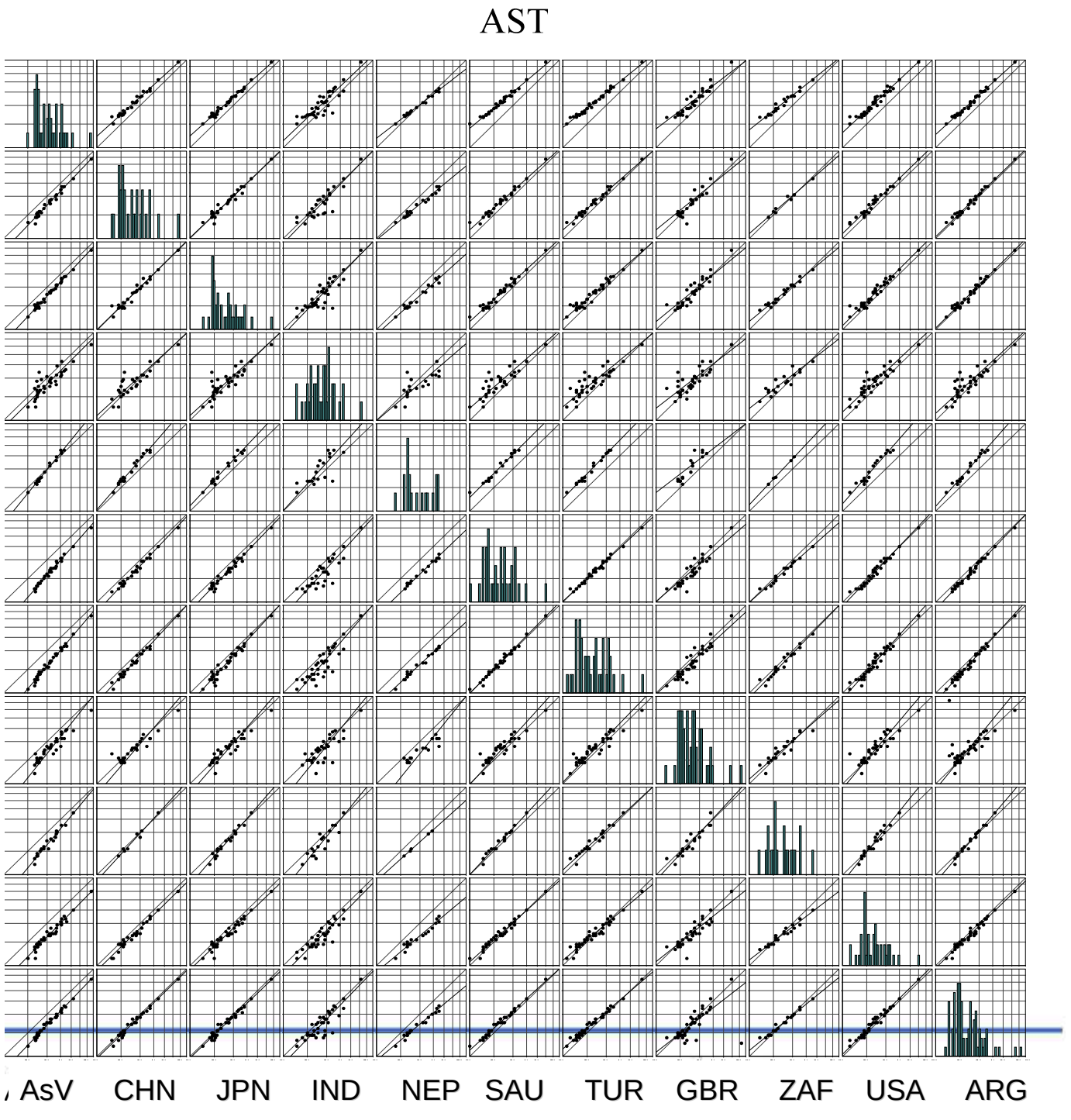
The use of the panel allows highly reliable recalibration of RVs for all analytes

Based on the panel test results, a between-laboratory value conversion scheme

# Comparison of panel test results for AST

Based on the linear relationship of the assigned and measured values, the test results were recalibrated.

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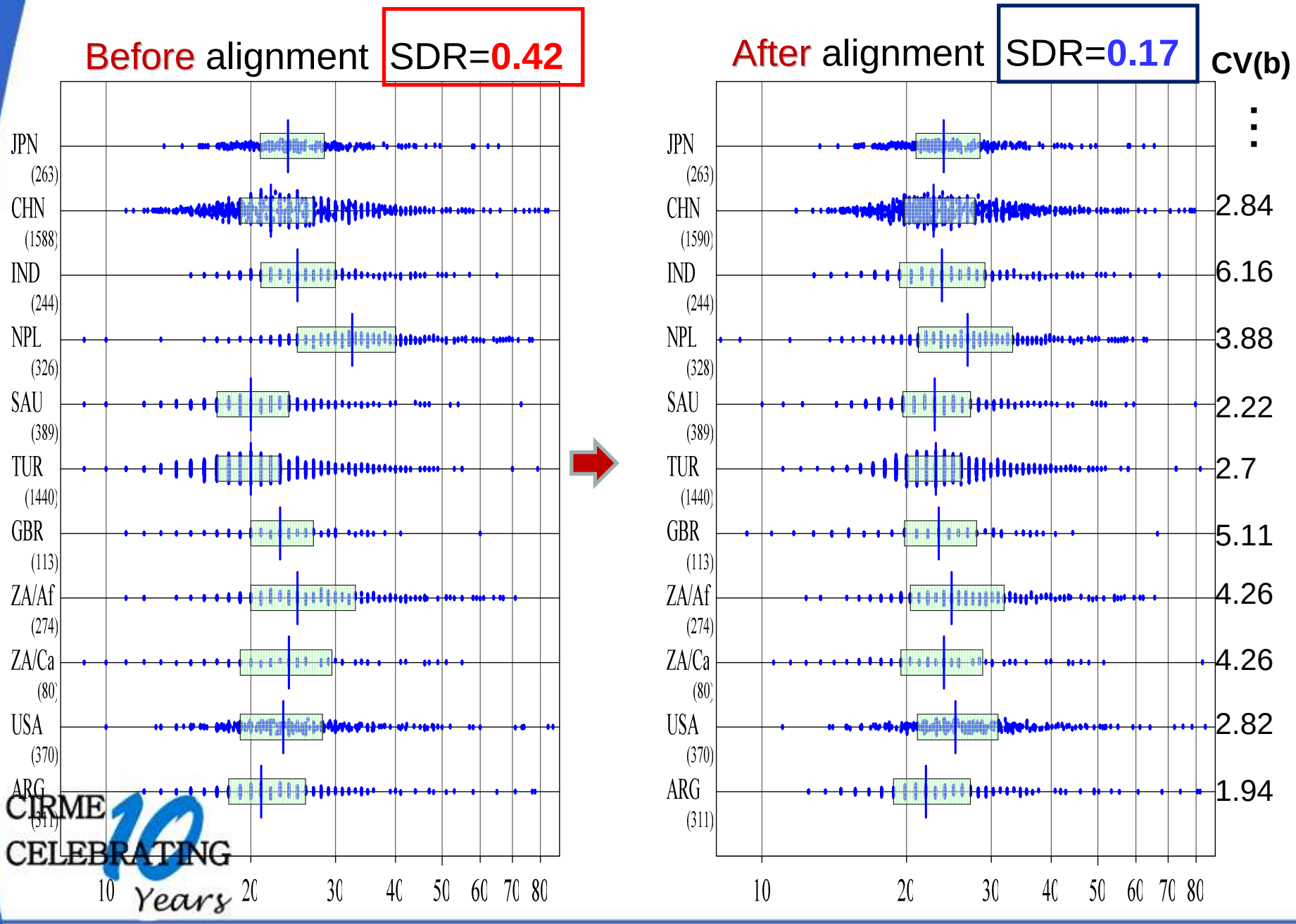
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After alignment SDR=0.17
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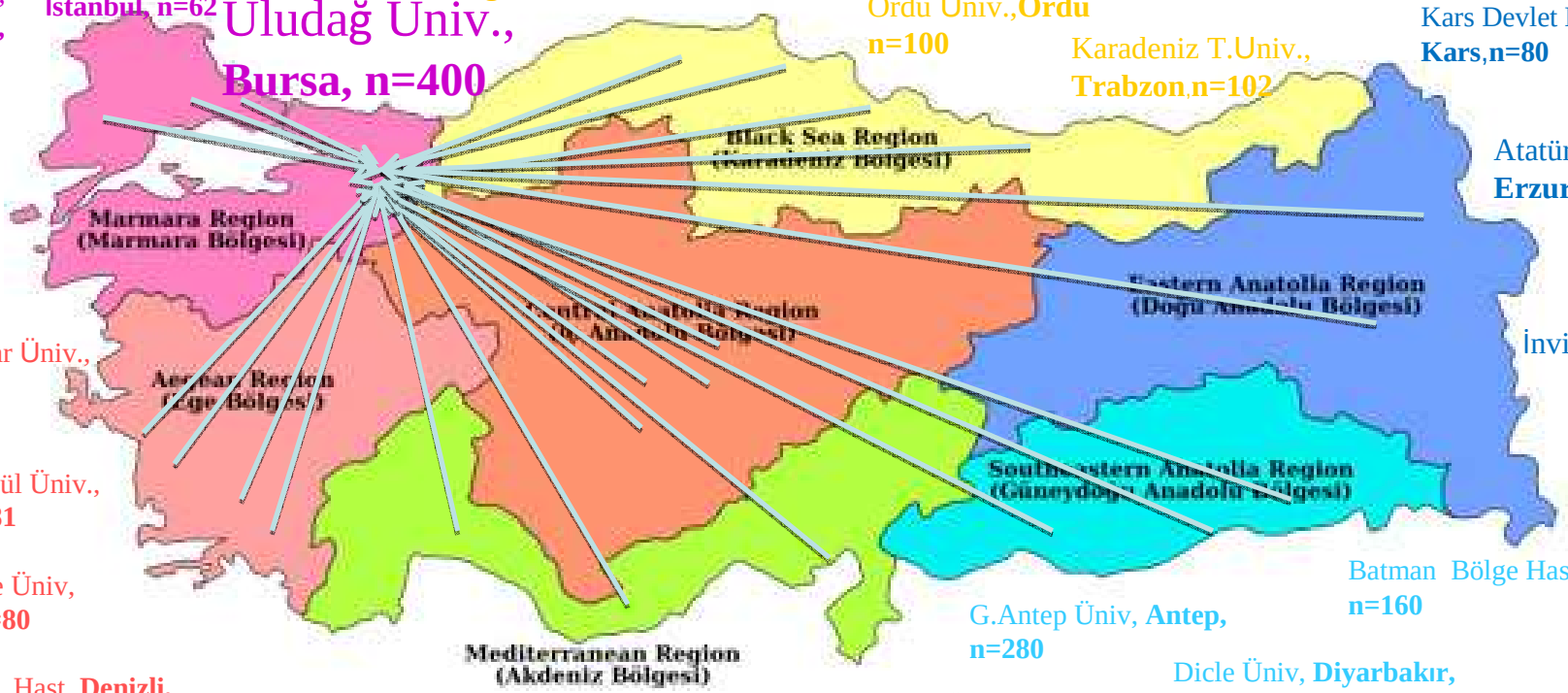
JPN (263)
CHN (1588)
IND (244)
NPL (326)
SAU (389)
TUR (1440)
GBR (113)
ZA/Af (274)
ZA/Ca (80)
USA (370)
ARG (311)
JPN (263)
CHN (1590)
IND (244)
NPL (328)
SAU (389)
TUR (1440)
GBR (113)
ZA/Af (274)
ZA/Ca (80)
USA (370)
ARG (311)
2.84
6.16
3.88
2.22
2.7
5.11
4.26
4.26
2.82
1.94
10 20 30 40 50 60 70 80
AST U/L
10 20 30 40 50 60 70 80
AST U/L

# Multicenter, nationwide RI study for common biocehmical analytes in TURKEY




Selçuklu Üniv., Selçuklu, **Konya,n=100**

Ankara Eğitim Hast, **Ankara,n=69**

Hacettepe Üniv., **Ankara,n=119**

GATA, **Ankara,n=40**

NEB Üniv., Meram, **Konya,n=80**

İstanbul Univ., Kard. Enst. **İstanbul, n=80**

Lüleburgaz Dev. Hast., **Kırklareli, n=48**

Şişli Etfal Eğitim Hast., **İstanbul, n=62**

Karaelmas Üniv., **Zonguldak,n=102**

OM Üniv.,**Samsun n=100**

Keçi Ören Eğitim Hast., **Ankara,n=40**

Ordu Univ.,**Ordu n=100**

Karadeniz T.Univ., **Trabzon,n=102**

Kars Devlet Hast., **Kars,n=80**

Atatürk Üniv., **Erzurum,n=240**

İnvitro Lab, **Ela**

Celal Bayar Üniv., **Manisa, n=120**

Dokuz Eylül Üniv., **İzmir, n=81**

Pamukkale Üniv, **Denizli,n=80**

Servergazi Hast, **Denizli, n=115**

Akdeniz Üniv, **Antalya, n=45**

Mersin Üniv, **Mersin,n=100**

Adana Başkent Üniv, **Adana,n=100**

G.Antep Üniv, **Antep, n=280**

Batman Bölge Hast., **Batman, n=160**

Dicle Üniv, **Diyarbakır, n=128**

Medical Park Hast. **Antalya, n=80**

SRMs and panel of sera used to ensure the traceability and comparability of the test results in Bursa.

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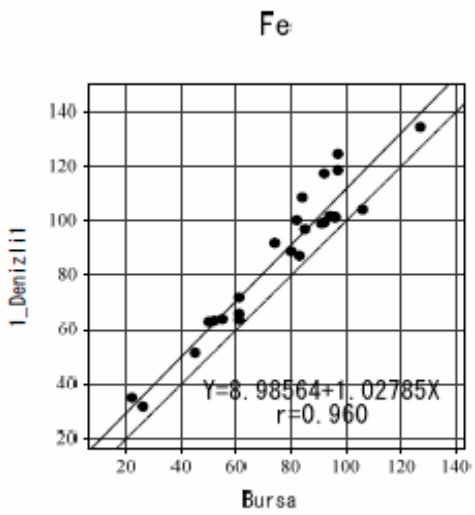
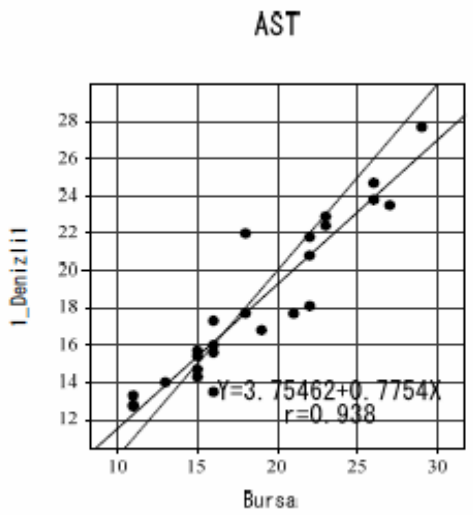
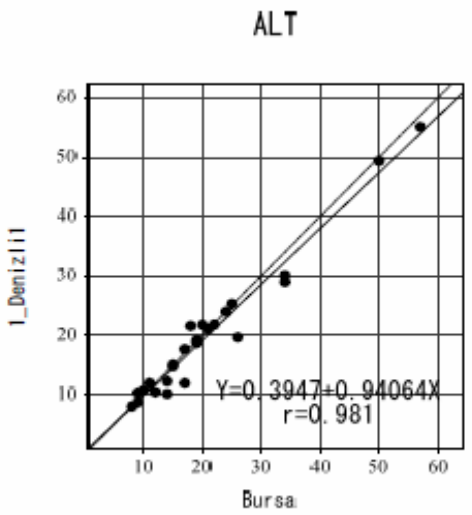
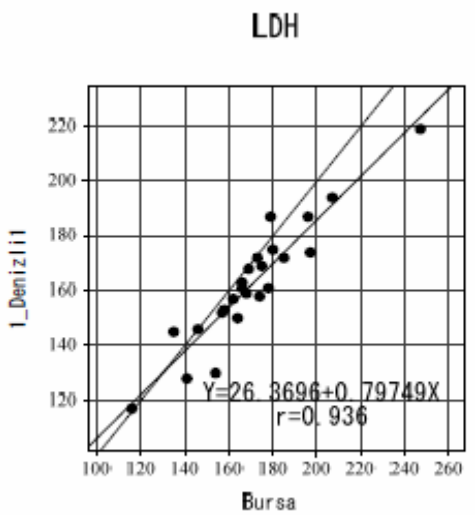
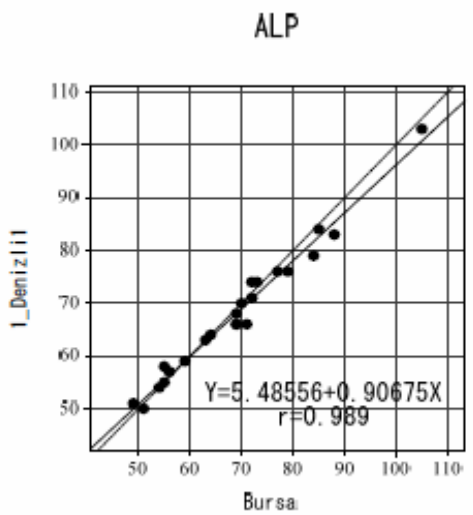
As there were no significant differences, we obtained nation-wide CRIs for Turkey.

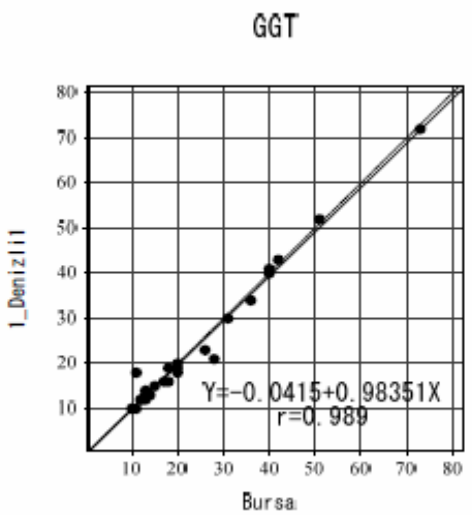
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Using the regression lines, laboratory-specific RIs derived for each parameter

Biochemia Medica 2016;26(1):5-16

## Multicenter studies can be organised as -

1) Only the central laboratory is to analyse all the samples from all the participating laboratories (simpler, more reliable results)

2) Each participating laboratory is to analyse its own samples (more complex planning)

## as an example of the 2.option

## Multicenter, nationwide RI study for hematological parameters in TURKEY

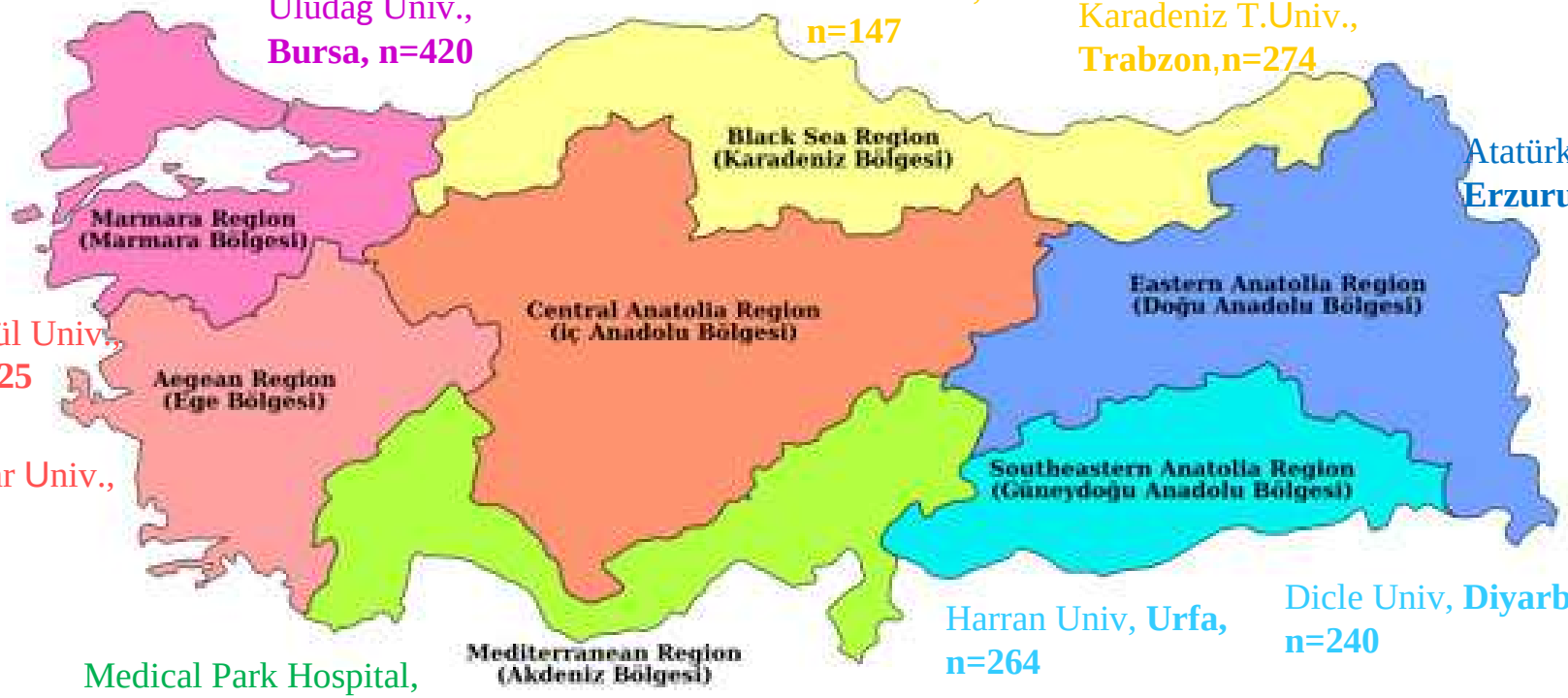
Selçuklu Univ.,
Selçuklu,
**Konya,n=260**

Keçi Ören Hosp,
**Ankara,n=401**

Uludağ Univ.,
**Bursa, n=420**

Ordu Univ.,**Ordu**
**n=147**

Karadeniz T.Univ.,
**Trabzon**,**n=274**




Atatürk Univ.,
**Erzurum**,**n=48(**

Dokuz Eylül Univ.,
**İzmir, n=225**

Celal Bayar Univ.,
**Manisa,**
**n=201**

Harran Univ, **Urfa,**
**n=264**

Dicle Univ, **Diyarbakır,**
**n=240**

Medical Park Hospital,
**Antalya, n=150**

Mersin Univ,
**Mersin,n=230**

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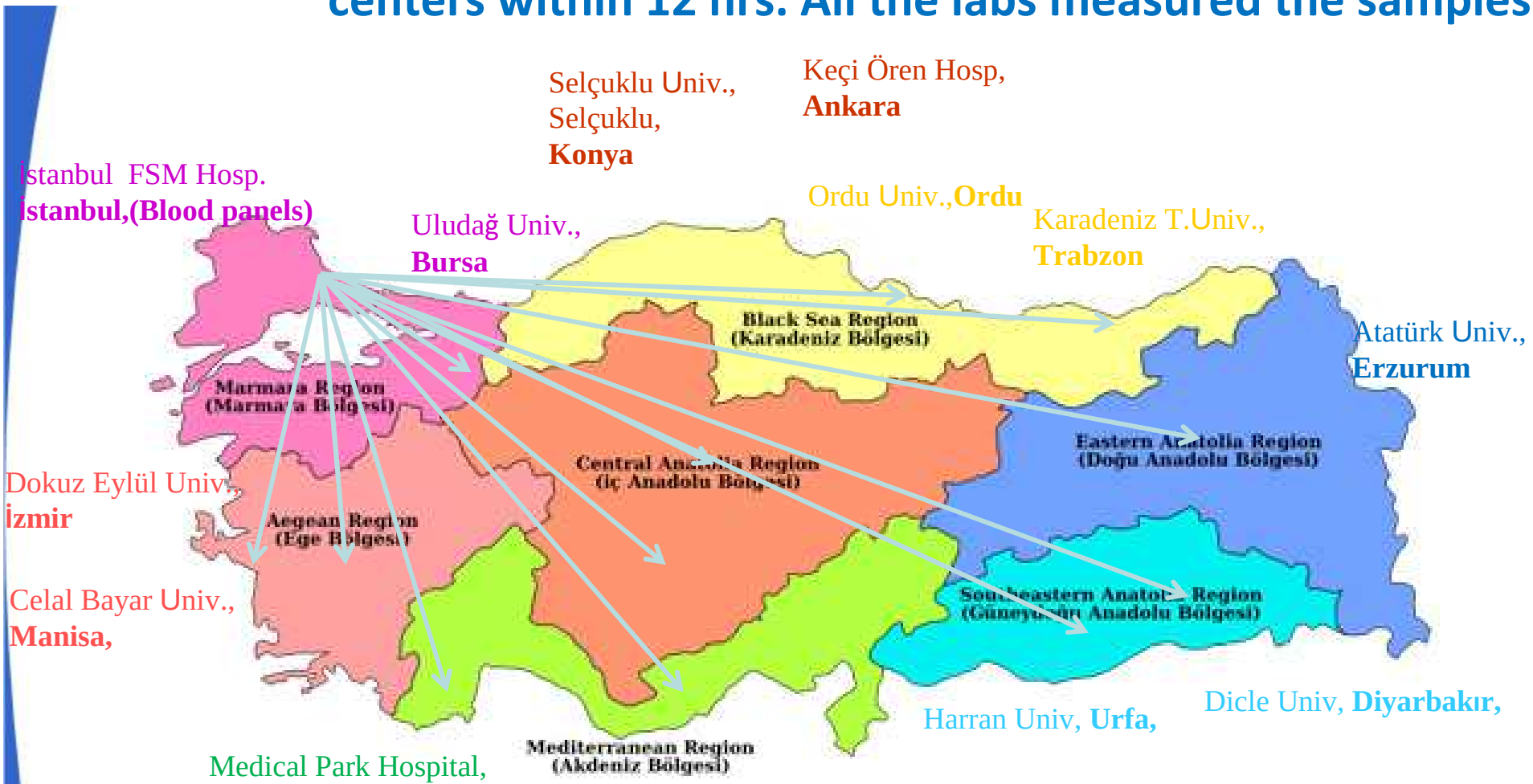
The EDTA blood samples analyzed within 2 hrs in the participating labs

# Panel of EDTA blood prepared in a single centre, distributed to all the centers within 12 hrs. All the labs measured the samples




**There is no SRM for most of the hematological parameters**

# The results of ANOVA

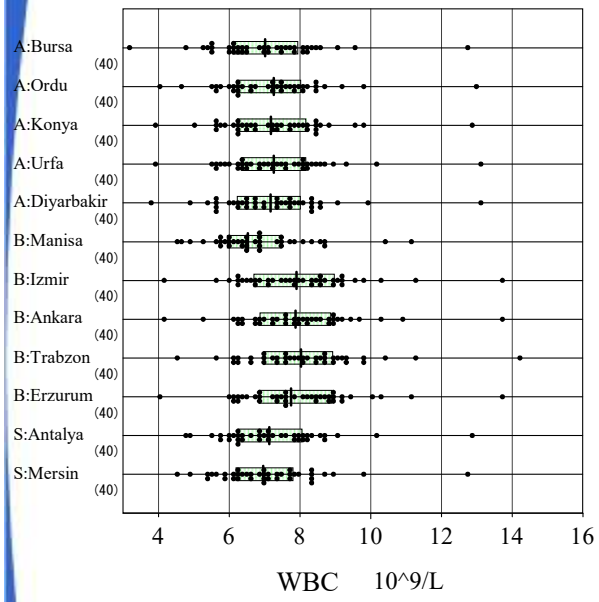
## Panel test results

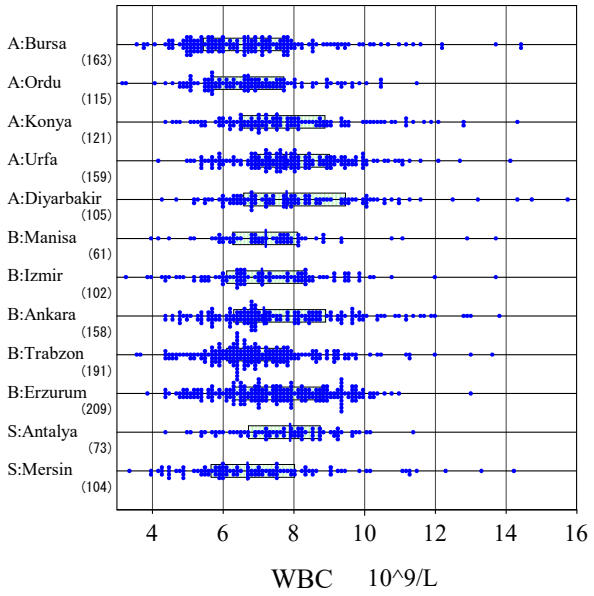
## Volunteer test results

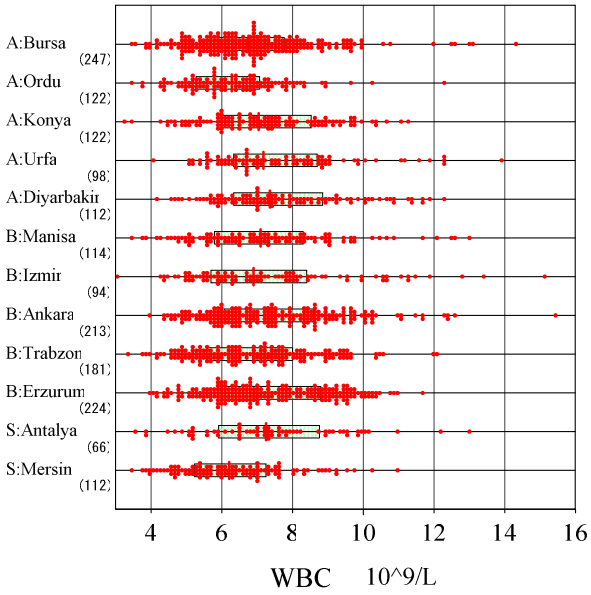
$SDR_{BL1}$=0.24

$SDR_{BL2M}$=0.27

$SDR_{BL2F}$ =0.23




Male

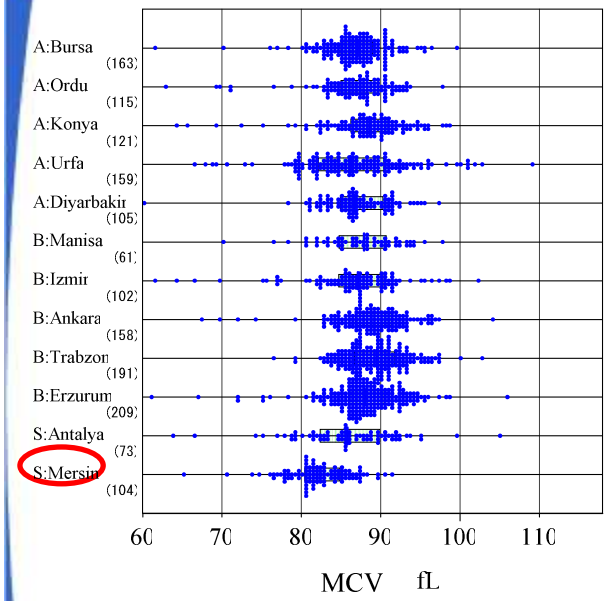
Female

there was no difference among the participating labs

# The results of ANOVA

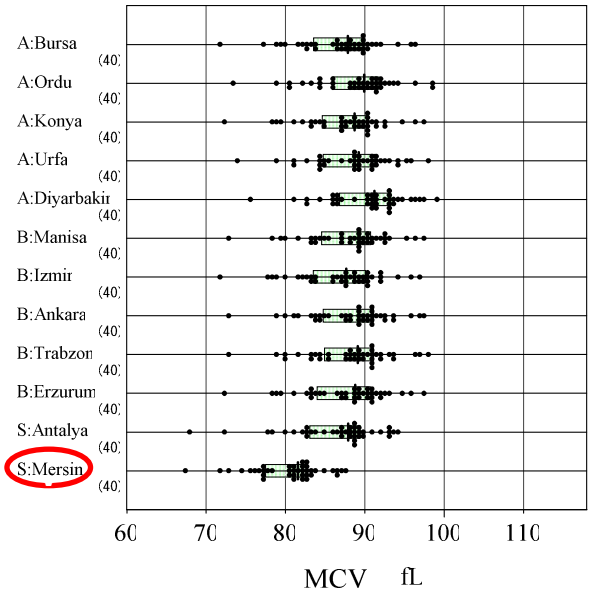
## Panel test results

$SDR_{BL1}$ =0.44⇒0.15*

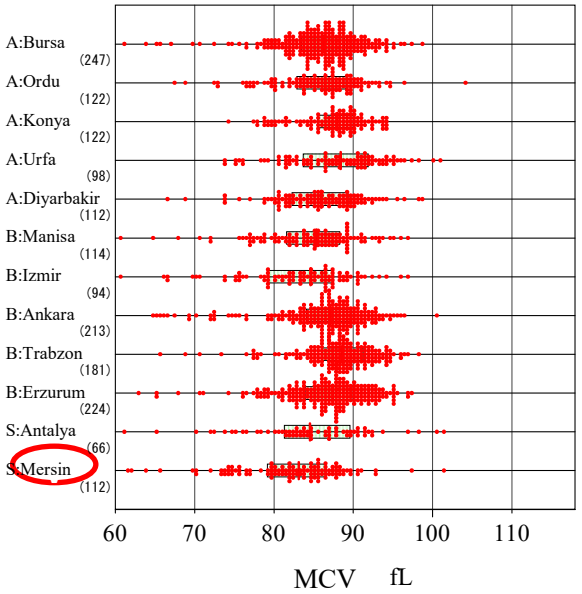



## Volunteer test results

$SDR_{BL2M}$ =0.36⇒0.22*




$SDR_{BL2F}$ =0.31⇒0.27*




* between-lab SDR after excluding Mersin

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the data to be combined and CRIs to be derived

Clinica Chimica Acta 432 (2014) 4–7

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Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

# Harmonization of laboratory testing — Current achievements and future strategies

Jillian R Tate [a,*], Roger Johnson [b], Julian Barth [c], Mauro Panteghini [d]

| Phase | Requirements | Vested stakeholders |
|---|---|---|
| Pre-pre-analytical | 1. Use of evidence-based guidelines for appropriate test selection. | 1. Clinicians; the laboratory community; guideline organizations. |
| | 2. Plan for implementation and educational phases. | 2. Professional societies; the laboratory community. |
| Pre-analytical | 1. Standardize pre-laboratory/external pre-analytical processes. | 1. Healthcare practitioners e.g. phlebotomist; laboratory personnel. |
| | 2. Implement SOPs to reduce error and ensure patient safety. | 2. WHO World Alliance for Patient Safety; CLSI; IFCC WG-LEPS. |
| Analytical | 1. Harmonize patient results through a standardization and/or harmonization process. | 1. JCTLM; national metrology institutes; reference material providers; IFCC; IVD manufacturers; EQAS organizers; clinical laboratories. |
| | 2. Harmonize laboratory test names and units. | 2–4. Clinical terminology and information systems providers; IUPAC; IFCC C-NPU; Governments; patient safety groups. |
| | 3. Standardize test requesting and reporting for the EHR. | |
| | 4. Harmonize report formats where there are patient safety issues. | |
| | 5. Monitor reliability of analytical systems and analytical quality of measurements. | 5. IVD manufacturers; EQAS organizers; clinical laboratories. |
| Post-analytical | 1. Harmonize reference intervals and clinical decision limits. | 1–2. Professional societies; IFCC C-RIDL; the laboratory community; clinicians. |
| | 2. Plan for implementation and educational phases. | |
| | 3. Report critical patient values according to an agreed critical test list. | 3. Laboratory personnel; clinicians; GPs. |
| Post-post-analytical | 1. Educate users about the meaning of laboratory tests. | 1. Clinicians; GPs; consumer advocate groups; patients. |
| | 2. Develop an on-going laboratory-clinical systems provider working relationship for long-term sustainability of pathology harmonization. | 2. The laboratory community; clinicians; systems providers. |

refers to the use of the CRIs across different platforms and/or assays for a specified analyte

## A checklist approach

Plan for the implementation of adult and pediatric CRIs

# Conclusions

- Common reference intervals are of great interest
- Need for standardized multicenter studies
- Traceability is the most critical issue
- Comparability of the laboratories
- Harmonization of RIs; **direct studies,** consensus procedure including indirect studies

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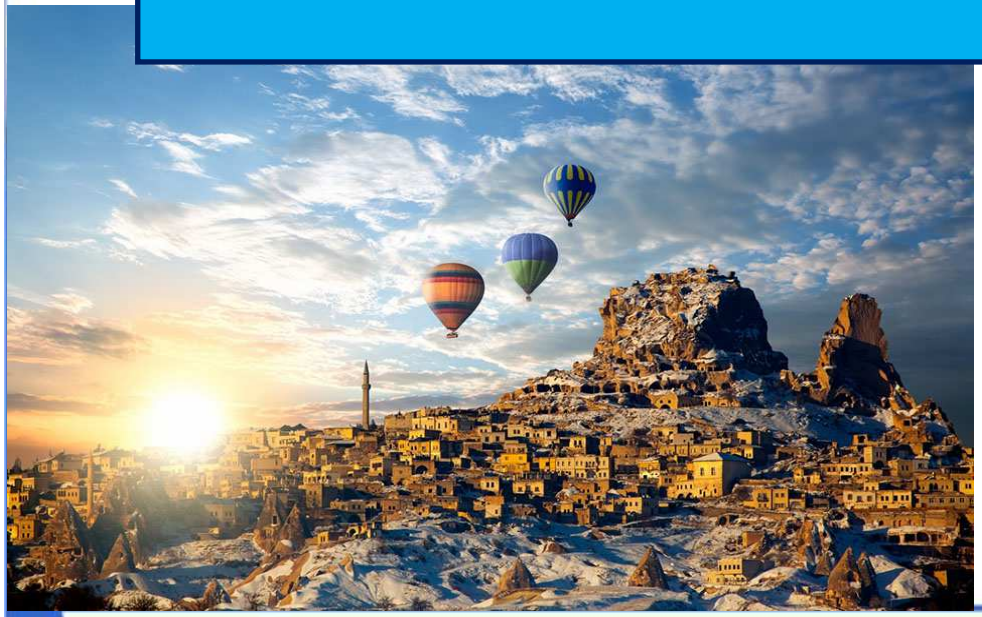
# ISTANBUL

*10th International Scientific Meeting. November 17-18, 2016*

# THANK YOU!



CAPPADOCIA



EPHESUS