

Picture 1

The Nordic Reference Interval Project 2000. Concept and consequences

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Many thanks for giving me this opportunity to go through the essentials of the Nordic Reference Interval project 2000, called NORIP from now on, and also to comment on what has happened since the project was finished.

Picture 2

Content

- Concept
- Accomplishment
- Discussion of results
- Implementation of reference intervals
- Spin-offs
 - NOBIDA: NORIP Bio-bank and database
 - New projects based on NORIP samples and data
 - NFKK Reference Serum X
 - Trueness verification
 - Use in EQA
 - Changes in certified values

First of all – NORIP is a joint effort by the Nordic laboratories to establish common reference intervals for the most requested quantities in medical biochemistry.

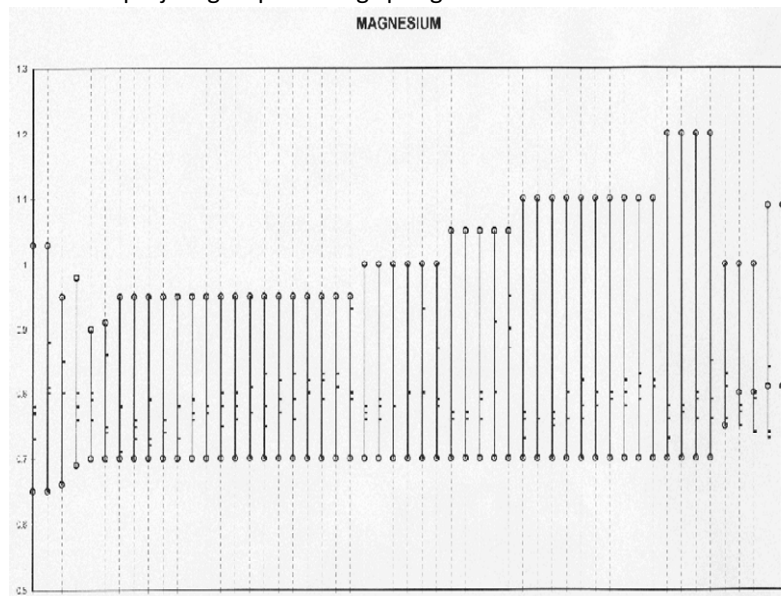
It is also a realization of the fact that the measurement quality has improved over time so that it is now possible to agree on which result is actually correct at least for these “simple” quantities.

First I will present the concept of NORIP, what was accomplished, then focus on the discussion afterwards and then the problems of putting the reference intervals in use where NFKK Reference Serum X is a vital aspect. Then there is the bio-bank and the database left after NORIP.

Picture 3

Prologue

- Inspiration: The Nordic Protein project. Why not the simple quantities?
- Adam Uldall serum pool HK97 used in Nordic EQA
- Visit to the DSKB board:
 - presentation of Norwegian results related to used reference intervals
 - Peter Felding and Per Hyltoft Petersen proposed a concept meant for common reference intervals in the Copenhagen area
- Decided to apply NFKK for economical support and help for establishing a Nordic project group
- First project group meeting spring 1998



The inspiration for this project was the Nordic Protein Project which was finished in 1994. In 1997 was conducted a survey on the use of RI in Norway where the results were presented as this example for magnesium. The commutable serum pool HK97, produced by Adam Uldall in Denmark, was used in three different EQA surveys through the year, and the results were plotted, see black dots in the plot, together with the RI that the laboratory used.

The plots showed that

- 1 - the laboratories had a fairly good quality on their measurements
- 2 - there was no obvious relation between the trueness of the method and the used RI

This inspired us to take action of some kind to standardize the use of RI.

A contact with the Danish society started a process where a project for harmonizing the RI in the Copenhagen area, based on a concept by Peter Felding and Per Hyltoft Petersen, was extended to a Nordic project. After involving NFKK to select members of the project group and support it with money for meetings, this group met in Oslo for the first time at the end of March 1998 with the following members:

Picture 4

The project group

- Project group
 - Denmark
 - Peter Felding, secretary
 - Per Hyltoft Petersen
 - Iceland
 - Leifur Franzson
 - Finland
 - Veli Kairisto
 - Norway
 - Pål Rustad, leader
 - Sweden (at different times)
 - Gunnar Skude
 - Kristoffer Hellsing
 - Per Simonsson
- Some important affiliates
 - Adam Uldall, DEKS
 - DEKS, materials and tubes
 - Heidi Steensland, NKK
 - First initiative, enzymes
 - Ari Lahti, Finland
 - Partitioning and calculation
 - Gunnar Nordin, EQUALIS
 - Equalis, haematology
 - Minna Loikkanen, Labquality
 - Labquality

From Denmark, Peter Felding and Per Hyltoft Petersen

From Iceland, Leifur Franzson

From Finland Veli Kairisto

Myself from Norway

and from Sweden, Gunnar Skude, later followed by Kristoffer Hellsing and Per Simonsson

Some important affiliates were:

Adam Uldall from DEKS, Denmark responsible for materials and tubes

Heidi Steensland from NKK in Norway responsible for the first initiative to this project and the data treatment of the enzymes

Ari Lahti from Finland creating the theory for partitioning

Gunnar Nordin from EQUALIS in Sweden, responsible for the hematology part of NORIP

and at last Minna Loikkanen from Labquality in Finland

Picture 5

Concept

The quantities

Medical biochemistry	Enzymes
Albumin	Alanine transaminase
Bilirubin	Aspartate transaminase
Calcium	Creatinekinase
Calcium, albumin corr.	Alkaline phosphatase
Carbamide (urea)	γ -glutamyl-transferase
Cholesterol	Amylase
Creatinine	Amylase, pancreatic
Iron	Lactate dehydrogenase
Iron saturation	
Glucose	Hematology
HDL Cholesterol	B-Hemoglobin
LDL Cholesterol	B-EVF
Magnesium	B-Erc
Potassium	Erc-MCV
Phosphate	Erc-MCH
Protein	Erc-MCHC
Sodium	B-Lkc
TIBC	B-Trc
Transferrin	Lkc differential count
Triglycerides	
Urate	

Then the concept – first the quantities to be measured. Only general medical biochemistry quantities were considered from the start, later was included a project on hematology conducted by Veli Kairisto, Finland and Gunnar Nordin, Sweden.

Picture 6

Concept

- Some definitions: RI: Reference interval, LRL and URL : Lower – and upper reference limit, respectively
- Concept
 - Laboratories collect samples (serum, plasma, buffy coat) from at least 25 reference individuals evenly distributed on gender and age incl. personal information. Samples should be frozen until measurement.
 - Laboratories will receive five control samples on dry ice intended to be measured together with the reference samples
 - CAL (NORIP “calibrator”)
 - NFKK Reference Serum X
 - P (serum pool from women using P-pills)
 - HIGH (serum pool concentrated by freezing)
 - LOW (HIGH diluted 1:2 with dilution of CaCL₂)
 - Measure serum from all and plasma from 10 % of the reference individuals and all control samples together in one series for 25 quantities.
 - Data on reference individuals and on measurement method and results from controls and samples should be submitted to central database.
 - The samples (7 serum, 1-2 plasma, 1 buffy coat) should be submitted for central storage (now at DEKS, Herlev hospital, Denmark).

Then a short description of the instruction to the participating laboratories:

- Collect samples (serum, plasma and buffy coat) from at least 25 reference individuals evenly distributed on gender and age, including personal information, and freeze samples until measurement.(KLIKK)
- You will receive 5 liquid control samples frozen on dry ice: The project calibrator CAL with reference method values for many quantities, a serum pool called X with no reference method values, a serum pool from women using P-pills called P, a serum pool concentrated by freezing – called HIGH, and a 1:2 dilution of HIGH called LOW. (KLIKK)
- Measure serum from all and plasma from 10 % of the reference individuals and all control samples together in one series for 25 quantities. (KLIKK)
- Submit data on reference individuals, measurement method and analytical data for controls and reference samples to the central data base. (KLIKK)
- Send 7 serum, 1-2 plasma and 1 buffy coat, all 1 mL each, from each individual to the central bio-bank.
- Reference intervals will be calculated centrally.

Picture 7

Sample handling

- Collection
 - Standard technique with least possible use of stasis
 - Serum: Plain tubes (without gel)
 - Plasma: Li-heparin
 - Buffy coat: EDTA plasma
- Storage
 - Kept in dark when possible
 - Tubes for serum: At room temp. until centrifugation within 30 and 90 min
 - Tubes for plasma: At room temp. before centrifugation within 15 min
 - Tubes for hematology and buffy coat: At room temp. or 4-8 °C before analysis or freezing within 24 h
- Centrifugation
 - 10 min at >1500xg (> 3000 rpm at r=16 cm)
- Aliquoting
 - Serum: Within 2 h
 - Plasma: Within 30 min
- Freezing
 - <-20 °C within 4 h
 - <-70 °C within 1 month
- Analysis
 - Thaw > 1 h in the dark
 - Turn 10 times
 - Flocculation ⇒ centrifugation
 - Analysis within 4 h
 - Fresh serum or plasma: At room temp. < 8 h and at ~4°C < 24 h

Because I have heard numerous times that the NORIP reference intervals is so narrow because of the strict sample handling rules, let's take a brief look at the instructions for sample handling, not to go through them in detail, but so that you can judge by yourself if this is actually true. At least the project group tried to make rules that is widely accepted and used in the Nordic laboratories.

What the participants have done in practice is another question – it might very well be that they have tried to do the sample handling as perfect as possible. We should perhaps have stressed that, in this case, it would have been better to be only average good than very good.

Picture 8

Traceability

The Nordic Trueness Project 2002: use of reference measurement procedure values in a general clinical chemistry survey. Scand J Clin Lab Invest 2004; 64



The traceability of the calibrator CAL is for 12 of the NORIP quantities mainly based on the Nordic Trueness Project described in one of the articles in the NORIP issue of SJCLI, where CAL and X got transferred values from IMEP 17 Material 1 through parallel measurements during 5 days by up to 136 Nordic laboratories.

Picture 9

Traceability for the NORIP calibrator CAL

Component	Reference laboratory (DGKC, Germany, 1997)	Nordic Trueness Project (IMEP-17, 2002)	NORIP consensus (2000)
ALT			
ALP			
Albumin			
Amylase			
Amylase, pancreatic			
AST			
Bilirubins			
Calcium			
Carbamide (urea)			
Cholesterol			
CK			
Creatinine			
γ GT			
Glucose			
HDL Cholesterol			
Iron			
LD			
Magnesium			
Phosphate			
Potassium			
Protein			
Sodium			
Transferrin			
Triglycerides			
Urate			

So - a general picture describing the CAL traceability is shown in this picture. For the enzymes the traceability for the reference intervals is always the consensus of IFCC compatible methods even if there are reference method values for CAL for ALT, CK and gamma GT.

Picture 10

Results

Clinical chemistry

- Medical biochemistry
 - 102 Nordic laboratories participated
 - 3035 reference individuals
 - Buffy coat from 13 %
 - 161 181 measurement results
 - Serum: 57 %
 - Plasma: 30 %
- Hematology
 - 1826 reference individuals
 - ~60 % of all, mainly Finland and Sweden

At last 102 Nordic laboratories were willing to participate. They collected samples from more than 3000 individuals with buffy coat from 13 % of them, giving rise to over 160 000 measurement results of which 57 % was from serum and 30 % from plasma.

In addition hematology measurements were made on about 60 % of the reference individuals, mainly from Finland and Sweden.

Picture 11

Calculation

- Reference values
 - Enzymes measured by routine methods compatible with new IFCC reference method
 - Non-enzyme results (R) corrected according to measurements of the project calibrator CAL ($T_{CAL}/M_{CAL} \cdot R$)
 - Hematology: routine methods
- Outlier detection
 - Based on extreme values for one or two quantities
- Reference interval
 - Central 95 % of the reference distribution
- Partitioning of age and gender
 - Principles by Ari Lahti:
<0.9 % or >4.1 % of a subpopulation outside common RI suggest partitioning

As mentioned earlier the enzyme results used for RI calculations are only from IFCC compatible methods.

Non-enzyme results are corrected with a factor calculated for each measurement series to give agreement with the target value for CAL.

For hematology and the enzymes no such corrections were made.

The outlier detection for individuals was based on extreme values from one or two quantities.

The Reference interval was calculated as the central 95 % of the distribution of reference values.

For partitioning according to gender and age, we used the principles outlined in the doctor work by Ari Lahti and is shortly summarized in this way: Partitioning should be done if <0.9 % or >4.1 % of the reference values from the subpopulation is outside common RI.

New IFCC methods for enzymes

- New methods
 - Reanalysis of selected samples by new IFCC methods
 - ALP (n = 1237)
 - Amylase (n = 719)
 - Amylase, pancreatic type (n = 497)
 - LD (n = 459)
- No changes (wet and dry chemistry)
 - ALT (n = 2300)
 - AST (n = 2056)
 - CK (n = 801)
 - GT (n = 1089)
- Traceability
 - Only results from IFCC compatible methods are used as reference values

New IFCC recommended methods for the enzymes ALP, amylase and LD during the project made it necessary to reanalyse selected samples for these quantities by 3 selected laboratories using adequate methods. Therefore the number of samples used for establishing RI are limited for these 3 as you can see.

Picture 13

<p>NOBIDA (bio-bank and database)</p> <p>NORIP conclusions</p> <p>Traceability</p> <p>Implementation of NORIP reference intervals</p> <p>NORIP documents</p> <p>Participating laboratories</p> <p>Preliminary project data</p> <p>Hematology data (27/6-03)</p> <p>Project members</p> <p>Other relevant E-mail addresses</p> <p>Links</p>	<h1>Documentation</h1> <p>NORIP home site: http://www.furst.no/norip</p> <ul style="list-style-type: none">– Scand J Clin Lab Invest. 4 (64). 2004– Raw data and descriptive statistics<ul style="list-style-type: none">• All reference values• All Refval reports• Serum/plasma• etc, etc, etc– Information/discussion <p>Clin Chem Lab Med 2004; 42(7):685</p> <p>Proposal for <u>guidelines to establish common biological reference intervals</u> in large geographical areas for biochemical quantities measured frequently in serum and plasma Rustad P, Felding P, Lahti A</p>
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Then the documentation:

To the left is shown the main menu from the NORIP home site. Here is presented all the relevant data from the project including the papers in SJCL's special issue on NORIP from 2004. In addition all raw data and extensive descriptive statistics including all the Refval reports from the calculation of RI.

In addition I want to mention an article we wrote for the special issue of CCLM on RI, also this published in 2004, where we have tried to summarize the experiences from NORIP to a guideline for establishing common RI in large geographical areas.

Picture 14

Information/discussion

NORIP home site

10 years anniversary for NORIP

[A comment from NFKK](#)

Data for leucocyte differential count

[Presentation at NKKs annual meeting March 2010 based on data from Gunnar Nordin](#)

How many Nordic labs use suggested NORIP reference intervals?

Summary

Norway 2010: [Norwegian laboratories asked to give their reference interval for a man, 40 years old](#)

Denmark 2009: [DSKB has made a survey on use of NORIP reference intervals in Denmark](#)

September 2008: [Reference intervals used by Nordic laboratories participating in Labquality EQA program](#)

Denmark (March 2007): [Ens referenceintervaller og harmoniserede resultater inden for klinisk biokemi i de nordiske lande](#)

Denmark (May 2006): [DSKB with info/advice on how to introduce NORIP reference intervals in Danish Laboratories](#)

Sweden (March 2006): [Effekt på skattade kreatininclearance och GFR vid övergång till bättre kreatininmetoder](#)

Sweden (November 2005): [SFKK has officially accepted the corrected reference interval for S/P-kreatinin \(Nov. 2005\) SJCLI on NORIP](#) (see also "Creatinine corrected reference intervals" below)..

[Angående NORIP:s referensintervall för LD och ALP](#). Klinisk Kemi, nr 4, 2005. Christian Löwbeer och Hans-Joachim Löffler

[Swedish discussion on unsolved problems with NORIP reference intervals and related proposals](#)

[Comments from NORIP project group](#)

Results of an inquiry to Nordic laboratories about the NORIP project (1.3.2005):

[Norwegian results](#)

[Swedish results](#)

[Creatinine corrected reference intervals](#)

Sweden (December 2004), Klinisk Biokemi i Norden, Nr. 3, vol 16, 2004:

- [Varför har finländare så höga CK nivåer? Anders Larsson](#)

[Er øvre referansegrense for leukocyter for lav? Brev fra Først Medisinsk Laboratorium.](#)

[Reference interval suggested in "Läkartidningen" and "Tidsskrift for Norsk Lægeforening", a comparison](#)

Here is a part of the "Information/discussion"-page of the NORIP home site – the 2 additions at the top was made yesterday. If you have suggestions for more information – please give me a hint!

Picture 15

[Scand J Clin Lab Invest 2004; 64](#)

Transnational Biological Reference Intervals Procedures and Examples from the Nordic Reference Interval Project 2000

- The Nordic Reference Interval Project 2000:recommended reference intervals for 25 common biochemical properties.
- Prerequisites for establishing common reference intervals.
- Minimally processed **fresh frozen human reference sera**: preparation, testing, and application to international external quality assurance.
- The **Nordic Trueness Project** 2002: use of reference measurement procedure values in a general clinical chemistry survey
- Certificate of analysis: NFKK Reference Serum X: a reprint
- Reference individuals, blood collection, treatment of samples** and descriptive data from the questionnaire in the Nordic Reference Interval Project 2000
- Descriptive analytical data and consequences for calculation of common reference intervals in the Nordic Reference Interval Project 2000
- Reference intervals for eight **enzymes** in blood of adult women and men measured in accordance with the IFCC reference system at 37°C - A part of the Nordic Reference Interval Project 2000
- A multicentre study of reference intervals for **haemoglobin, basic blood cell counts and erythrocyte indices** in the adult population of the Nordic countries
- Effect of analytical quality on establishing the common reference intervals and their use
- Are the common reference intervals truly common? Case studies on **stratifying biochemical reference data** by countries using two partitioning methods
- Nordic Reference Interval Project Bio-bank and Database (NOBIDA)**: a source for future estimation and retrospective evaluation of reference intervals
- LETTER TO THE EDITOR**: Creatininium reference intervals for corrected methods

The 2004 special issue of SJCLI contain all the vital documentation on NORIP, separate papers dealing with the production of control materials, traceability through the Nordic Trueness project, a description of the reference individuals and sample collection and handling, a separate evaluation of the enzyme RI, a description of the hematology part of the project, a new theory of partitioning reference values, a description of the NORIP bio-bank and database called NOBIDA and at last a suggested correction to the originally calculated creatinine RI.

Picture 16

Consequences

- Enzymes
 - Upper limit increased significantly
 - ALT
 - Fat liver patients within RI (Läkartidningen)
 - CK
 - Why does the Fins have such high CK levels? (KBN no 3, 2004)
 - GT
 - Increased alcohol consumption?
- Electrolytes
 - Narrower reference intervals (sodium, potassium, calcium, magnesium)
 - Calcium method differences reduced significantly in later years
 - Potassium: Few have adopted the upper limit for serum!
- Albumin
 - Nearly all laboratories have too high level - is the certified value correct?
 - Retesting confirmed the original certified value!
- Creatinine
 - Better traceability for Jaffé methods achieved by method correction
 - Use of Jaffe methods decreased dramatically
 - Many laboratories have not adopted the +5 $\mu\text{mol/L}$ for men URL and -5 $\mu\text{mol/L}$ down for women URL.
- Iron
 - No gender differences

Here is a summary of some consequences:

For the enzymes the main impression is the increase in upper reference limit.

For ALT this resulted in several papers in Läkartidningen where the problem was that fat liver patients have ALT results within the reference interval.

The high CK, especially for the Fins, has been commented in Klinisk Biokemi i Norden in 2004 and increased alcohol consumption has been an explanation for the high upper limit for GT. (KLIKK!!!)

For the electrolytes the focus was of course on the narrow reference intervals giving rise to all the comments on too strict sample handling rules in NORIP that I have commented on earlier. In recent years the between method variation for calcium has decreased as judged by EQA assessment, making it easier to adopt the NORIP RI. For potassium we will see later that few labs have adopted the upper reference limit. (KLIKK!!!)

For albumin the problem was that nearly all the laboratories had too high results giving rise to a suspicion that the certified value was too low. Retesting has later confirmed that the original value was correct within uncertainty.

For creatinine the dominant methods at that time was the Jaffe methods with all their interferences. These were nearly eliminated in the NORIP results by a correction making them very comparable to the results obtained by enzymatic methods. The following correction to the reference intervals has however not reached all laboratories. The use of Jaffe methods has since decreased dramatically.

For iron it was a surprise that no partitioning on gender was necessary.

Picture 17

NFKK Reference Serum X Can I use the reference interval???

- Purpose
 - Help in verification of local method trueness
- Method
 - A spreadsheet was made where a suggested method of trueness verification is suggested:
 - Run NFKK Reference Serum X and local calibrator in 10 replicates each in one series
 - Method bias relative to X including uncertainty is calculated, tested for significance and compared to a quality goal ($|\text{bias}| < 0.375 \cdot \text{CV}_{\text{bio,tot}}$) based on biological variation estimated from NORIP data
- Results
 - Bias for 82 Danish, Icelandic and Norwegian laboratories are presented for all NORIP quantities in plots sorted on method and compared to quality goals on the NORIP home site and published in KBN no 2, 2005
- Conclusion
 - Strange that for many quantities there are still much variation in spite of removing so many uncertainty sources ([albumin](#))

NFKK Reference Serum X was made to facilitate the introduction of the new RI in the laboratory. This material is not only a link to the NORIP reference intervals, but also a valuable help to assess absolute trueness for many components. We have therefore made a relatively simple spreadsheet, available to all laboratories, where local results of up to 10 replicate measurements of X and the local calibrator can be entered. The bias is then calculated and evaluated according to statistical significance and quality specifications based on NORIP biological variation.

We collected the results from 82 Danish, Icelandic and Norwegian laboratories and sorted them according to bias and methods. The results have been published in Klinisk Biokemi i Norden no 2, 2005 and is available at the NORIP home site.

It seems strange to me that the variation in the results still is large for many quantities even if so many of the obvious sources of uncertainty has been removed.

Here is an example for albumin.

I will also mention a special use of X in External Quality Assessment from Labquality where target values for EQA liquid samples are made by transferring values from X by 4 laboratories using different routine methods.

Picture 18

Implementation of NORIP reference intervals Status

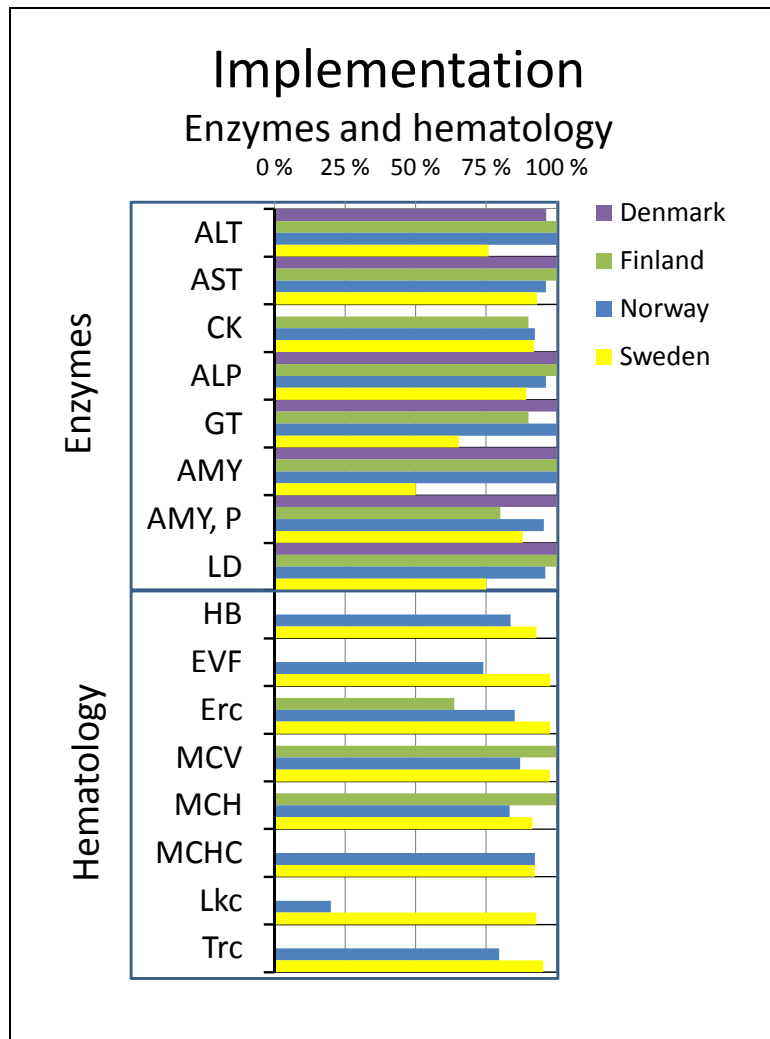
- Denmark
 - DSKB-Nyt 2/2009 (NORIP home site)
- Iceland
 - All laboratories: All components except calcium, potassium and haematology
- Finland
 - 10 laboratories replied
- Norway
 - 65 laboratories replied
- Sweden
 - 43 laboratories replied

In the last month I have made an effort to find out how many of the Nordic laboratories have implemented the RI suggested by NORIP. In Denmark a survey was carried out in autumn 2008 and published in DSKB-Nyt last year. The publication is available from the NORIP home site.

For Iceland I have been informed that the reference intervals for all quantities except calcium, potassium and hematology have been accepted by all laboratories.

For Finland, Norway and Sweden, an enquete was sent out to give the reference interval for a man, 40 years of age, for the NORIP quantities. In Finland the NORIP email addresses were used – that is surely the reason why only 10 laboratories have replied, Norway and Sweden achieved a much higher number as you can see.

Picture 19



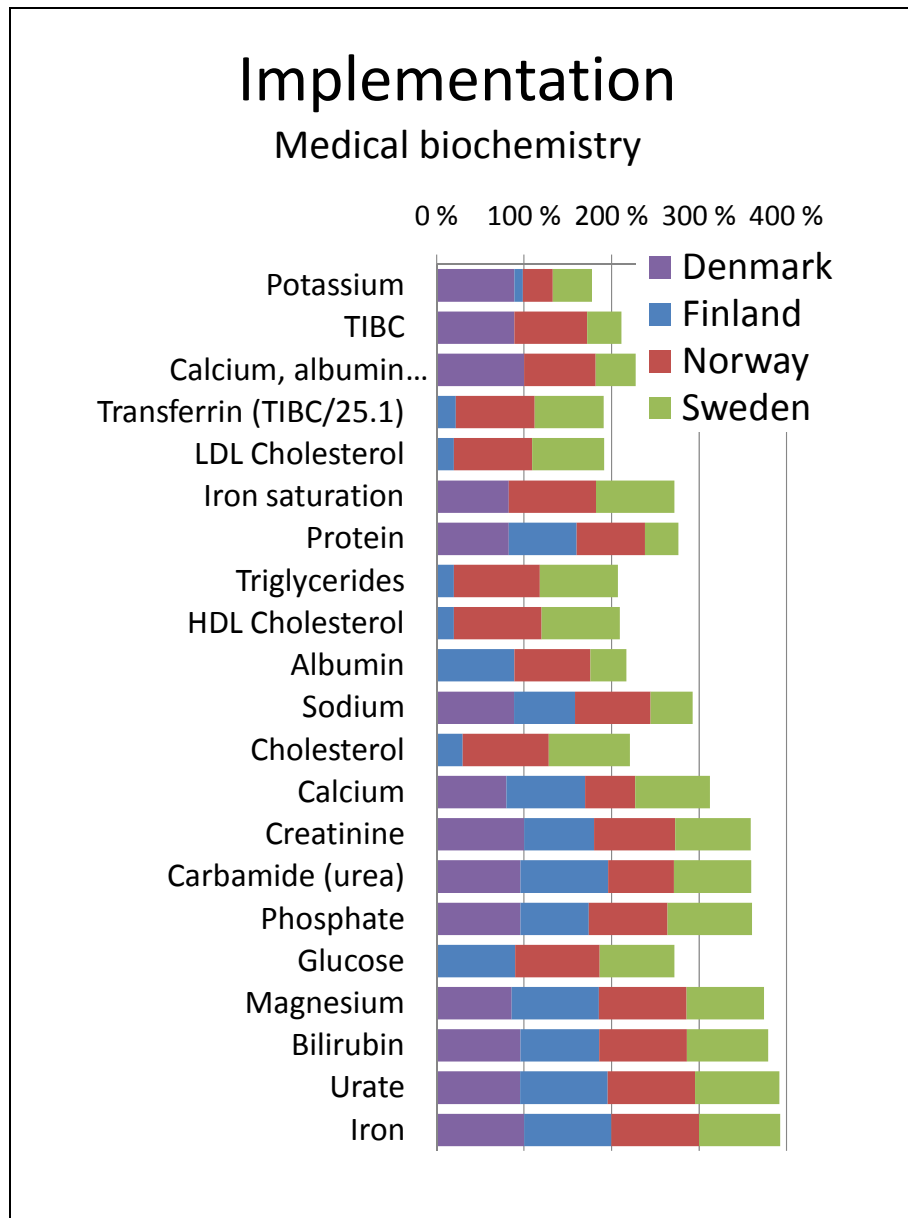
So – let us first look at the enzyme and hematology results. These are still preliminary but will later be checked and published on the NORIP home site in more detail. I have accepted small deviations of no practical importance from suggested reference limits.

Here is plotted the percentage of the laboratories that measure the quantity and have implemented the NORIP enzyme- and hematology reference intervals.

For the enzymes on top, there are no Danish data for CK (no violet bar). Generally the intervals has been implemented to a high degree for the enzymes, but there is a tendency for Sweden (in yellow) to have a slightly lower percentage than the other countries. The discussions on the elevated upper reference limits for some of the enzymes and that IFCC has published suggested reference intervals, surely is the reason for less than 100 % support.

For hematology we have no data for Denmark. Generally Sweden has adopted all the suggested reference intervals, also Norway, but here especially the leukocyte reference interval has very low percentage caused by the low upper reference limit suggested. In this figure it seems that the Finnish laboratories only have implemented erythrocyte count, MCH and MCV, but the reason for the missing bars is that Finland must have agreed on different reference intervals than those suggested by NORIP, for instance all laboratories use exactly the same intervals for leucocytes and trombocytes.

Picture 20



For the rest of the quantities the plot is a little different as the percentage from each country are stacked and sorted on the mean percentage – 4 countries give max 400 % implementation. There are no data from Denmark for lipids, albumin and glucose – therefore the violet part of the bar representing Denmark is absent for these quantities.

It is a lot to say about this picture, but the time is limited, so just a few comments:

For the quantities implemented to a high degree shown at the bottom, there are no large differences between the countries but for calcium we see that Norway has the lowest percentage.

For the mid part, Finland has low percentages for cholesterol, triglycerides and HDL- and LDL-cholesterol as decision limits has been registered instead of reference limits.

At the top is potassium with least acceptance as expected.

Picture 21

NOBIDA

Nordic Reference Interval Project

Bio-bank and Database

[NORIP home site - NOBIDA](#)

- [Apply for samples from NOBIDA](#) (Klinisk Biokemi i Norden, 2004, 4)
- Application to The NOBIDA Committee for samples/data from NOBIDA ([MS Word format](#))
- NOBIDA committee:
 - Ulrik Gerdes Klinisk Biokemisk Afdeling, Århus Amtssygehus
 - Jón Jóhannes Jónsson Landspítallin, IS-101 Reykjavík
 - Veli Kairisto Clinical Laboratory Dept., Turku University Central Hospital
 - Arne Mårtensson EQUALIS
 - Pål Rustad, Først Medical Laboratory, NO-1051 Oslo
- [Establishment and administration of NOBIDA](#) (Documents produced by NFKK related to establishment of NOBIDA and the committee)

Then there is the bio-bank and the database which NFKK administers through the NOBIDA committee. As mentioned earlier the information about NOBIDA can be found on the NORIP home site where some documentation can be found (PEK), the members of the committee representing all the Nordic countries (PEK) and of course most importantly - the application form for samples and data.

Picture 22

Applications for samples

No	Year	Applicant	CN	Samples
1	2004	Axler	SE	600 plasma
		Apolipoprotein M		
2	2004	Hilsted	DK	500 plasma
		Thyroid quantities, PTH, insulin, hormones on Roche E170 an possibly Elecsys		
3	2004	Bjerner	NO	500 sera
		CEA, CA125, MUC1, thyroglobulin with AB, NSE, PSA (total and free), SCCA, ProGRP, AFP, CA19.9, HCG		
4	2004	Mansoor	NO	250 sera
		Thiobarbituric acid reactive substances (TBARS)		
5	2004	Østergaard	NO	200 sera
		Troponin I, 99 percentile for Abbott Architect		
6	2005	Møller	DK	240 sera
		sCD163, free light chains in serum		
7	2005	Nissen	DK	384 buffy coat
		Genetic variations in the genes LDLR, APOB, PCSK9, SREBP2 and CASR		
8	2005	Kokkala	FI	160 Finnish samples
		PAPP-A levels in normal individuals		
9	2007	Cerioti	IT	400 sera
		AST, ALT, GT. International RI		
10	2007	Dalbäck	SE	Rest Axler (2004)
		GAS 6		
11	2007	Paus	NO	Rest Bjerner (2004)
		ProGastrin-Releasing Peptide (proGRP)		
12	2008	Bjøro	NO	600 serum
		Testosterone, FSH, LH, SHBG (RI concerning hormonal outcome for patient with prostatic and testicular cancer after variuos treatments)		
13	2008	Friis-Hansen	DK	120 m+740 f, sera
		AMH (anti-Müllerian hormone)		
14	2009	Bolstad	NO	Rest Paus (2007)
		HE4 (human epididymis protein 4) - probably included as a tumor marker for ovarian cancer		
15	2010	Almasi	DK	200 sera
		Cocaine and amphetamine-regulated transcript (CART)		

Here you can see a list of all applications for samples since the start in 2004, only 15, 3 of them have reused samples from other projects - 5 from Denmark, no one from Iceland, 1 from Finland, 6 from Norway and 2 from Sweden.

We can see that also Italy is represented by dr. Cerioti who on behalf of an IFCC project on international RI wanted 400 samples for measurement of AST, ALT and GT.

Picture 23

Applications for data

No	Year	Applicant	Country
	Quantities		
1	2004	Niemelä	FI
	Comparison with Southern Ostrobothnia Project: Alcohol induced diseases and markers for alcohol consumption		
2	2004	McFarlane	Australia
	Data for comparison to establish reference intervals in Australia		
3	2004	Seljeskog	NO
	TBARS-values in relation to data from the NOBIDA database		
4	2004	Eikvar	NO
	GFR and creatinine clearance		
5	2005	Mårtensson	SE
	GFR and creatinine clearance		
6	2005	Mikkelsen	NO
	GFR and creatinine clearance		
7	2006	Grodzinsky	SE
	Compare levels of proteins in elderly (> 80 years) with existing reference values (NORIP).		

There has been 7 request for data, one Finnish comparison with another project concerning markers for alcohol consumption, one from Australia for comparison of reference intervals, 3 studies on GFR and creatinine clearance and at last one Swedish study comparing levels of proteins in the elderly with NOBIDA levels.

Publications from these studies are available for some, but the intention is to collect the references and put them on the NORIP home site in the future.

Picture 24

NOBIDA Bio-bank

Status 1.3.2010

- Reference samples
 - Buffy coat: 2429
 - Li-heparin plasma: 3687
 - Sera: 14292
- Control samples
 - CAL: 0
 - High: 298
 - Low: 298
 - P: 298
 - X: 1757

The status for the samples in NOBIDA is shown here. As you can see there is quite a lot of samples remaining after nearly 10 years, about 2500 buffy coat, 3600 plasma and 14 000 serum samples. Of the controls there are still 1700 left of NFKK Reference serum X and even the other NORIP control samples except CAL.

Picture 25

Looking forward

- Pediatric reference intervals
 - Nordic project with no ends
 - New promising project in progress
 - 2000 Danish children 6-16 years
 - Method: Roche Modular/Elecsys
 - 26 quantities – e.g. [creatinine](#)
 - Contact person: Linda Hilsted, Rigshospitalet, Denmark

10 years anniversary for NORIP

- Comments from NFKK
KBN 1/2010, Johan Bjerner
 - Common RI has resulted in good trueness for NORIP quantities!
 - A new NORIP?
 - Changes in the population
 - » Change in diet
 - » Larger minority groups
 - Better methods
 - NOBIDA – use the samples!!!

So – what should be the continuation of the NORIP spirit?

Some years ago was started a project with the aim to establish pediatric reference intervals. To my knowledge this project has gone into a deep coma, but as I have been informed, not entirely dead.

But a new promising project in this field is near its end. Linda Hilsted at Rigshospitalet in Denmark has measured 2000 samples from children 6-16 years of age for 26 quantities on a Roche Modular or Elecsys system. I want to show you an example from this study showing the steadily increasing levels of creatinine with age. (KLIKK)

In the last issue of Klinisk Biokemi i Norden, NFKK by Johan Bjerner has commented on NORIP at its 10 years anniversary. He states from personal experience that the introduction of common RI has created an increased awareness of measurement trueness. He also speculates if it is time to think about a new project – the diet and the composition of the population has changed and the quality of the methods have improved. Should other quantities be included? At the end he reminds us of all the samples that are left in the bio-bank – please make use of them! I can't agree more!

Let these thoughts be an inspiration to look forward – for now....

Picture 26

Thank you for your
attention!

