Taylor&Francis
healthsciences

Scand J Clin Lab Invest 2004; 64: 431–438

Nordic Reference Interval Project Bio-bank and Database (NOBIDA): a source for future estimation and retrospective evaluation of reference intervals

P. RUSTAD,* P. SIMONSSON,† P. FELDING‡ & M. PEDERSEN§

*Fürst Medical Laboratory, Oslo, Norway; †University Hospital MAS, Malmö, Sweden; ‡Copenhagen General Practitioners' Laboratory, Copenhagen, Denmark; §Danish Institute for External Quality Assurance for Laboratories in Health Care (DEKS), Herlev University Hospital, Copenhagen, Denmark

Rustad P, Simonsson P, Felding P, Pedersen M. Nordic Reference Interval Project Bio-bank and Database (NOBIDA): a source for future estimation and retrospective evaluation of reference intervals. Scand J Clin Lab Invest 2004; 64: 431–438.

In the Nordic Reference Interval Project 2000 (NORIP) serum, Li-heparin plasma and EDTA buffy coat were collected at 102 laboratories in 5 Nordic countries from healthy individuals aged 18 years or more and evenly distributed for laboratory, gender and age. Multiple aliquots of these samples from each of about 3000 persons are now stored at the Nordic Reference Interval Project Bio-bank and Database (NOBIDA) at a temperature of below −80°C. The commutable NFKK Reference Serum X with certified values traceable to reference methods and measured in NORIP in the same series as the samples is also available from NOBIDA. Data describing the person and the sample conditions are stored together with analytical results and data describing the measurement systems. The bio-bank along with material and data is administered by the NOBIDA committee on behalf of the NFKK (Scandinavian Society of Clinical Chemistry) to be used by Nordic laboratories for any purpose beneficial to the development of clinical biochemistry in general and particularly for creating reference intervals for other biochemical properties than those established by NORIP. Furthermore, research on the already stored information alone is encouraged. Thus colleagues are now welcome to use this extensive material for research and development in clinical biochemistry.

Key words: Certified; NORIP; reference material; reference samples; reference values

Pål Rustad, Fürst Medical Laboratory, Søren Bulls Vei 25, NO-1051 Oslo, Norway. E-mail. prustad@furst.no

INTRODUCTION

A bio-bank and the attached database were established as a part of the Nordic Reference Interval Project 2000 (NORIP) [1]. Reference intervals were established for 25 common clinical components in serum or plasma.

Reference samples (serum, Li-heparin plasma)

DOI 10.1080/00365510410006694

TABLE I. Summary data from questionnaires completed by 3035 reference individuals (47% M, 53% F).

	Yes	No	Not answered
Nordic origin	96%	4%	0%
Diabetes in family	12%	85%	3%
Chronic disease	5%	95%	0%
Oestrogen use	17%	82%	0%
Medication	17%	79%	4%
Physical activity last week	14%	86%	0%
History of blood donations	16%	76%	8%

from at least 25 reference individuals evenly distributed for gender and age were collected by each of 102 Nordic laboratories and measured on their local measurement system together with 5 reference materials (controls)—CAL, X (later named "NFKK Reference Serum X"), P, HIGH, LOW—so that linearity could be verified and a common metrological reference point could be obtained.

Reference samples, all measured values, information on each reference individual and on the measurement system were submitted for central storage. Reference values traceable to reference measurement procedures were calculated centrally.

The reference population and bio-bank

The reference individuals were subjectively healthy, above 17 years of age and without major chronic disease. From all laboratories, individuals were evenly distributed for gender and age. Although 16% of the individuals had a history of blood donation, no subject had given blood in the last 5 months before sample collection. The samples were collected from sitting individuals from a cubital vein with minimal stasis. More than half of the samples were collected from fasting individuals in the morning. The reference individuals were further characterized as described in Tables I and II and elsewhere [2].

The samples were treated as follows: serum from the individuals was separated from the blood cells within 2 h and frozen within 4 h from sampling. Li-heparin plasma was separated from the blood cells within 30 min (centrifugation started within 15 min) and frozen within 4 h from sampling. The buffy coat was frozen within 24 h from sampling. The frozen material could be kept below $-20^{\circ}C$ for up to one month and should thereafter be stored below $-70^{\circ}C$ until shipment on dry ice to the bio-bank [2].

In relation to the bio-bank, a trueness control material is available: the NFKK Reference serum X — a fresh-frozen pool from blood donors with certified target values [3]. All NORIP reference intervals are traceable via this reference serum.

The database

As a part of NORIP a database was established with information on the participating laboratories, information on used measurement systems, information on each reference individual and the measurement results on reference samples and controls.

Ethical considerations

The future use of the bio-bank should follow rules imposed by the ethics committees which approved NORIP (see Table III).

In Denmark, Finland and Iceland no new application to the ethics committees is necessary for use of the material in future studies of reference intervals. This is needed for samples obtained in Sweden and Norway.

NOBIDA

The NOBIDA committee

Members of the Nordic Reference Interval Project Bio-bank and Database (NOBIDA) committee appointed by the Scandinavian

TABLE II. Summary data from questionnaires concerning tobacco and alcohol consumption.

Tobacco consumption [cigarettes/day]	0	1–5	>5	Not answered
	83%	6%	10%	2%
Alcohol consumption* [units of alcohol/week]	0	1–21	>21	Not answered
	45%	53%	0%	1%

TABLE III. Rules for future projects imposed on NORIP by ethics committees, authorities or the consent formula signed by the reference persons.

Problem	Denmark	Finland	Iceland	Norway	Sweden
Is permission necessary for use of samples from reference persons to projects within the scope of the initial NORIP description, i.e. projects related to production of reference values?	Permission is not necessary	Permission is not necessary	Permission is not necessary	Norwegian ethics committee should be notified when samples are used	Permission from the Swedish ethics committee or a Nordic ethics committee for the new project in question is necessary
Permission to use samples to projects beyond the scope of the NORIP description	Permission from the ethics committee of the new project	Permission from the ethics committee of the new project	Permission from the ethics committee of the new project	As above	Permission from the ethics committee of the new project and the reference person
Withdrawal from the bio-bank of samples from a person on request from that person	Can be denied	Is the right of the person	Is the right of the person	Can be denied	Is the right of the person
Information to the person about pathological results	NOBIDA cannot identify the person who has donated a given sample. A reference individual identified as such by name on the consent paper at the local lab. has on request the right to the results from local analyses in the initial project but no further results	NOBIDA cannot identify the person who has donated a given sample. A reference individual identified as such by name on the consent paper at the local lab. has on request the right to the results from local analyses in the initial project but no further results	The reference individual can be traced from the sample number via the local labs in the initial project. In new projects, the ethics committees of the new projects should make decision about such information	NOBIDA cannot identify the person who has donated a given sample. A reference individual identified as such by name on the consent paper at the local lab. has on request the right to the results from local analyses in the initial project but no further results	The reference person can be traced from the sample number via the local labs in the initial project. In a new project, the ethics committees of the new projects should make decision about such information

NORIP = Nordic Reference Interval Project, NOBIDA = Nordic Reference Interval Project Bio-bank and Database

Society of Clinical Chemistry (NFKK) (January 2004) are:

Ulrik Gerdes, Klinisk Biokemisk Afdeling, Århus Amtssygehus, DK-8000 Århus C., Denmark. Tel.: +45 8949 7307. E-mail: gerdes@aas.auh.dk

Jón Jóhannes Jónsson, Landspitallin, IS-101 Reykjavik, Iceland. E-mail: jonjj@landspitali.is

Veli Kairisto, Clinical Laboratory Dept., Turku University Central Hospital, Kiiamyllynkatu 4-6, FIN-20520 Turku, Finland. Tel.: +358 2 261 16 11. Fax: +358 2 261 39 20. E-mail: veli.kairisto@utu.fi

Arne Mårtensson, EQUALIS, Box 977, SE-751 09 Uppsala, Sweden. Tel.: +46 18 69 31 64. Fax: +46 18 69 31 46. E-mail: arne.martensson@equalis.se

Pål Rustad (Chairman), Fürst Medical Laboratory, Søren Bulls Vei 25, NO-1051 Oslo, Norway. Tel.: +47 22 90 95 54. Fax: +47 22 90 96 06. E-mail: prustad@furst.no

Goals

The goals of the bio-bank are to contribute to any sensible project for the development of the clinical area in general and in particular to:

- establish new reference intervals for clinical biochemical components. This may be done by using the reference samples in the same way as has been done by NORIP, but by measuring other components;
- establish/verify traceability for measurement systems to the reference intervals found in NORIP. This can be done by using the NFKK Reference Serum X;
- relate reference values to phenotype and environmental and other influences;
- relate reference values to genotypes (by use of the buffy coat).
- store new information related to the reference samples, reference intervals and NFKK Reference Serum X.

Bio-bank

Reference samples. If all 94 laboratories that are registered with samples in the bio-bank submit all their samples, there will be samples from 2794 individuals in the bio-bank (Jan. 2004):

- Denmark: 18 laboratories (max. 554 individuals);
- Finland: 23 laboratories (max. 754 individuals);
- Iceland: 1 laboratory (max. 67 individuals, not buffy coat);
- Norway: 28 laboratories (max. 783 individuals);
- Sweden: 24 laboratories (max. 636 individuals).

From each reference individual there are maximum 7×1 mL serum, 2×1 mL heparin plasma, 1×1 mL buffy coat. If all laboratories registered in the bio-bank submit all requested samples there will be a maximum of approximately 28 000 samples.

Control materials. Reference serum with certified values:

- NFKK Reference Serum X: 3000×5 mL
- Reference sera used as controls in the NORIP project:
  - NFKK Reference Serum P: ca. $300 \times$ 2.5 mL, in addition about 1650 mL in bulk
  - NFKK Reference Serum HIGH: $303 \times$ 2.5 mL, in addition about 1400 mL in bulk
  - NFKK Reference Serum LOW: Ca. $300 \times$ 2.5 mL LOW, in addition about 1400 mL in bulk.

Location, storage and quality assurance of the bio-bank. The Danish Institute for External Quality Assurance for Laboratories in Health Care (DEKS) has responsibility for the bio-bank. It is stored in three -80°C freezers. All the freezers are located at Herlev University Hospital, Herlev, Copenhagen. The freezers are equipped with acoustic alarms and are under constant electronic surveillance. A warning is activated by a temperature higher than -60°C. A warning initiates either immediate repair of the freezer or removal of the samples to another freezer.

DEKS employees inspect the freezers at least three times a week during which the temperatures displayed electronically on the freezers are registered in a logbook.

Database

Content. The type of information available from the database is described in the application form in Appendix 1. A summary of data registered from the questionnaires filled out by the reference individuals is presented in Tables I and II. Further information on

reference individuals is given by Felding *et al.* [2] and on reference values and measurement systems by Rustad *et al.* [4].

Location, storage and quality assurance of the database. The MS® Access database is located at the Fürst Medical Laboratory on a server with access only for the person in charge and the local IT administrator. The content of the server is backed up each day to tape and stored in a fire-proof cabinet. Back-up is available for 3 months by the local IT administrator. A copy of the database is also stored on a compact disc located in another building and is accessible only to the person responsible.

Request for NFKK Reference Serum X and other control materials

Clinical laboratories in the Nordic countries can request NFKK Reference Serum X, High, Low and P. The materials should, for the specified price, immediately be delivered from the local EQA-organization. The materials are sent on dry ice.

Application for reference samples and data and response

Application for sets of reference samples. After approval of a project by the NOBIDA committee, Nordic laboratories can request reference samples including NFKK Reference Serum X from DEKS for a specified price.

Who is eligible for use of the bio-bank and data obtained from the database? Laboratories engaged in the measurement of routine clinical components can apply.

What are the restrictions concerning samples obtained from the bio-bank? A minimum of 130 samples from the bio-bank has to be requested. NFKK Reference Serum X and where analytically reasonable HIGH and LOW must be measured in the same series as the samples.

The applicant will be informed about possible restrictions in the use of the material, number and selection of samples and the data that are available from the database.

How to prepare an application? The application should be short and of no more than 2–3 pages (application form: Appendix 1).

The application should include information concerning:

1. The principle investigator for the project and other key participants.
2. The aim of the study.
3. A brief plan for the project including information about the components to be measured, the method to be used as well as the statistical analyses to be made.
4. A description of the samples needed (e.g. number, age, sex, nationality).
5. A description of information requested from the database.
6. A description of sample and data handling and storage during and after the study.
7. If relevant, a copy of acceptance from the local ethics committee.
8. Information about transport, storage during use and the fate of the samples after the study has been completed (returned or destroyed).
9. Information about publications.

Where and when to submit the application? The application should be submitted in electronic form to the chairman of NOBIDA. Name and address can be identified at the NFKK homepage: http://nc.ibk.liu.se/nfkk/. An application can be submitted at any time.

What is to be done once the project is finalized? When the project is finalized, a brief report should be send to NOBIDA that will forward it to the board of the NFKK. The results should be presented in peer-reviewed journals if relevant or at least in Klinisk Biokemi i Norden or at the NFKK homepage: http://nc.ibk.liu.se/nfkk/.

Results of new measurements performed on the reference samples should be made accessible via the database. The format of data to be submitted to the database will be specified to the applicant when the project is accepted.

Handling of application. The application will generally be handled within 2 months of receipt.

If the committee cannot reach unanimity, the board of the NFKK will make the decision.

The committee handles each application according to the requirements from the local ethics committees having approved the NORIP project. This implies that samples from some countries may not be used in some studies.

The NOBIDA chairman will give a written decision to the applicant with information on possible restrictions in the use of the materials and information on number and selection of samples and what data are attached from the database.

Refusal should be motivated.

APPENDIX 1: APPLICATION FORM

An electronic version is available on the NORIP home site (www.furst.no/norip)

Application for samples and/or data
To:

Pål Rustad
Fürst Medisinsk Laboratorium
Søren Bulls Vei 25
NO-1051 Oslo
Norway

By applying for samples and/or data from NOBIDA, you give consent to the following conditions:

The samples and/or data must not be used for purposes other than those explained in this application.

The results from the project should be published in peer-reviewed journals if relevant and should be made available in the NOBIDA database.

The data produced by using NOBIDA samples must be kept in their original form for a minimum of 5 years.

The samples and/or data received from NOBIDA should be destroyed after the project is finished. If, for any reason, any part of these data has to be stored as original data, this should be specified in the application or NOBIDA notified at the end of the project at the latest.

Investigator

Principle investigator:
Institution:
Address:
Telephone no:
E-mail address:

Information on project

Component(s) to be measured:
Purpose of project:
Measurement system(s):
Traceability of method(s):
Storage of samples:
Time frame:
Publication of results:
General usefulness of project data:

Specification of request

Samples

Reference samples: Number of samples (1 mL in each vial):

Serum, Li-heparin plasma or buffy coat:

Specify information on reference persons by underscore: Age, gender, height, weight, date of 1st day of last menstrual period (women), ethnic origin, heredity for diabetes, number of years residing in a Nordic country, chronic disease(s), medication, strenuous exercise last week, alcohol consumption, habitual smoking, number of hours since the last meal, date of blood sampling, number of total blood donations.

Controls: NFKK Reference Serum X, number of vials (5 mL); HIGH, number of vials; LOW, number of vials.

Data

Specify requested data by underscore:

Reference person data: Person ID, age, gender, height, weight, date of 1st day of last menstrual period (women), ethnic origin, heredity for diabetes, number of years residing in a Nordic country, chronic disease(s), medication, strenuous exercise last week, alcohol consumption, habitual smoking, number of hours since the last meal, date of blood sampling, number of total blood donations, country of sample collection.

Analytical and measurement system data are available from the NOBIDA database for the following components: Alanine transaminase, albumin, amylase, amylase pancreatic, aspartate transaminase, alkaline phosphatase, bilirubin, calcium, carbamide, cholesterol, HDL-cholesterol, glucose, creatininium, creatinine kinase, γ-glutamyltransferase, iron, lactate dehydrogenase, magnesium, phosphate, potassium,

protein, sodium, TIBC, triglyceride, urate. Analytical data are also available for the following derived components: albumin-corrected calcium, iron saturation, LDL-cholesterol.

Analytical method: Instrument manufacturer, instrument name, method group, method name, unit, slope and intercept ($V_s = V_i \times \text{slope} + \text{intercept}$ where V_s is submitted value and V_i is original measured value). Control analytical data for CAL, X, P, LOW, HIGH: Control ID, measurement date, series no., measurement value.

Reference person analytical data: Person ID, measurement date, series no., material (serum or plasma), material handling (fresh or thawed), measurement value.

Additional specification

Format of requested data

Signature and date

REFERENCES

1 Rustad P, Felding P, Franzson L, Kairisto V, Lahti A, Mårtensson A, Hyltoft Petersen P, Simonsson P, Steensland H, Uldall A. The Nordic Reference Interval Project 2000: recommended reference intervals for 25 common biochemical properties, Scand J Clin Lab Invest 2004; 64: 271 – 84.

2 Felding P, Rustad P, Mårtensson A, Kairisto V, Franzson L, Hyltoft Petersen P, Uldall A. Reference individuals, blood collection, treatment of samples and descriptive data from the questionnaire in the Nordic Reference Interval Project 2000. Scand J Clin Lab Invest 2004; 64: 327 – 42.

3 Pedersen MM, Rustad P, Simonsson P. Certificate of analysis: NFKK Reference Serum X: a reprint. Scand J Clin Lab Invest 2004; 64: 321 – 26.

4 Rustad P, Felding P, Hyltoft Petersen P, Lahti A. Descriptive analytical data and consequences for calculation of common reference intervals in the Nordic Reference Interval Project 2000 (NORIP). Scand J Clin Lab Invest 2004; 64: 343 – 70.

Received: 22 January 2004
Accepted: 23 March 2004