NeoPrediX B.1

Instructions for Use

These Instructions for Use apply to the following software version:

V1.2.0

REF	NeoPrediX B.1
LOT	V1.2.0
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English

Background information of NeoPrediX B.1

Applied computer model for prediction of bilirubin progression

The NeoPrediX B.1 algorithm is based on a mathematical computer model that characterizes and predicts bilirubin progression over postnatal age. The mathematical computer model consists of a production and elimination part for bilirubin. For healthy individuals beyond the neonatal period, production and elimination are in an equilibrium, resulting in constant bilirubin levels. In preterm and term neonates, production can be increased over the first days of life, and elimination may be reduced after birth. This construction principle increases bilirubin levels in the first days of life, followed by a subsequent decline. In addition, individual neonate characteristics, i.e., delivery mode, gestational age, and birth weight, are included in the mathematical model. The mathematical computer model consists of parameters that must be adjusted to describe bilirubin changes.

The product uses the input data to calculate the predicted course of the bilirubin level in the patient through an algorithm. The mathematical model for characterizing and forecasting bilirubin progression B over postnatal age t consists of a production and elimination part for bilirubin. Details about the mathematical structure of model can be found in the patent EP3688473 (B1).

The computer model consists of several parameters that must be adjusted to describe bilirubin changes in an individual neonate. Every model parameter has a population value describing the average behavior in the population. To characterize individuals in a population, model parameters follow a log-normal distribution. Hence, in addition to the population value, an estimate of the variance of random effects is necessary to characterize inter-individual variability.

Contents

1.   General use of the product

1.1   General

Our General Terms and Conditions of Sale apply in their current version. Agreements deviating from these do not restrict the statutory rights of the buyer.

As the product manufacturer, NeoPrediX AG assumes no liability for direct damage or consequential damage caused by improper use or handling.

Non-observance of the instructions below, improper handling or improper use of the products supplied by us leads to the exclusion of any guarantee and liability claims. It is not possible to hold NeoPrediX AG liable for any resulting damage.

1.2   This product is intended solely for use by healthcare professionals who have been specifically trained. The specialist staff decides on the suitability for the intended application.

1.3   Intended Use

The NeoPrediX B.1 algorithm characterizes and predicts bilirubin progression over postnatal age in newborns.

1.4   Indications for Use

NeoPrediX B.1 is intended to be utilized with all conditions and indications, with the restriction that phototherapy treatment must not be undertaken prior to the first bilirubin measurement. The product is intended to be used for neonates born with a gestational age between 34+0 and 42+6 (week + day).

For the prediction, the following input parameters are required:

- Date and time of birth in hh:min between 0 hrs and 24 hrs
- Gestational age measured in weeks + days at the day of delivery, between 34+0 and 42+6
- Birth weight in g or oz between 1500 g and 5000 g or 52.9 oz 176.3 oz. The minimal birth weight for gestational age ranging from 34+0 until 36+6 is 1500g. The minimal birth weight for gestational age 37+0 or higher is 2500g
- Delivery mode: vaginal or cesarean section
- One or multiple bilirubin values within a range of > 17.1 μmol/l and < 256.5 μmol/l or > 1 mg/dl and < 15 mg/dl measured either optically (transcutaneous bilirubin (TcB) with any registered TcB device in the respective market) or as total serum bilirubin (TSB)

NeoPrediX B.1 predicts bilirubin progression up to 48 hrs after the last measurement. Bilirubin progression is visualized on a graph displaying bilirubin in μmol/l or mg/dl over postnatal age in hours.

1.5   1.2.2   Contraindications

If one or more of the following contraindications is present, NeoPrediX B.1 cannot be applied.

List of contraindications:

- Phototherapy prior to first bilirubin measurement
- Neonatal cholestasis (congenital or acquired liver dysfunction of various causes during neonatal period)
- Hydrops fetalis
- Neonatal sepsis
- Severe asphyxia (Apgar1score < 4)
- Hypoxic ischemic encephalopathy
- Malformation of the digestive tract and / or liver
- Systemic antibiotic treatment
- Congenital metabolic diseases

1.6 Foreseeable Misuse

- Utilizing output as therapy decision

2   Safe Use

The operator is responsible for ensuring that all persons who handle the product understand and follow the information and instructions in this document.

- Read these instructions and keep them for future reference.
- Ensure that these instructions are accessible at all times.
- Use the prediction software only as indicated.
- Ensure that the prediction software is only utilized by properly trained and qualified professionals.
- Ensure that the attending physician has mastered the recognized treatment techniques both in theory and in practice.
- The attending physician is responsible for the proper recording of the values and data.
- The attending physician is responsible for properly carrying out treatment.

2.1   Data Security

- The Licensee is responsible for establishing an appropriate set of security measures and a secure environment outside of the software system mentioned herein (e.g., security of the operating system, browser, restricted physical access to specific areas of the use environment of the software system., This includes ensuring that proper security is maintained during the operation and application of the software system.

- The Licensee must:
  o ensure required level of security for the operational environment, including required infrastructure (e.g., latest version of browsers, network, physical access)
  o ensure that personnel are properly trained and available in case of security issues
  o ensure that system is used as prescribed by manufacturer guidelines (e.g., no physical access by unauthorized users, password policy compliance)
  o ensure that prescribed maintenance is conducted as required, including acceptance and installation/deployment of security updates/ patches provided by the manufacturer
  o notify the manufacturer (e.g., Microsoft, NeoPrediX) without delay of any suspected security event
  o including information regarding what, where and how data is stored, as well as any security controls to safeguard the data in the cloud environment (e.g., encryption)

- The manufacturer's assumptions regarding the IT security of the Licensee and operating environment are stated in the Instruction for Use. The IFU should inform the operator about:
  o the security-by-default principle: the software system provides the highest possible security settings by default
  o applying best-practice security standards and the need for the Licensee to follow the manufacturers' published IT-security requirements
  o user requirements in terms of training / required skills (no special training or skills are required in the context of cybersecurity and the use of the software system)
  o user roles and corresponding access privileges/permissions to the software system or with regard to software system usage
  o the description of assumptions regarding requirements related to the use environment
  o minimum requirements for operation/the workstations intended for user operations (e.g., use only a computer, not a tablet or other mobile devices)
  o using the latest update of compatible browsers (including a list of compatible browsers)
  o securing the computer (e.g., protection from unauthorized access)
  o keeping anti-malware software up to date
  o turning off features/applications that are not used and do not contribute to security (relevant also outside of the software system, e.g., applications on the runtime environment)
  o protection of healthcare data and personally identifiable information (outside of the software system, including exported and printed .pdf files)

- o password and password policy, including:
    - change of default passwords during first login
    - that the operator should use sufficiently complex passwords

- o necessary information about planned updates/ patches and information with the latest version of software and a description of backup and update procedures by the manufacturer

- o how forensic evidence is captured, including any log files kept for a security event. For example: log files descriptions include how and where the log file is located, stored, recycled, archived, and how it could be consumed by automated analysis software

- o how the design enables the device to announce when anomalous conditions are detected (i.e., security events). Security event types could be configuration changes, network anomalies, login attempts, anomalous traffic (e.g., send requests to unknown entities)

3   Symbols

3.1   Warning notices

Warning notices will be displayed as pop-ups:
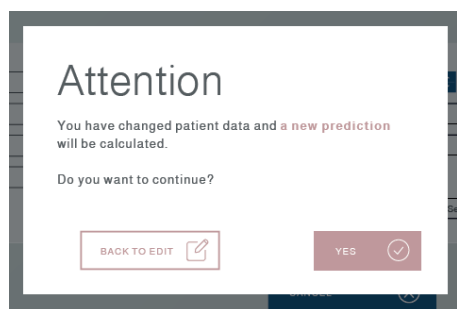
3.2   Symbols Glossary

Operational symbols in the software tool:

	optical measurement / none-invasive / transcutaneous bilirubin (TcB)
	total serum bilirubin (TSB)
	Nomogram curve show/hide
	Prediction show/hide

Other product symbols:

REF	Reference Number
UDI	Unique Device Identification
LOT	Software Version
	Manufacturer
	Instruction for Use
CE 0297	CE-Mark / Identification of Notified Body

4. Specifications

Technical Minimum Specifications

- PC with input options or Tablet-PC
- Internet connection (DSL with min. 1 Mbit/s or higher connection speed)
- Browser (Google Chrome, Microsoft Edge, Mozilla Firefox), no older than 6 months
- Processor: 1 GHz or higher
- RAM: 1 GB or more
- Display resolution: 1376 × 768 pixels

Medical Minimum Specifications

- Formats
  - Date: yyyy:mm:dd
  - Time: 24-hour scale hh:min
- Birth Mode
  - Vaginal
  - Cesarean Section
- Gestational age in weeks and days, between 34+0 and 42+6
- Birth weight in g or oz., between 1500 and 5000 g or 52.9 and 176.3 oz.
  - The minimum weight for a gestational age between 34+0 und 36+6 is 1500 g.
  - The minimum weight for a gestational age greater than 37+0 is 2500 g.

Maximum Bilirubin Values

- Bilirubin values for TSB or TcB:
  - 17.1 – 256.5 µmol/l (1 decimal place)
  - 1 - 15 mg/dl (1 decimal place)
- TcB, with any device registered for measuring TcB with CE mark or FDA clearance.
- Scale limits
  - x-axis: Postnatal age between 0 and 144 hours
  - y-axis: Bilirubin between 0 and 428 µmol/l and mg/dl
- The forecast has been proven to be more than 95% accurate. However, in order to compensate for measurement accuracy, we work within a safety margin which ranges from 5 to 25% over time.
- Option to show/hide the percentile limits per the Bhutani nomogram

Postnatal Age (PNA) in Hours	Maximum Bilirubin Value	
	mg/dl	µmol/l
between ≥ 8 and ≤ 60	15.0	256.5
between > 60 and ≤ 72	16.0	273.6
between > 72 and ≤ 84	17.0	290.7
between > 84 and ≤ 96	18.0	307.8

5.   Login information

5.1 Customer name, user, password

CUSTOMER NAME	
USER	
PASSWORD	

LOGIN

Forgot your Password? Click here!

The customer's name is the name of the institution.

User is the user´s name.

The initial password will be delivered to you by the administrator. On your first log in you will be requested to set your own private secure password.

The login credentials will be transmitted issued through the operator.

5.1.2 Forgot Password
If you have forgotten your password, click on the link displayed on the login page to have the password reset. You will then receive an email with the option to reset your old password or assign a new one.

5.2 Change language
Set user interface language to either „English" or „German" after login.

6. Dashboard for patient overview

6.1 Patient Overview

Patient Overview page shows patient data sets already stored in the system. By default, they are sorted by Day of Birth and time. Sorting can be changed in the respective column headings by clicking the left mouse button.

The following patient information is displayed for each patient:

- Patient File ID
- Child name
- Day of birth
- Age in hours
- Hours since last measurement
- Value of bilirubin in measurement units mg/dl or μmol/l, depending on the region or the hospital

7. Enter and edit Patient Data

7.1 Entering data from patient

Click „ADD NEW PATIENT" to create a new patient.

Child Data

LAST NAME	
FIRST NAME	
MIDDLE NAME	
PATIENT ID	

Input data as shown to create a new data set (all fields allow each max. 50 characters)

- Last name (only letters and no numbers)
- First name (only letters and no numbers)
- Middle name
- Patient ID (unique ID for each patient)

Mandatory field is: Patient ID

- The Patient ID field is mandatory and must follow the rules such as:
    o The patient file ID is unique for each individual customer
    o the file ID has max 50 char. (min length 1)
    o no special/control characters are used (characters that are not allowed: ".", "'", Unicode-characters U+007F - U+009F / special characters that are allowed: ";", ",", "/", "?", ":", "@", "&", "=", "+", "$", "." + in combination with a word

	three days ago	Sunday, March 6	
	two days ago	Monday, March 7	
DAY OF BIRTH	yesterday	Tuesday, March 8	⌨
	today	Wednesday, March 9	
TIME OF BIRTH	00 hours	00 minutes	am ‖ pm
GESTATIONAL AGE	week 40	+ 3	
BIRTH WEIGHT	3480 gram		
DELIVERY MODE	Vaginal birth	‖ Cesarian Section	

The following information is mandatory for the forecast of the bilirubin development:

- Date and time of birth
- Birth weight
- Gestational age in weeks + days (ranging from 34+0 to 42+6) determined at day of birth
- Delivery mode: vaginal or cesarean section

7.2 Enter bilirubin measurement

Bilirubin measurements can be entered in two different ways. The first method is by editing the patient data set.

The second method is by using the last column in the dashboard to add a new measurement.

Upon selecting "Add Measurement," the input interface opens on the display. Previously entered information in the patient data set is shown to the left.

7.2.2 General information about rules for inputting bilirubin values

Bilirubin values must be measured either transcutaneously or in blood serum/capillary blood, with the first measurement taken ≥ 8 hrs and ≤ 72 hrs postnatal. Subsequent measurements must be ≥ 24 hrs and ≤ 96 hrs postnatal at intervals of ≥ 8 hrs after the previous measurement.

Notes regarding measurement:
For TcB and TSB, the device requires that the first measurement be taken within ≥ 8 hrs and ≤ 72 hrs postnatal and at least two further measurements at ≥ 24 hrs and ≤ 96 hrs.

7.2.3 Detailed input rules for all possible scenarios

Refer to the input rules below for all possible scenarios.

Prediction up to 24 hours:

Scenario 1: TSB/Capillary measurements only
The tool requires one TSB/capillary measurement at ≥ 8 hrs and ≤ 72 hrs postnatal.

Prediction up to 48 hours:

Scenario 2: TSB/Capillary measurements only
The tool requires the first TSB/capillary measurement at ≥ 8 hrs and ≤ 72 hrs postnatal and at least one additional TSB/capillary measurement ≥ 24 hrs and ≤ 96 hrs postnatal.

Scenario 3: First measurement TSB/Capillary and all further measurements TcB only
The tool requires the first TSB/capillary measurement at ≥ 8 hrs and ≤ 72 hrs postnatal and at least one additional TcB measurement at ≥ 24 hrs and ≤ 96 hrs postnatal.
For this scenario we follow this procedure: The first TSB measurement is converted to TcB by adding 14.36 µmol/l (0.84 mg/dl) to the TSB value. This is done according to "TcB value is presented in parenthesis. Adjusted based on Taylor et al. (2015) (https://pubmed.ncbi.nlm.nih.gov/25601981/)"

TcB can be measured using any registered TcB device in the respective market with either CE or FDA approval.

Scenario 4: TcB measurements only
The tool requires the first TcB measurement at ≥ 8 hrs and ≤ 72 hrs postnatal and at least two additional TcB measurements ≥ 24 hrs and ≤ 96 hrs postnatal. TcB can be measured using any registered TcB device in the respective market with either CE or FDA approval.

7.2.4 Edit/change patient data

Use the patient list to open desired data set

Click on „EDIT PATIENT DATA" to edit an input.

The birth time is unique and cannot be edited when there are bilirubin values entered into the system.

Perform necessary edits and save new input.

8. Prediction of bilirubin progression

The precision of predicted bilirubin progression can vary due to intra-individual variability such as biological factors, as well as measurement errors in laboratories. The NeoPrediX B.1 provides dynamics of bilirubin progression for up to 48 hrs after the last measurement with a potentially maximal prediction horizon of 144 hrs postnatal. Bilirubin progression is visualized on a graph displaying bilirubin in µmol/l or mg/dl over postnatal age in hours.
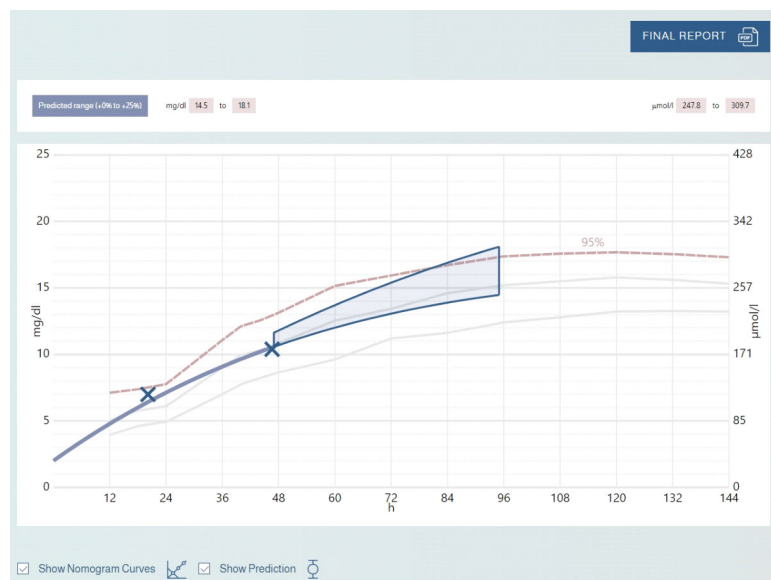
9. Final report as PDF

Click on „FINAL REPORT" to generate a PDF, which will open automatically.

NeoPrediX B.1

NeoPrediX

Final Report

Patient Information

Last name	Jackson	Date of birth	2021-Oct-04
First name	Lamar	Time of birth	11:30
Middle name		Birth weight	3070 Grams
Patient ID	32345	Gestational age	39 Weeks + 0 Days
		Delivery mode	cesarean section

Predicted range (+0% to +25%)   (mg/dl)   14.5 - 18.1   (µmol/l)   247.8 - 309.7
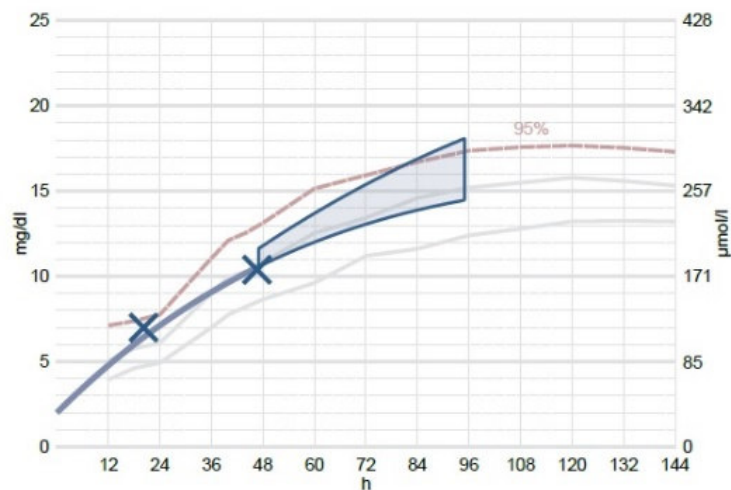
Bilirubin measurements

Hours after birth	Date	Time	Bilirubin (mg/dl)	Bilirubin (µmol/l)	Method TSB / TcB
20	2021-Oct-05	07:40	7.0	119.7	
46	2021-Oct-06	10:07	10.4	177.8	

Final Report 32345 - 2022-Feb-17 14:04:39

10. Cybersecurity

The operator is responsible for providing an appropriate set of security information and a security environment outside of the software system referred to herein (e.g., security of the operating system, browser, restricted physical access to certain areas of the software system's usage environment), which includes ensuring that security is maintained during the operation and use of the software system.

The operator should:

- Ensure the required security levels for the operating environment, including the required infrastructure (e.g., latest version of browsers, network, physical access)
- Ensure that personnel are properly trained and available in case of security issues
- Ensure that the system is used in accordance with manufacturer's guidelines (e.g., no physical access by unauthorized users, compliance with password policies)
- Ensure that prescribed maintenance is performed as required, including acceptance of installation and deployment of security updates/patches by the manufacturer
- Inform the manufacturer immediately of any suspected security incident

The manufacturer's assumptions regarding the IT security of the operator and the operating environment are specified in the instructions for use (IFU). The IFU should inform the operator of the following:

- about the security-by-default principle: By default, the software system provides the highest possible security settings, including information about what, where and how data is stored, as well as security controls to protect the data in the cloud environment (e.g., encryption)
- best practice security standards are to be applied, and the operator should follow the published IT security requirements of the manufacturer
- about user requirements related to training/required skills: no special training or skills related to cybersecurity and the use of the software system are required
- about user roles and corresponding access rights/authorizations to the software system or in relation to the use of the software system
- about description of assumptions regarding the requirements of the operating environment
- minimum requirements for operation/workstations intended for user operation (e.g., use only computer, noy tablets or other mobile devices)
- using the latest update of compatible browsers (including a list of compatible browsers)
- securing your computer (for example, protecting against unauthorized access)
- keeping anti-malware Software up to date
- Switching off functions/applications that are not used and do not contribute to security (relevant also outside the software system, e.g., applications on the runtime environment)
- protection of health data and PII (personally identifiable information) (outside the software system, including exported and printed PDF files)
- password und password policy, including:
    - changing default passwords at first login
    - that users should create sufficiently complex passwords

- Necessary information about planned updates/patches and information about the latest software version and description of the backup and update procedure by the manufacturer
- how forensic evidence is captured, including any log files retained for a security event. For example: Descriptions of log files include how and where the log file is located, stored, recycled, archived, and how it could be used by automated analytics software.
- how the design allows the device to report when anomalous activity is detected (i.e., security events). Types of security events can include configuration changes, network anomalies, logon attempts, anomalous traffic (for example, sending requests from unknown entities).

11. Sample Patient Data

Before every use, please check, by inputting the sample patient data below, if the output aligns with the Final Report shown on the previous page. If the comparison does not match, stop using NeoPrediX B.1 for prediction of the bilirubin progression for newborns. Report the incident to NeoPrediX.

Date of birth: 2021.10.4

Time of birth: 11:30

Birthweight 3070g

Gestational age: 39 + 0

Delivery mode: cesarean

First measurement: 2021.10.5   7:40   7 mg/dl TSB

Second measurement: 2021.10.6   10:07   10,4 mg/dl TSB

Contact

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Support

Online support is available via the Help function in the application.

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