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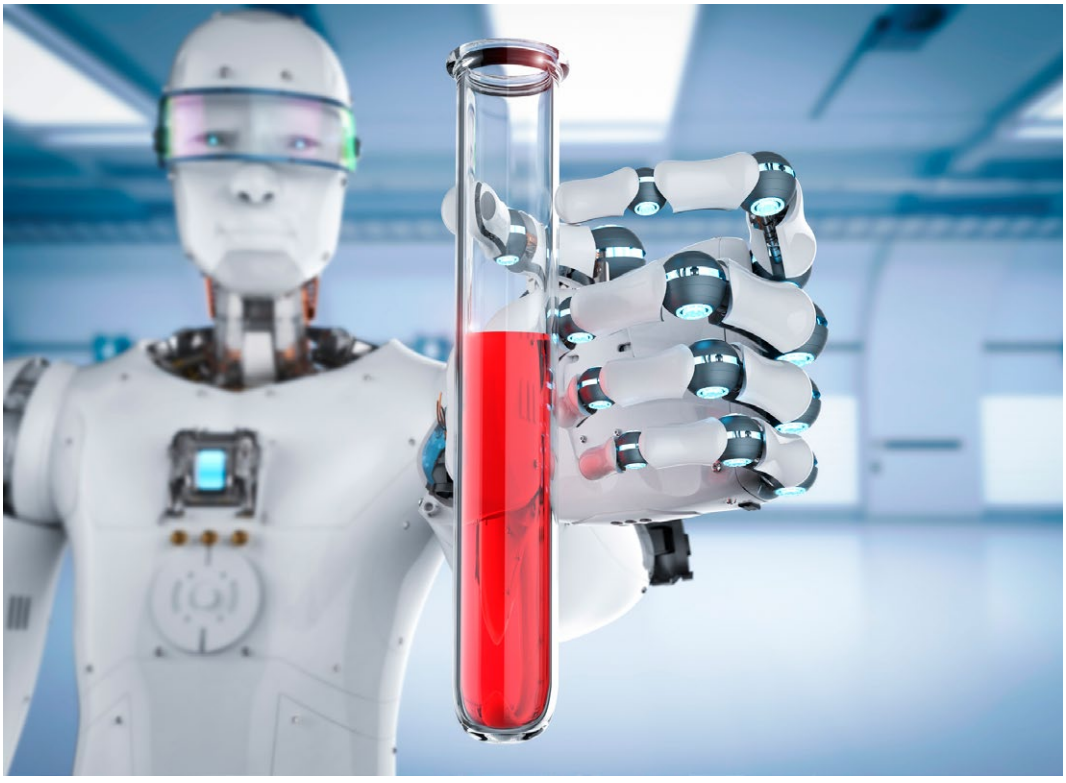
Klinisk Biokemi i Norden



Nordisk Forening for Klinisk Kemi

Nr. 2 · vol. 36 · 2024

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INDHOLD

Front page: *Do you wonder if the phlebotomy process can be automated? Go to page 38.*

Glykosylering eller inte glykosylering – det är frågan

Anders Larsson
Klinisk kemi och Farmakologi, Uppsala
anders.larsson@akademiska.se

To be, or not to be kommer från Hamlet och eftersom Hamlet var dansk prins så borde väl det tillhöra området för KBN? Hamlet reflekterade över livet, döden och de inre konflikter som han kände. Vi reflekterar också över dessa frågor, men kanske ännu mer över analysernas riktighet. En grundbult i vår verksamhet är att vi skall ha samma utslag i våra analysinstrument för proverna som för kalibratorerna. I annat fall riskerar vi att drabbas av analystekniska problem och bias. Våra prover är i princip alltid från människor med en glykosyleringsform typisk för människa även om glykosyleringen kan variera mellan olika prover. Problemet är att vi ofta inte vet hur glykosyleringen av våra kalibratorer är och, om vi pratar immunologiska tester, var antikropparna binder in. Eftersom det kan vara svårt att samla in stora mängder provmaterial för att skapa nativa kalibratorer så kan vi nog misstänka att många av kalibratorerna är icke-nativa och skulle kunna skilja sig vad gäller glykosylering mot nativa proteiner. Egentligen pratar vi ganska lite om post-translationella modifieringar.

Sarah Bernhardt in Hamlet (1899). Lafayette Photo, London, Public domain, via Wikimedia Commons.

Glykosylering är en post-translationsförändring som medför att kolhydratgrupper binds till proteiner. Det är en viktig process som påverkar proteinets struktur, stabilitet och funktion. Det finns olika typer av glykosylering av proteiner som skiljer sig åt i hur kolhydraterna kopplas till proteinet. Här är några av de vanligaste formerna av glykosylering:

N-länkad glykosylering: I denna typ av glykosylering kopplas en kolhydratgrupp till aminosyran asparagin (N) i proteinet. Kolhydratgruppen består främst av N-acetylglukosamin och manos. Denna form av glykosylering sker i endoplasmatiska nätverket och Golgi-apparaten.

O-länkad glykosylering: I denna typ av glykosylering kopplas en kolhydratgrupp till aminosyran serin eller treonin (O) i proteinet. Kolhydratgruppen består främst av N-acetylglukosamin och galaktos. Denna form av glykosylering sker främst i Golgi-apparaten.

C-länkad glykosylering: Denna typ av glykosylering är ovanligare och innebär att en kolhydratgrupp kopplas till en aminosyra via en kolatom (C) istället för en syreatom. Kolhydratgrupperna som används i denna form av glykosylering är ofta mer komplexa än de som används i N- och O-länkad glykosylering.

Skillnaderna i glykosylering av proteiner beror främst på vilka aminosyror som är involverade och vilka kolhydratgrupper som används. Varje typ av glykosylering påverkar proteinets egenskaper och funktion på olika sätt.

Det finns också andra typer av posttranslationella modifieringar som tex karbamylering hos njursjuka patienter. Vi använder dessa posttranslationella modifieringarna tex när vi mäter HbA1c. Vi vet däremot

MAGLUMI® Chemiluminescence Immunoassay Test Menu

(236 Parameters)

Glyco Metabolism

C-Peptide	IAA (Anti Insulin)
Insulin	Proinsulin
GAD 65	*Glucagon
Anti-IA2	*Anti-ZnT8
ICA	

Hepatic Fibrosis

HA	Laminin
PIIIP N-P	Cholyglycine
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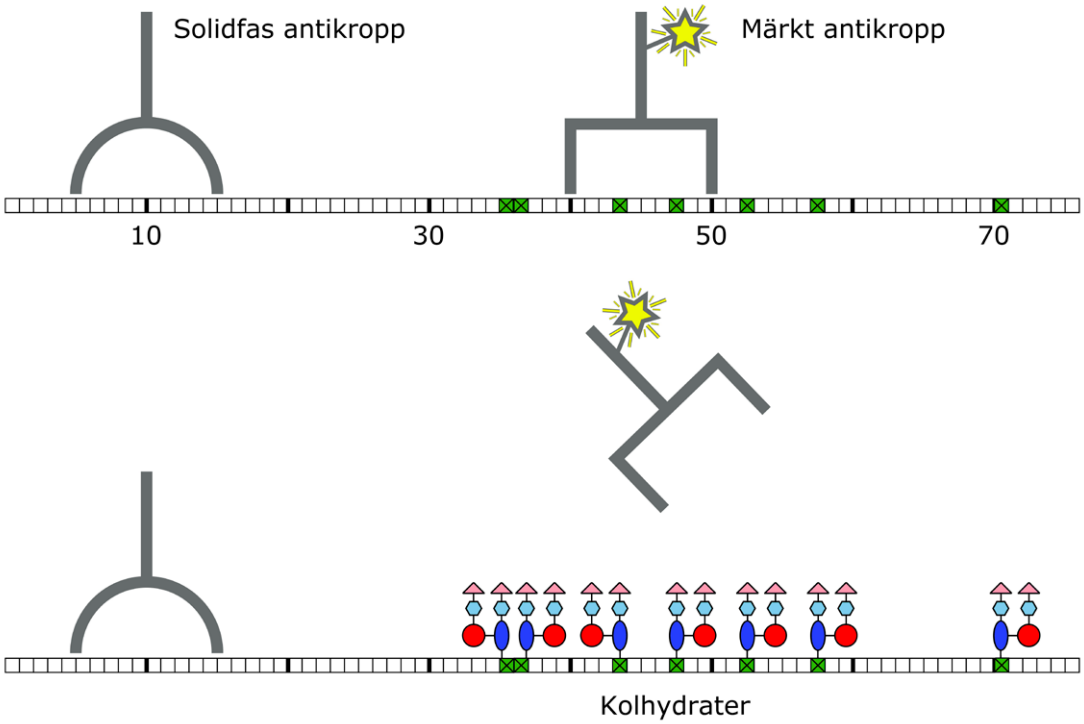

Figur: Schematisk presentation av att glykosylering av NT-proBNP hämmar bindningen av signalantikroppen till polypeptidkedjan. Figuren er ritad av Henrik Alfthan.

ofta inte hur vanliga dessa modifieringar är för våra andra analyser. Det kanske är betydligt vanligare än vad vi normalt tror?

Analysproblem på grund av glykosylering av NT-proBNP

För ett tag sedan blev jag uppmärksammad på att glykosylering av NT-proBNP kunde ge upphov till analysproblem. Roche är den helt klart ledande tillverkaren av NT-proBNP reagens sedan många år. De antikroppar som Roche använder är riktade mot icke-glykosylerade epitoper i de normalt glykosylerade regionerna i NT-proBNP molekylen. Det innebär i sin tur att nativa NT-proBNP molekyler ger en svagare signal då glykosyleringen hämmar bindningen. NT-proBNP är ju en högvolymsanalys vilket innebär att det kommer att vara svårt att få tillräckligt stora mängder nativt NT-proBNP för kalibrering av alla tester, och det förefaller också så att glykosyleringsskillnaderna är störst i det låga intervallet, vilket gör att nivåerna av NT-proBNP påverkar glykosyleringsgraden. Det innebär ytterligare svårigheter att använda sig av nativa kalibratorer.

Om vi byter ut antikropparna mot antikroppar som binder till icke-glykosylerade regioner så kommer kalibrator och prov se mer lika ut och vi kommer få högre NT-proBNP värden. Problemet är att Roche metoden är helt dominerande på marknaden. Även om den då mäter fel, så kanske det ändå är rätt pga. att den är dominerande på marknaden. Det fanns tidigare ett liknande resonemang kring HbA1c där de gamla metoderna överbestämde HbA1c och även de gamla kreatininmetoderna (Jaffe) gav högre värden. Då pratade vi om feltolkningsrisker framför allt om skillnaderna inte var så stora att man begrep att det var en helt annan kalibrering. En av de viktigaste orsakerna till att vi bytte från HbA1c i % till HbA1c i mmol/mol var att minska risken för feltolkningar.

Om vi nu får nya NT-proBNP metoder med antikroppar som inte påverkas av glykosyleringsgraden så kommer de ge högre värden. Vi pratar någonstans i intervallet 2–10 gånger vilket helt förvrider de beslutsgränser som våra hjärtsviktsdoktorer normalt arbetar med. Hur hanterar vi det i rutinsjukvården? Faktoriserar ner dem till en Roche nivå som är felaktig då den

påverkas av glykosyleringsgraden? Faktoriserar upp Roche metoden? Har 2 olika metoder parallellt? Det är ett svårt problem att lösa. Vi kan anta att det finns många liknande fall där glykosyleringen har betydelse i förhållande till det antikroppar som används i testen. För oss på laboratoriet kommer det vara svårt att veta när vi har påverkan eller inte.

Olika NPU koder for metoder med olik glykosyleringspåverkan?

Eftersom glykosyleringspåverkan troligen kommer omfatta många olika proteiner och kommer vara beroende av de specifika antikropparnas bindningsplatser på proteinet, så kommer vi behöva en övergripande strategi. Mitt förslag skulle vara att vi går mot en definiering av analysmetoderna utifrån om de påverkas av glykosylering eller inte och att vi har olika NPU koder för metodgrupperna. Tex NT-proBNP glykosylerat och NT-proBNP icke-glykosylerat. Andra förslag? Det ger oss åtminstone möjligheter att få kunskaper om ev. metodskillnader.

När frågade ni senast er tillverkare av era immunologiska reagens hur den posttranslationella modifieringen var hos firmans kalibratorer i förhållande till patientproverna? Förstod firmarepresentanten frågan och kunde de ge ett begripligt svar?

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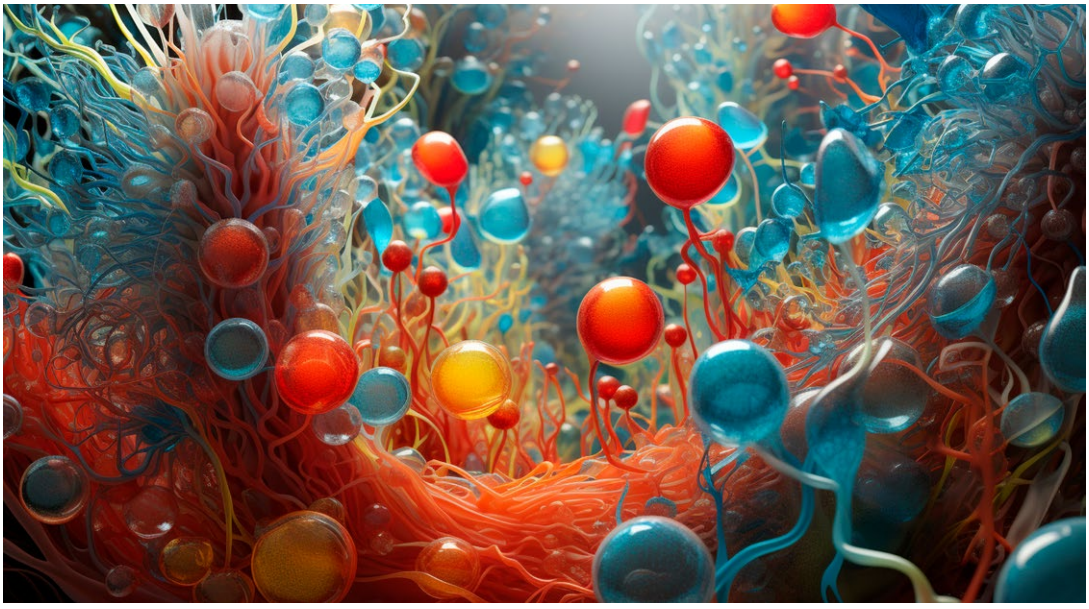

Documenting the intricate arrangement of molecules in a glycoprotein (Adobe Stock, genererad med AI)

Ordförandespalten

Per Bjellerup
NFKK chairman

Dear KBN reader!
I have just read that we have had the coldest April since 1997 and I think they are right! Spring is fighting against Winter and will eventually win! That is for sure even though it is snowing here today!

The fight against Alzheimer's disease
In this issue we have a very interesting article about the current status of biochemical diagnosis of Alzheimer's disease written by PhD-student Joel Simrén and Professor Henrik Zetterberg. Henrik and Professor Kaj Blennow at Gothenburg University Hospital have, over decades, produced internationally renowned results in this field. Furthermore, Henrik has recently been awarded the *Ingvarpriset* by the *Swedish Society of Medicine* for his invaluable contribution to clinical neuroscience! Henrik was also awarded the Society's *20-year jubilee bronze medal.* Our congratulations to Henrik!

There are rapid developments in the field of dementia. The Alzheimer's Association, a nonprofit organization located in Chicago, are in the process of upgrading their criteria for the diagnosis and staging of Alzheimer's disease which will include blood biomarkers. A draft of their recommendations is available and has already been discussed in the *Swedish Läkartidningen* (https://lakartidningen se/opinion/debatt/2024/04/biomarkortest-foreslas-inte-ensamtdiagnostisera- alzheimer/). The Alzheimer's Association's final report is anticipated later this year.

The XXXIX Nordic Congress in Clinical Chemistry September 2024
Regarding Alzheimer's disease, we are very pleased that Professor Kaj Blennow will give a plenary lecture at our Nordic Congress. In this issue of KBN you will have more detailed information about the Congress and the program. **Do not hesitate, register today! Now! At https://nfkk2024.se/ The early bird price will end the 31th of May.**

The Congress Program
The program is almost finalised and you can find it in this issue. I think that it is a very well composed program that the Scientific Board with chairman Professor Uwe Tietge has delivered with several very prominent speakers, several really hot topics and with contribution from all the Nordic countries.

Poster abstracts
As of now the Congress has received more than 40 abstracts and as you have already read, there are two tracks for the posters, one **Scientific** and one **Developments and Improvements**.

The NFKK Board 2024
Our Board meeting in Helsinki was on a cold and snowy day in April but the atmosphere was warm and pleasant and everything was very well organized by our Finnish hosts. Many issues were on the agenda. One crusial issue is the future of the Nordic Congress. The congresses in 2020 and 2022 were cancelled due to the pandemic and turned expected incomes to economic losses. We look forward to a high number of participants in September. And I am sure, if you just read the Scientific program, you will want to be there.

The NFKK working groups
At present we have one group up and running, it is *The Recommendations from The Nordic preanalytical scientific working group* with Mads Nybo as chairman. They will present their work at the Congress. We are looking forward to this.

If you have an idea and want to start a new working group supported by NFKK, please send me a mail and we will see what we can do.

By the way, our Norwegian tennis player Casper Ruud won his first ATP500 tournament in Barcelona last week! Congratulations to Casper and our Norwegian friends!

The days are getting warmer, enjoy!

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Welcome to the 39th Nordic congress of Clinical Chemistry in Stockholm!

Anna Engberg[1], Stina Kronberg[2], Maysae Quttineh[2], Inga Zelvytė[3], Johan Skogö[3], Per Bjellerup[4], Charlotte Gran[5]

[1] The Swedish association of Clinical Biochemists session, SSKF

[2] The Institute for Biomedical Laboratory Science session, IBL

[3] The Swedish Society for Clinical Chemistry session, SFKK

[4] The Nordic Society for Clinical Chemistry session, NFKK

[5] Klinisk Kemi, Karolinska University hospital, Karolinska

Welcome to the Nordic Congress in Clinical Chemistry 2024, where leaders, innovators, and practitioners converge to explore the latest advancements and challenges in laboratory medicine. Hosted by Karolinska University Hospital, in collaboration with The Swedish Association of Clinical Biochemists, The Institute for Biomedical Laboratory Science, The Swedish Society for Clinical Chemistry, and the Nordic Society for Clinical Chemistry, this year's program promises a rich tapestry of scientific inquiry and professional development.

Under the theme of "Development and Improvement," the congress will delve into the dynamic landscape of laboratory operations, focusing on key areas driving scientific research forward. Laboratories serve as the backbone of innovation, and this track will highlight efforts to enhance efficiency, accuracy, and the overall scientific process. From leveraging information technology to fostering healthy workplaces, attendees will explore strategies to elevate laboratory competence and address future challenges. One highlight of this track is the session on "Laboratory Medicine in the Times of Crisis," where frontline staff from humanitarian organization Médecins Sans Frontières will share their experiences navigating healthcare and laboratory operations amidst extreme circumstances, including natural disasters and conflict zones.

The program also features sessions curated by the co-organizations such as The Swedish Association of Clinical Biochemists, The Swedish Society for Clinical Chemistry, and The Institute for Biomedical Laboratory Science. These sessions delve into pressing issues facing the field, from optimizing hormone level measurements to promoting wise choices in clinical chemistry testing.

The Swedish association of Clinical Biochemists session

Suboptimal levels of sex hormones, including androgens, impact several aspects of the wellbeing of women, ranging from fertility, libido and physical performance. The increased availability of LC-MSMS in clinical laboratories have opened up the possibility to determine very low levels of sex hormones. This development enables a more precise diagnosis, monitoring and potential for treatment of patients.

The Swedish association of Clinical Biochemists are very pleased to introduce two experts in this field: associated professor Henrik Ryberg who will walk us through the technical aspects of measurement of low levels of sex hormones with LC-MSMS at a clinical laboratory. Furthermore, Professor Angelica Lindén

Hirschberg will share her proficiency in reproductive endocrinology and metabolism, with a special emphasis on the importance of adequate levels of testosterone in women.

The Swedish Society for Clinical Chemistry session

Few would deny that quality, not quantity, lies at the heart of healthcare and that less is sometimes more. There is an international discussion among clinicians whether we have reached a point where we as health care providers are sometimes doing too much for our patients, where additional investigation and treatment are doing more harm than good for the individual, that there are unnecessary procedures and test.

The choosing wisely campaign, founded in the USA more than 20 years ago, is an international movement that aims to reduce the use of unnecessary, low-value medical services through conscious choice since each patient's situation is unique. A big part of these conversations is related to laboratory tests. The Swedish Medical Association has established a national branch of the choosing wisely campaign in Sweden and clinical chemistry testing is a big part of the conversation.

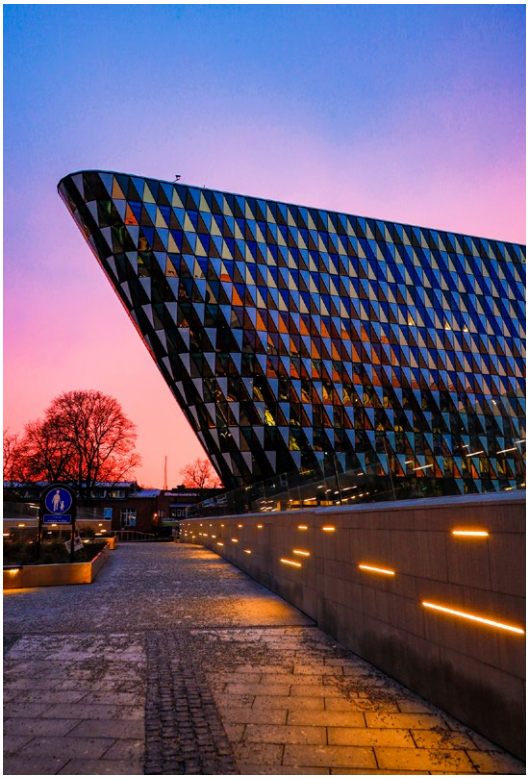
The Swedish Society for Clinical Chemistry are very happy to invite you to a conversation about wise choices in Nordic clinical chemistry and to hear the experiences from professor Ketil Størdal, national spokesperson for Choosing Wisely Norway in the Norwegian Medical Association, and past president of the Norwegian Paediatric Association who will, among other things speak about the "Ikke stikk meg uten grunn" (don't prick without reason) campaign in Norway. We will also hear from Senior Consultant emergency doctor Kristina Bengtsson Linde on how to choose clinical chemistry analysis wisely in the emergency department.

The Institute for Biomedical Laboratory Science session

Biomedical laboratory scientists (BLS) are essential for health care diagnostics, which is a field that is developing rapidly due to improvements in medicine, methodology, and technology. However, three of four Nordic countries report current and future challenges in BLS workforce. In this session we will discuss changes, challenges, and opportunities in the context of the BLS profession and its development.

The Vasa Museum on Djurgården will host the congress dinner where the Lorentz Eldjarn Prize and the poster price winners will be presented.

The Institute for Biomedical Laboratory Science is thrilled to present two distinguished speakers who will enlighten us on various facets of the field. First up, Associate Professor G. Lillsunde Larsson will delve into "70 years with the International Federation of Biomedical Science (IFBLS)," offering insights into the organization's rich history and global impact. Additionally, she will cap off the session with an invigorating discussion on the "Action Plan for the Future," focusing on the current landscape for biomedical laboratory scientists in Denmark, Finland, Norway, and Sweden. Next in line, Biomedical Laboratory Scientist Å. Gyberg-Karlsson will lead us through an exploration of "Future Developments in Biomedicine and Health," shedding light on emerging trends that hold the potential to shape both our profession and society at large. Their expertise promises to spark thought-provoking conversations and inspire innovative approaches within the field of biomedical laboratory science.



The sponsor exhibition and poster mingel will be held at the main congress hall, Aula Medica at Karolinska Institutet.

The Nordic Federation of Clinical Chemistry sessions

Nordic screening programs

Professor Kristinsson, leading researcher world-wide in the field of multiple myeloma, will describe the Iceland Screens, Treats, or Prevents Multiple Myeloma study (iStopMM), the first population-based screening study for MGUS including a randomized trial of follow-up strategies. Icelandic residents born before 1976 were offered participation.

Professor Bratt, chair of the Swedish National Organised Prostate Cancer Testing (OPT) Group, will present their work and the newly updated program with the aims to make today's PSA testing more equal and structured throughout Sweden. How to reduce overdiagnosing prostate cancer will also be discussed.

Plenary session: Clinical metabolomics, a new era for laboratory medicine

The future is here! Masspectrometry (MS) technology and computer power have made it possible to go from analysis of individual biomarkers to mapping large patterns of metabolites in tissues and body fluids. The disease phenotype described using global metabolomics and images of the spatial distributions of chemicals on surfaces (mass spectrometry imaging) will be highlighted in this session. The interpretation challenges and the role of the laboratory doctor in this new area of precision medicine will also be discussed.

Recommendations from The Nordic preanalytical scientific working group

Preanalysis has been considered an important area for 10 years or more, and working groups have been established under NFKK and EFLM. There are however many aspects that still need awareness and (hopefully) finalisation. The Nordic preanalytical scientific working group will therefore try to wrap up a number of preanalytical subjects, namely pneumatic tube systems, a Nordic blood sampling recommendation, how to handle haemolysis indices, and a Nordic fasting recommendation. This could be an important step!

Join us in Stockholm on September 17-20, 2024, for discovery, collaboration, and advancement in clinical chemistry. Together, we'll shape the future of laboratory medicine and pave the way for healthier communities worldwide.

Preliminary scientific program and confirmed speakers as of 6th May 2024

Please note that order and title of sessions, keynotes and lectures may change. The program is continuously updated on the homepage: https://nfkk2024.se/programme/scientific-program

Tuesday 17th September 2024			
12:30	**Opening Ceremony**		
12:45	**Plenary session on Cardiovascular disease: Lipid profile and cardiovascular disease** **Chair: U Tietge** (Sweden) **Prof. BG Nordestgaard** (Denmark)		
13:30	**Break**		
13:45	**The Lorentz Eldjarn Prize Competition for Best Publication** **Prof. JP Berg, Managing Editor of SJCLI** (Norway) The three nominated authors will present their articles The price ceremony will be held at the congress dinner on Thursday at the Vasa museum		
15:15	**Coffee & Exhibition**		
15:30	**Clinical chemistry through the ages: milestones, discoveries and innovations** **Chair: H Dahl** (Sweden) **Assoc Prof. A Kallner** (Sweden) **Prof. K Pulkki** (Finland)	**Kidney function measurement – what is needed in clinical practice?** **Chair: U Tietge** (Sweden) **Prof. M de Borst** (The Netherlands) Kidney function: glomerular filtration rate and beyond **PhD MD P Delanaye** (Belgium)	**Session by NFKK: Recommendations from The Nordic preanalytical scientific working group** **Chair: M Nybo** (Denmark) **Prof. J Cadamuro** (Austria) Progress in Europe on the preanalytical area? **PhD J Pelanti** (Finland) How do we use pneumatic tube systems in the Nordic countries? **PhD B Willman** (Sweden) Survey on Nordic blood sampling recommendation/status for blood sampling QC **PhD GBB Kristensen** (Norway) Recommendation on how to handle hemolysis indices **Assoc prof. M Nybo** (Denmark) Nordic fasting recommendation – how to proceed?
17:15	**Poster reception and mingle in Aula Medica**		

Wednesday 18th September 2024			
07:30		**Educational session** **Hematology – selected case discussion** **PhD MD S Beshara** (Sweden)	**Educational session** **Hot debate - Pros and cons of large-scale screening** **PhD MD N Bark** (Sweden)
08:15	**Break**		
08:30	**Nordic screening and testing programs** **Chairs: L Franson** (Iceland) & **P Bjellerup** (Sweden) **Prof. SY Kristinsson** (Iceland) Screening for monoclonal gammopathy of undetermined significance: a nationwide randomized clinical trial **Prof. O Bratt** (Sweden) Outcome of organised PSA testing in Sweden - Is there enough benefit?	**Erythrocyte disorders** **Chair: S Beshara** (Sweden) **Prof A Iolascon** (Italy) New insight in red cell membrane disorders: diagnosis and treatment **PhD MD O Klingenberg** (Norway) **PhD MD S Beshara** (Sweden) **MSc A Lundholm** (Sweden)	**Predicting the unpredictable? Novel developments to personalize healthcare** **Chair: P Parini** (Sweden) **Prof. S Meijer** (Sweden) **Prof. M Benson** (Sweden) Digital twins of individuals for predictive, preventive and personalised medicine
10:00	**Coffee & Exhibition**		
10:30	**Serum biomarkers for diagnosing cancer – where do we stand today?** **Chair: M Hansson** (Sweden) **PhD MD R Nome** (Norway)	**Alcohol and drug testing - new substances and new analytical problems** **Chair: G Eggersten** (Sweden) **Assoc Prof. A Helander** (Sweden)	**Transfer of PFAS from the mother and associated metabolic and neurodevelopmental changes in the child** **Chair: I Hokstad** (Norway) **PhD MD AL Bjørke-Monsen** (Norway)
11:00	**Break**		
11:15	**The Margareta Blombäck plenary session on Coagulation: Thrombotic Microangiopathies (TMA) - many diseases not so many tests- Special Focus om Preeclampsia** **Chair: Prof. J Antovic** (Sweden) **Prof. V Garovic** (USA)		
12:00	**12:00-13:45 Lunch & Exhibition**		
12:30	**Company session**	**Company session**	**Company session**
13:00	**12:00-13:45 Lunch & Exhibition**		

Wednesday 18th September 2024			
13:45	**Laboratory Medicine in times of crisis** **Chair: M Lambert** (Sweden) **Médecins Sans Frontières** **MD C Tosterud** (Sweden) - Healthcare during war	**Thrombotic microangiopathies - many diseases not so many tests** **Chair: J Antovic** (Sweden) **Prof. J Antovic** (Sweden) New approaches in the laboratory diagnosis of HUS/TTP **PhD MD M Farm** (Sweden) Laboratory role in the diagnosis and follow up the treatment in HIT **MD A Kimiaei** (Sweden) Implementing the ISTH guidelines for the diagnosis of lupus anticoagulant - our experience and lessons learned	**Session by Institutet för biomedicinsk laboratorievetenskap** **Chair: S Kronberg** (Sweden) and M Quttineh (Sweden) **Assoc Prof. G Lillsunde Larsson** (Sweden) 70 years with the International Federation of Biomedical Science (IFBLS) **Biomed lab scientist Å Gyberg-Karlsson** (Sweden) Future developments in biomedicine and health with the potential to impact our profession (and the society) **Assoc Prof. G Lillsunde Larsson** (Sweden) Actionplan for the Future- the situation for biomedical laboratory scientists in Denmark, Finland, Norway, and Sweden
15:15	**Coffee & Exhibition**		
15:45	**Healthy Workplaces, Healthy Workers: Tips and Tricks for Lab Pros** **Chair: A Dahlin** (Sweden) **RN. CCN. MSc. M Flodberg** (Sweden) **Å Malmenklev** (Sweden) **S Lööv** (Sweden)	**New targets, new opportunities? Cardiovascular biomarkers today and tomorrow** **Chair: U Tietge** (Sweden) **Prof. U Tietge** (Sweden)	**Liver diseases - an expanding medical field** **Chair: M Hansson** (Sweden) **Dr. M van Berkel** (Netherlands) **Adjunct Prof. H Hagström** (Sweden) Diagnosis and prognosis of steatotic liver disease
17:15	**End of day**		

Sunset view of Gamla stan in Stockholm.

Thursday 19th September 2024			
07:30	**Educational session** **Dyslipidemia – selected case discussion** **Prof. G Eggertsen** (Sweden)	**Educational session** **Coagulation** **PhD MD M Farm** (Sweden)	**Educational session** **New aspects on Vitamin B12 and folate deficience and the toxic effect of laughing gas** **Assoc Prof. H Nilsson-Ehle** (Sweden)
08:15	**Break**		
08:30	**Improvement and development** **Chair: A Linko-Parvinen** (Finland) **Assoc Prof. T Männistö** (Finland) Hypothyroidism is increasing – is it true or overdiagnosis? **Assoc Prof. S Wittfooth** (Finland) Recent developments in troponin assays	**AI - the future colleague in clinical chemistry** **Chair: P Parini** (Sweden) **Dr. G Menichetti** (USA) **Assoc Prof. N Fyhrquist** (Sweden)	**Session by the Swedish Association of Clinical Biochemists - Clinical importance of measurements of low levels of sex hormones** **Chair: A Engberg** (Sweden) **Prof. A Lindén Hirschberg** (Sweden) **Assoc Prof. H Ryberg** (Sweden) High-sensitive mass spectrometric assays for androgens and estrogens in the clinical lab
10:00	**Coffee & Exhibition**		
10:30	**Mass is King - Novel mass spectrometric applications in clinical chemistry** **Chair: L Tjernberg** (Sweden) **Prof. J Lehtiö** (Sweden) Proteomics for diagnosing disease **PhD S Gaunitz** (Sweden) Glycomics at Clinical chemistry	**Navigating Clinical Laboratory Values in the Era of CAR-T and CAR-NK Cell Therapy: Challenges and Opportunities** **Assoc Prof E Alici** (Sweden)	What clinical chemists should know about the interpretation of blood tests in transgender individuals **Prof. M den Heijer** (Netherlands)
11:00	**Break**		
11:15	**Plenary session on Neurodegenerative disease: Fluid biomarkers for Alzheimer's – finding the place of blood and CSF tests at the memory clinic and in the clinical chemistry lab** **Chair: L Tjernberg** (Sweden) **Prof. K Blennow** (Sweden)		
12:00	**12:00-13:45 Lunch & Exhibition**		
12:30	**Company session**	**Company session organised by Roche** **Step into the future with cobas Mass Spec analyzer, i601**	**Company session**
13:00	**12:00-13:45 Lunch & Exhibition**		

Thursday 19th September 2024			
13:45	**How paradigm shifts shape the future of laboratory medicine** **Chair: I Bartuseviciene** (Sweden) **Assoc Prof. P Conner** (Sweden) Prenatal paradigm **External quality assessment in laboratory medicine: what, how and why** **Chairs: L Spendrup & M Johansson** (Sweden) **Assoc Prof. L Björndahl** (Sweden) How new standards are developed – the professions can be in charge	**Blood biomarkers - A new era for diagnosing Alzheimer disease?** **Chair: L Tjernberg** (Sweden) Dr. T Karikari (Sweden) pTau variants predict disease **Assoc Prof. S Schedin Weiss** (Sweden) Glycans as novel biomarkers for Alzheimer disease **Prof. L Jönsson** (Sweden) Can we justify screening for Alzheimer disease?	**Laboratory and cancer associated thrombosis (CAT) - where we are** **Chair: J Antovic** (Sweden) **Prof. A Falanga** (Italy) Cancer associated thrombosis overview **Prof. J Odeberg** (Sweden) Proteomics in cancer associated thrombosis **PhD MD C Gran** (Sweden) The role of extracellular vesicles, tissue factor, and NETosis in cancer associated thrombosis
15:15	**Coffee & Exhibition**		
15:45	**External quality assessment in laboratory medicine: what, how and why** **Chairs: L Spendrup & M Johansson** (Sweden) **BSc Å Claesson** (Sweden) The significance of accreditation for the laboratory **MSc M Dajaku** (Sweden) Differences between ISO 15189:2012 and ISO 15189:2022	**Precision medicine: dream or reality?** **Chair: P Parini** (Sweden) **Prof. P Parini** (Sweden) **Assoc Prof. Å Wheelock** (Sweden)	**Session by BALM** **Chair: U Tietge** (Sweden) **PhD MD V Banys** (Lithuania) & **M Bieliauskas** (Lithuania) Roadtrip towards harmonized reporting of laboratory results in Lithuania. **MD J Meisters** (Latvia) **PhD A Tamm** (Estonia) Digital transmission of laboratory data in Estonia.
17:15	**End of day**		

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Friday 20th September 2024			
07:30		**Educational session** **Brain calcification – selected case discussion** **Assoc Prof. U Diczfalusy** (Sweden)	**Educational session - Analytical interference in Clinical chemistry** **MD M Karlman** (Sweden) **PhD MD P Bjellerup** (Sweden)
08:15	**Break**		
08:30	**The future of laboratories: trends, challenges and opportunities** **Chair: G Dahlfors** (Sweden) **PhD B Schadenberg** (Netherlands) **Biomed lab scientist L Nyman** (Sweden)	**Career and competence in laboratory medicine: challenges, trends and best practices** Session in Swedish **Chair: M Shafaati Lambert** (Sweden) **BSc N Hourani Soutari** (Sweden) -Integrerad forskning och kliniskt arbete **MSc H Stenling** (Sweden) - Norrtäljeprojektet **Biomed lab scientist A Collberg** (Sweden) - Runda Bordet **BSc M Kjellén & BSc J Borrman** (Sweden) - Kompetensväxling vid proteinbedömningar	**Session by Svensk Förening för Klinisk Kemi -** **Using labs wisely – laboratory medicine in an era of choosing wisely.** **Chair: J Skogö** (Sweden) **Prof. K Størdal** (Norway) Choosing Wisely - #More is not always better **MD K Bengtsson Linde** (Sweden) Testing wisely to the right tree in the wood - how the Emergency department use laboratory testing in clinical decisionmaking
10:00	**Coffee & Exhibition**		
10:30	**The NFKK Young Researcher Award** **Prof. MD LM Rasmussen** (Denmark) The three awarded will present their scientific work		
12:00	**Lunch Break**		
12:30	**Plenary session by the Nordic Federation of Clinical Chemistry - Clinical metabolomics, a new era for laboratory medicine:** **Chairs: YT Bliksrud** (Norway) and **P Bjellerup** (Sweden) **PhD Msc K Elgstøen** (Norway) Global metabolomics, why and how **Prof. RMA Heeren** (Netherlands) Imaging Mass Spectrometry **PhD MD YT Bliksrud** (Norway) Interpretation challenges, the need for the medical doctor in the laboratory		
13:15	**Closing ceremony with presentation of NFKK Young Researcher Award and welcome to NCCC2026 Århus, Denmark**		
14:00	**End of the Conference**		

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Enhancing Pedagogical Skills:

A Course for Clinical Chemistry Professionals

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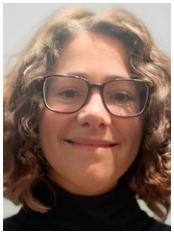

Are you looking to elevate your teaching abilities and deepen your understanding of learning dynamics? Look no further than the Pedagogy Course for Residents in Clinical Chemistry, offered in conjunction with the Nordic Congress in Clinical Chemistry in September 2024 in Stockholm.

Led by Maria Farm, a Senior Consultant in Clinical Chemistry, MD, and PhD, this course is designed to equip participants with a comprehensive toolkit for effective teaching and learning. Over the course of two half-days, attendees will engage in a variety of interactive sessions covering topics from traditional lectures to teaching methods tailored for different learning environments such as seminars, student projects, and clinical workplace settings. Through small group discussions, literature studies, and reflective exercises, participants will explore practical strategies for fostering meaningful learning experiences.

This course is ideal for resident MDs in clinical chemistry seeking to enhance their pedagogical skills, but it is open to all laboratory professionals interested in advancing their teaching capabilities. Upon completion, participants will receive a certificate confirming their participation and successful completion of the course, with all necessary course literature included in the registration fee of 500 kr.

Register at www.nfkk2024.se before August 27, 2024. Don't miss this opportunity to invest in your professional development and join us for an enriching journey into the art and science of teaching and learning in clinical chemistry.

For further information or inquiries, please contact Maria Farm, Course Director and Program Director for resident training in clinical chemistry at Karolinska University Hospital.

Region Stockholm

KAROLINSKA UNIVERSITY HOSPITAL

The course is arranged with the support of region Stockholm.

Monday 16/9	**11.00-12.00**	**Registration and lunch outside Nanna Svartz**
	12.00-13:00	Introduction to teaching and learning a neuroscientific approach Tobias Karlsson, Dept. Of Neuroscience, KI
	13.00-13.15	**Break**
	13.15 - 14.00	*Journal Club* Effective small group learning Maria Farm, Clinical Chemistry Karolinska
	14.00-14.15	**Break**
	14.15-15.00	Lecturing to promote student learning: strategies from applied cognitive psychology Marcus Lithander, Unit of Digital Learning, KTH
	15.00-15.15	**Break**
	15.15-16.00	Lecturing to promote student learning: strategies from applied cognitive psychology Marcus Lithander, Unit of Digital Learning, KTH
	16.00-16.30	Workshop Application of strategies to facilitate knowledge building Marcus Lithander, Unit of Digital Learning, KTH
	16:30-17:00	Daily Round-up

Tuesday 17/9	**08:30-09:20**	Mentoring Workplace Based Learning Agnes Elmberger, LIME, KI
	09:20-09:30	**Break**
	09:30-10:00	Mentoring Workplace Based Learning Agnes Elmberger, LIME, KI
	10:00-10:20	**Break**
	10:20-11:00	Mentoring Scientific Projects Jenny Flygare, Teaching and Learning, KI
	11.00-12.00	*Journal Club* Professional development in the many roles of a teacher Maria Farm, Clinical Chemistry Karolinska
	12.00-12.30	**Lunch outside Nanna Svartz**


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The Arctic Experience 2024

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Baltic participants included for the first time

I think all participants of the Arctic Experience writing course 2024 can agree on one thing - my journey to the event was definitely the most adventurous of them all. But first, hello everyone! I'm Kristiina, a laboratory medicine doctor and PhD student from Estonia and also the first ever Estonian participant of the Arctic Experience writing course. This year the Arctic Experience writing course opened its doors to all three of the Baltic countries for the very first time. I represented the Estonian organization ELMÜ (Estonian Society Laboratory Medicine), Jānis was from Latvia and Ricardas from Lithuania. None of us had ever met each other before and yes, the joke of having to travel all the way to Finse in the Norwegian mountains to do so, was brought up multiple times.

Delayed journey

Now first things first, this was my first time in Norway in about 20 years. So I had a plan! As our meeting time for the start was at 11:30 at the Oslo train station on Tuesday morning, I would travel there a day earlier, stay at a hotel for the night and see as much of Oslo as possible before heading to the event. By my calculations, I had about 2 hours in Oslo if I had an early morning. Lovely plan, right? Well... things did not really work out as planned. Things started going wrong at Tallinn airport on Monday at mid-afternoon.

The flight times between Tallinn and Oslo are not ideal so I had bought a ticket to travel Tallinn-Riga-Oslo, about a 4-hour route in total with 2 hours between flights. But … the first flight didn't go out at all. We sat on the plane for about 2 hours before it was announced that we cannot fly out due to bad weather. That is when I knew - my Oslo exploration was not going to happen. In addition, it was time for me to get to work to reorganize everything to actually make the event. The first thing I did was contact our lovely organizer Anne Stavelin to notify her of the situation and see how to go forward. The tickets were an easy fix as the airline did give me new ones ...exactly 24-hours later. Which meant there was no way I was going to make the 11:30 train. Nor the 16:23 one. Which left the 23:03 night train and arrival at Finse at 3:47 at night as the only option.

Let me tell you right there, once I realized that, I really did have to sit down and really think about what that meant. As the breakfast started at 7:30 that would only leave me a maximum of 3 hours of sleep before delving into an intense writing course for two days. Would I really do that? Could I? Should I? The answer was a big resounding "Yes! Yes, I can! And I will!". Now looking back, I realize I absolutely made the right decision.

With my mind made up, I headed into my hotel for the night with the intention of getting as much rest as humanly possible before going back to the airport on Tuesday to try again. This time the flight went out and I reached Riga nicely. The flight to Oslo went out as well, even though the flight deck announced that it would be a turbulent flight due to storms, and yes, I made it, but that is not a flight I would care to repeat. I made it to Oslo airport around 19ish, made the train at 23, had a very interesting train ride in a night train bed and made it to Finse only two minutes later than planned at 3:49. For the first time during my trip, things worked out nicely and I made it to my room to start my three-hour nap, excuse me, sleep.

The work finally begins

This brings me to the start of the event, which for me was breakfast at 8 o'clock the next morning. Everyone else's first day had already been the day before with

The participants at The Arctic Experience 2024, including editors and organisers. Photo: Britt-Sissel Nesheim (Finse Hotel).

Participants from the Baltic countries. Jānis Meisters (Latvia), Ricardas Stonys (Lithuania) and Kristiina Kurg (Estonia). Photo: Anne Stavelin.

an Introduction lecture followed by an overview of the correct scientific manuscript structure, the presentation of the dataset we would be working with and working in small groups so everyone could meet each other. Overall, there were four groups with 4-5 members each with two supervisors per group. The task in front of us was quite daunting – writing a scientific manuscript for Scandinavian Journal of Clinical and Laboratory Investigation (SJCLI) based on the dataset given in only two full days of work.

And yet, the place chosen to accomplish this daunting task was amazing! A ski lodge in the Norwegian mountains right next to the train station. Imagine this – big windows opening up to the mountains around us, a roaring fire right next to us which spread an amazing wood smoke aroma all around and warmth from the

snow storm outside while we sat in our comfortable chairs. Mainly thinking oh my, how can this task be done and done well?

But let's come back to the first full day that I actually got to participate. After our breakfast, we started with the first lectures around 8:30 and worked in groups all day long. Quite daunting on only 3-hours of sleep, let me tell you that. Nevertheless, everyone was very supportive and my group members helped to ease me in right away and explained what we were going to do. Our mission was to write a scientific article based on a SKUP (Scandinavian evaluation of laboratory equipment for point of care testing) report on a glucometer cobas pulse. Luckily, we had been sent the SKUP report a week before the course so I had had time to read it through and bring myself up to speed with what we were going to do.

To sum up day one with just a few words – we got to work! Starting with a discussion about how we would put together the data and what we would present. We had been given the dataset but what exactly would we be writing the article about? Where to start? What angle should we present the data from? What to leave out or include? All of these decisions had to be made and made fast. The first half of the first day was filled with writing the Materials and Methods subsection, after which we would have a much-needed lunch break. Yet before lunch, we had a small plenary discussion. It could seem a bit weird, a plenary discussion about what? In reality, these frequent regrouping sessions were very helpful to hear about what others were doing, how they were tackling the same dataset, what angles they were working at and to get some much needed feedback from the mentors about how to continue forward. Following this feedback session, we were given a small overview about how to write Results and Figures and Tables sections. And then it was finally time for lunch.

I have to admit that at this point the 3 hours of sleep was catching up to me so I sadly only got to enjoy the delicious meat stew before retiring for my room for a much needed cat nap. But I was assured that the dessert was also really delicious. After lunch it was time to get back to work! This time we tackled the results section until our next plenary feedback session.

Social activity in the snowstorm

And finally the end of the first day had arrived – it was time for the social activity! The weather outside was just dreadful – there had been a nonstop snowstorm outside all day long. But the weather did not stop our social activity from going forward. After all, there is no wrong weather, only incorrect outfits. Everyone went back to their room and got dressed for a very exciting mini trip behind the hotel. You heard that right, our first social activity was to visit the Nansen house which was situated right behind Hotel Finse1222. Here, there was a reconstruction of the house used for arctic expe-

Working in groups.
Photo: Anne Stavelin.

The Arctic Winter Games, social activity in the snow.
Photo: Anne Stavelin.

ditions. Our tour guide gave us an overview of the Norwegian explorer Fridtjof Nansen's expedition to reach the geographical North Pole. Imagine us all sitting there in cramped conditions surrounded by artifacts from the expedition. As an absolute highlight, we got to try a traditional food made from dehydrated meat and animal fat. Our lovely tour guide kept telling us that it would be the worst thing we ever tried so a lot of us were quite hesitant to even try it. In reality...it really wasn't that bad. Quite a few people even reached in for seconds. After our mini trip we got ready for dinner which, sadly, I also didn't made to the end of. The main dish was delicious, that much I can say. The dessert? Sadly, I was already in bed when that arrived. After a sleepless night, I think I made the correct choice even if it meant skipping dessert.

Manuscript writing continues – and time for outdoor fun

Similarly to the first day, the next day we started with an early breakfast and headed into the first lecture again at 8:30. This time it was about how to write the Introduction and Discussion sections. After the lecture we got back to work trying to write the sections we had just learned about. On this day we had a special surprise – our social activity, the Arctic Games, started before lunch! We all went outside in our winter gear and geared up to play different team games. The events included who sledded down the hill fastest on a butt board, which team could make snowballs and throw them the most accurately and which team could run backwards the fastest. Sounds easy, doesn't it? In reality quite hard to achieve in arctic conditions after having a snowstorm the previous day. Then again, falling down into fresh snow was half the fun. Luckily, there were no casualties and we could head into our lunch break after an hour of outdoor fun.

Lunch was followed by another plenary discussion and then we got to work to complete our manuscripts. Even though we had only been given two days to complete them, I would say most groups did a marvelous job and had them almost done by the end of day two! To finish up the day, we had our last plenary discussion and listened to a lecture about what happens after the manuscript in submitted and how the peer review system works. This was followed by our last group work session to recap what we had done and to choose someone from our group who would present

Visiting the Nansen House in snow storm. Photo: Anne Stavelin.

it the next morning. Dinner was lovely as well with the main course being reindeer meat followed by a delicious crème brûlée.

Time to sum up and to say goodbye to Finse

On the last day, as usual, we started early, but this day was the shortest of the bunch. Our first and only session of the day was at our traditional 8:30 where all groups gave a short overview of what they had accomplished in the last two days. I would say all groups did an excellent job and it was quite amazing to see how many different routes you can take from just one dataset! After that, it really was time to leave and head back to Oslo. Our train came in nicely on time even though we had some doubts with the amount of snow that had come down during the night. Yet it came in on time and we made it to Oslo even a few minutes ahead of schedule.

Personally, I am very happy to report that my journey back home was much less eventful than the journey to Oslo. I would like to thank all the organizers for quite an amazing event as well as all the amazing participants I met while there. Thank you for inviting me and including your Baltic neighbors! I think I can speak for all the participants with saying that the event was very successful and we are all looking forward to seeing the final article when it is published in SJCLI.

Novel blood biomarkers for Alzheimer's disease – ready for clinical use?

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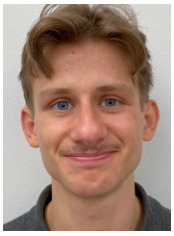
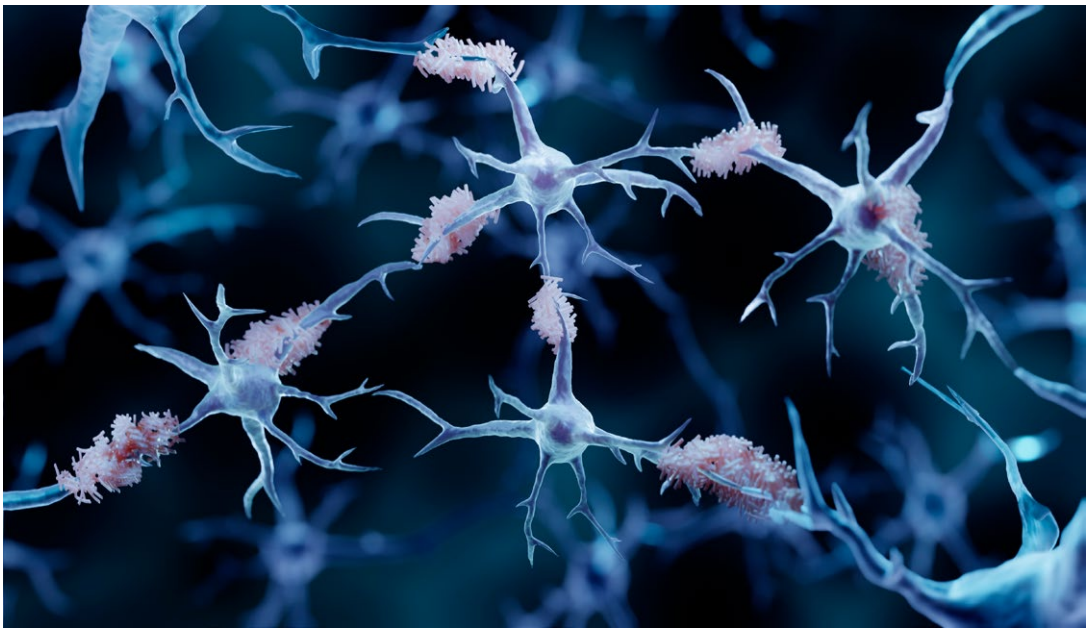



Alzheimer's disease (AD) is the most common neurodegenerative disease, with progressive amnestic symptoms being the most common presentation at clinical onset [1]. It is expected that roughly 50 million individuals suffer from the disease worldwide, making it a significant global health challenge [1]. Since its conception in 1907 by the German neuropathologist Alois Alzheimer, it is now well known that the disease has a preclinical phase of 10-20 years before symptom onset, involving extracellular cortical deposition of β-amyloid ("Aβ plaques", "A") and a subsequent deposition of hyperphosphorylated tau (tau tangles, "T") into intracellular aggregates, which – together with a progressive loss of neurons (neurodegeneration, "N") – constitute the hallmarks of the disease [2].

Historically, the disease has been clinically diagnosed using a combination of typical clinical features and excluding other causes of cognitive impairment, with a definitive diagnosis only being possible *postmortem* [3]. Although AD is the most common cause of cognitive symptoms, it appears that roughly



Amyloid plaques in Alzheimer's disease

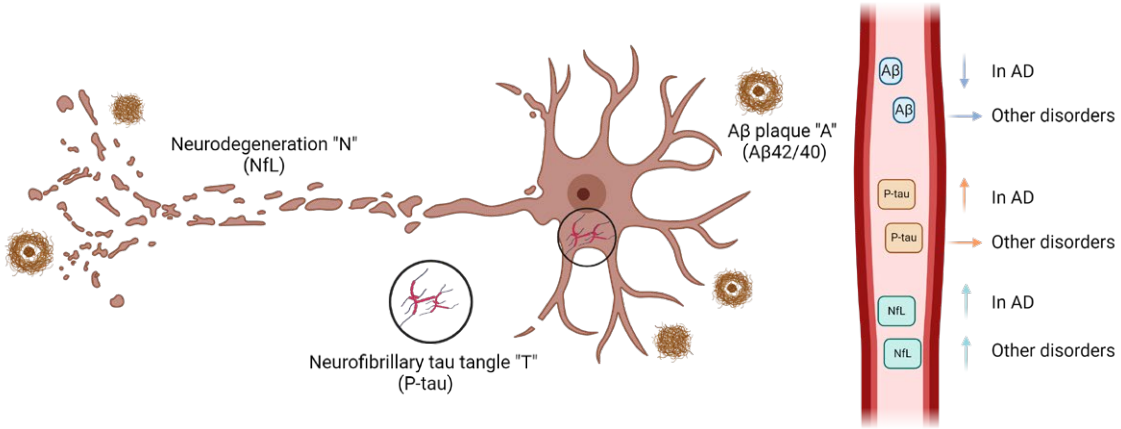


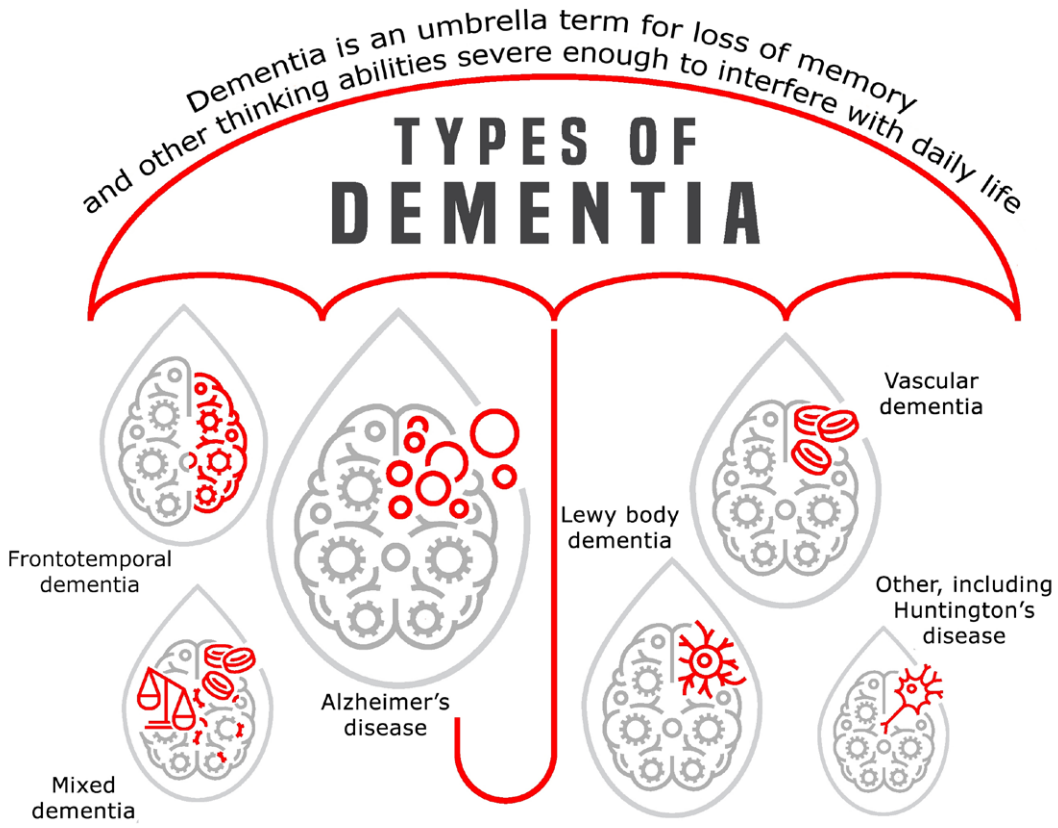
Figure 1. *Schematic drawing representing "ATN" biomarkers and their direction of change in AD and other neurological disorders. Created with BioRender.com.*

20-30% of patients with AD-like symptoms do not have AD pathological changes at autopsy [4]. New data suggest that many of these have a previously unrecognized condition tentatively referred to as Limbic Predominant Age-related TDP-43 Encephalopathy neuropathological change (LATE-NC), which is also a common co-pathology in AD [5] .

During the last decades, accurate biomarkers reflecting the disease hallmarks ("ATN") have been developed, including immunochemical cerebrospinal fluid (CSF) assays and positron emission tomography (PET) imaging methods, allowing for *in vivo* diagnostics during life [2]. Groundbreaking studies during the 1990s and early 2000s pioneered CSF assays measuring Aβ and tau proteins [6]. These are now widely available in specialized routine laboratories and can be measured on high throughput clinical chemistry instruments [7]. The emergence of these tests has altered the diagnostic procedures in memory clinics, allowing for etiological diagnosis in clinical routine. These developments have been key in the development of, and evaluation of, a novel class of intravenously administered drugs targeting aggregated Aβ in patients with symptomatic AD. These monoclonal antibodies clear Aβ plaques from the brains of people with AD, and lead to a modest, but significant slowing of cognitive decline [8,9]. One of these drugs, lecanemab, was first conceptualized in Sweden and is the first drug to be approved by the Food and Drug Administration (FDA) for the treatment of AD since the approval of memantine in 2005 [8]. The possible approval of this and other drugs in the same class in the next few years in Europe will lead to an even greater demand of making etiological diagnoses in investigations of cognitive symptoms in memory clinics.

Nevertheless, most investigations of cognitive symptoms are conducted in primary care, where lumbar punctures (LP) are generally not performed. To increase accuracy of diagnoses also in this setting, there have been intensive research efforts to develop biomarkers of AD also in blood. The early attempts to measure brain-derived proteins in blood were largely unsuccessful [10]. Owing to recent advances in ultrasensitive methodologies, such as Single molecule array (Simoa) [11] and NUcleic acid Linked Immuno-Sandwich Assay (NULISA) [12], and innovative immunoprecipitation mass spectrometry (IP-MS) techniques, a large body of evidence now suggests that the hallmarks of AD, "ATN" are now quantifiable in blood (Figure 1) [13].

The state-of-the-art method to quantify "A" using blood biomarkers is a ratio of Aβ1-42 (the predominant form of Aβ in cortical aggregates) and Aβ1-40 (correcting for physiological processing of Aβ and preanalytical factors), commonly referred to as Aβ42/40. It is best quantified using IP-MS assays and is decreased 10-15% in individuals with brain amyloidosis irrespective of clinical symptomatology, which precedes clinical symptoms with 15-20 years [14]. This low fold-change puts a high demand on analytical precision, as small deviations over time



may lead to misclassifying individuals as positive or negative for the test.

"T" blood biomarkers include measures of tau that is phosphorylated (p-tau) at amino acids (aa) known to be associated with disease (mainly aa 181, 217, and 231). These peptides, while being the constituent of tau tangles, increase in the blood in the presence of brain amyloidosis, which is currently thought of as a neuronal reaction to amyloid aggregates. The levels increase during the preclinical phase of the disease [15], and then further rise several folds in individuals with clinically manifest AD (dementia or mild cognitive impairment) compared with healthy elderly without AD pathology. Several studies in the past few years highlight that p-tau217 particularly holds promise to detect the presence of AD pathology with an accuracy to identify such changes of above 90% in the symptomatic phase of the disease [15]. Notably, p-tau217 is normal in other common differential diagnoses, such as frontotemporal and vascular dementias [16]. It is also encouraging that novel data suggest that p-tau217 can be accurately quantified both with IP-MS and with standard immunochemical methods, enabling it to be measured using common automated clinical chemistry platforms.

While the final classical hallmark of AD – "N" – is commonly identified using imaging methods, such as fluorodeoxyglucose (FDG)-PET or magnetic resonance imaging (MRI), the recent development of a blood assay measuring neurofilament light (NfL), a cytoskeleton protein found almost exclusively in neurons, has found broad clinically applicability to complement imaging measures to detect neuronal damage. In response to virtually any damage affecting the structural integrity of neurons, NfL is released into the extracellular space, which can then be detected as an increased concentration in the blood, proportional to the intensity of the damage [17]. Substantial evidence suggests its utility in a wide range of neurological conditions; neurodegenerative diseases (including AD), in neuroinflammatory conditions, CNS malignancies, and in acute neurological condi-

tions such as stroke and traumatic brain injury, both as a diagnostic, prognostic and disease monitoring tool [17]. Notably, when compared with AD, NfL is markedly increased in frontotemporal dementia, vascular dementia, and atypical parkinsonian disorders, which can be differential diagnoses for AD [18].

While the current limitations of blood Aβ42/40 makes it unlikely to reach widespread clinical use in foreseeable future, blood NfL has already been introduced as a clinical routine test in several laboratories, including the Sahlgrenska university hospital neurochemistry laboratory in Mölndal, Sweden [18]. It is currently being used to monitor treatments in multiple sclerosis and spinal muscular atrophy, where it decreases in response to effective treatments. Other current applications include investigating the presence of a neurodegenerative component in individuals with various neurological symptomologies. Future potential use may include monitoring therapeutic efficacy and safety when novel AD therapies are approved.

Excitingly, blood p-tau217 assays are also undergoing clinical validation procedures to become routine clinical chemistry tests. This may revolutionize the investigation of cognitive symptoms in both memory clinics, where it may be used as a pre-screening tool to decrease the need of expensive imaging examinations or invasive and time-consuming LPs [19], or potentially as a standalone test in those with contraindications to undergo an LP. This could lead to a larger capacity of memory clinics, which expect a surge in referrals with the approval of novel treatments. In the future, p-tau217 may also be used to monitor treatment efficacy in individual patients, with proof-of-concept recently demonstrated in *post hoc* analyses of phase 3 trials of anti-Aβ trials [9]. In primary care, however, the benefit may be even greater, with studies suggesting that up to 50% of patients with dementia in primary care receive an incorrect diagnosis with current diagnostic standards [19]. Having a test to detect or exclude AD pathology in these situations would improve clinical management, referral patterns and enable physicians to provide more accurate advice to patients and their relatives.

There is a large enthusiasm that the introduction of blood NfL and P-tau will improve neurology practice in general, and the investigation of cognitive symptoms in particular. Although it was less than five and ten years ago, respectively, since p-tau217 and NfL were first accurately measured in blood, a growing body of evidence has emerged that investigate how these biomarkers may best be incorporated into clinical workflows in primary, secondary and tertiary care. Prospective studies investigating this are underway, which will likely lead to a significant improvement in how individuals with AD and other devastating brain diseases are managed and support the therapeutic development that may lead to a slowing or potentially even halting of their progression. In the meantime, intense global research is ongoing to develop improved biofluid-based biomarkers for TPD-43 and α-synuclein inclusions, significant neurodegeneration-promoting pathologies in themselves and commonly co-occurring with AD.

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Reference limits for cardiac troponin T and N-terminal b-type natriuretic propeptide in elders

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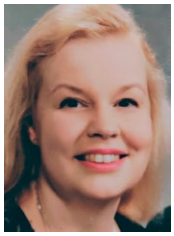


Troponin T and N-terminal b-type natriuretic propeptide levels rise with age

Older people´s troponin concentrations above the conventional cut-off threshold is a common everyday problem in clinical settings. Especially experienced clinicians often do not pay much attention to these unless there is a clinical suspicion of an acute heart condition behind the person´s symptoms. Nevertheless, troponin is often measured when an elderly person is admitted to the emergency room or sometimes even in non-acute settings, which may cause unnecessary worry and inadequate examinations or follow-up when reference ranges defined for general adult population are applied for the elderly.

As the high-sensitivity troponin assays have improved the analytical detection limits and improved the early detection of AMIs, they measure concentrations of cardiac troponins in a significant proportion of healthy adults as well, and in most older individuals (1–3). Levels of both cardiac troponin T (cTnT) and troponin I rise in myocardial ischemia but also in many other acute and non-acute ischemic and non-ischemic heart conditions such as inflammation of the heart, endothelial dysfunction, micro-vascular disease or left ventricular strain, and also with increasing age, and in renal failure (1–3).

For cTnT, only a reference limit defined for general adult population of 14 ng/L is used for ruling out or ruling in acute myocardial ischemia. This reference limit is defined as the 99th percentile limit for troponin T in an adult population. The diagnosis of AMI requires detection of an elevated cTn value above the 99th percentile upper reference limit with a rise or fall of cTn values (4).

Natriuretic peptide levels rise in left ventricular dysfunction. N-terminal b-type natriuretic propeptide (proBNP) is the natriuretic peptide that is most often measured in clinical practice for the diagnosis of heart failure (HF). A background of cardiovascular disease and especially previous AMI makes HF is more likely. The levels may also be increased because of renal impairment or atrial fibrillation (5,6). There is no consensus on the limits to diagnose HF, and different cut-offs are used although separate cut-offs for older people are usually applied.

In our recently published study, we measured cTnT and proBNP levels in an elderly population with no acute symptoms, and no cardiac or renal diseases to define reference limits for older age groups that would better reflect their concentrations of these biomarkers (7). This article summarizes the findings of the study.

The reference population

The study was part of a longitudinal epidemiological study, where all persons over 64 years of age living in the municipality of Lieto in southwestern Finland were invited to participate, and 82 % of those participated, 533 men and 727 women. A comprehensive baseline examination was conducted to each participant in 1998 or 1999 including blood samples and aliquots of serum stored, an interview with history, lifestyle, and previous diagnoses, Rose questionnaire[1],

1 *Roses questionnaire: A questionnaire used to detect ischemic heart pain for epidemiological surveys*

numerous laboratory analyses and an electrocardiogram examination (8).

After exclusion of those with heart or kidney diseases at baseline, the reference population was formed by 763 individuals aged over 64 years, with no diagnoses of heart or kidney diseases.

The median concentrations of cTnT and proBNP in different age groups among the reference population are shown in Table 1. The relation of cTnT proBNP concentrations with age in the reference population can be seen in Figure 1.

Age-specific reference limits

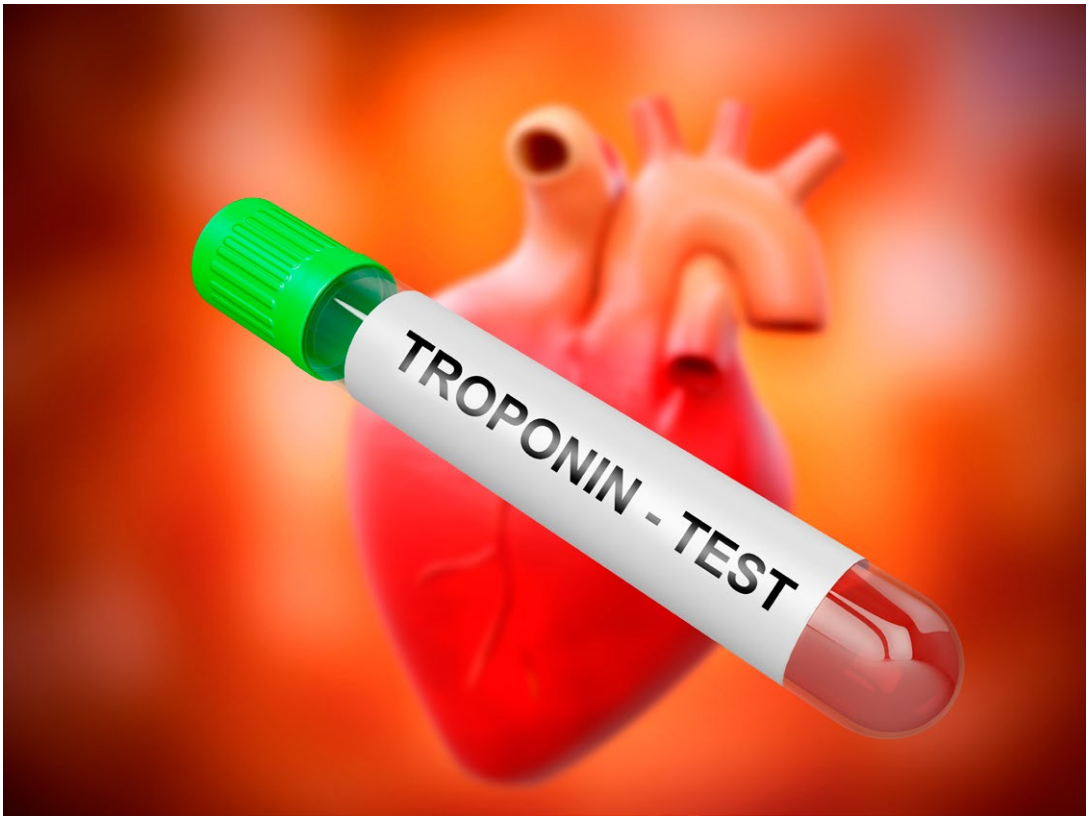
cTnT and proBNP concentrations increased significantly with age. The reference limits were defined separately for both genders in four age groups because of statistically significant age group and gender differences in cTnT and proBNP values.

Table 2 shows the 99% reference limits for cTnT and the 97.5% reference limits for proBNP.

Discussion on new reference limits and their application for elderly

The definition of reference limits in older population is complicated by comorbidities. We found that cTnT and proBNP concentrations are higher also in older population without diagnosis of a cardiac disease or cardiac symptoms, which is in accordance with previous studies (1,2,6,9). The concentrations of cTnT were higher in older men in comparison with older women in all age groups, and proBNP was higher in women, as most other studies have found as well (2,6).

Even if all participants in our study were carefully examined to exclude all persons with any signs or symptoms of a cardiac disease, some elderly individuals might have had asymptomatic cardiac conditions that were not diagnosed at the time of the baseline examination and were at a stable stage. As this might be a more relevant problem in the eldest group with more dispersion as seen in figure 1, we suggest using the reference limit of over 80-year-olds for all persons



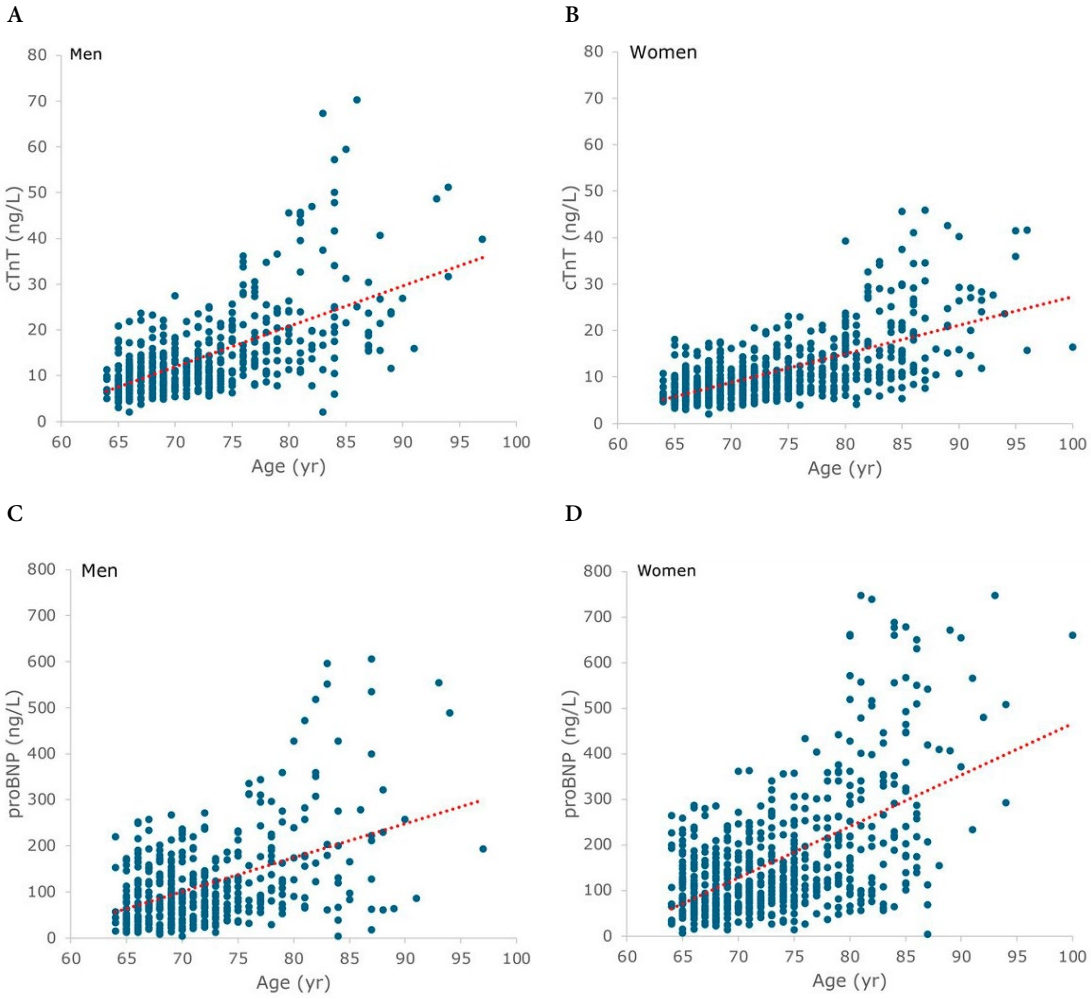


Figure 1. *The relation of cardiac troponin T (cTnT) in men (A) and women (B), and N-terminal natriuretic b-type propeptide (proBNP) in men (C) and women (D) with age in the reference population.*

over the age of 80, even if it is likely that the reference limit continues to rise with advancing age.

It is also noteworthy that the assays currently used like the Roche assay we used, measure both intact and degraded cTnT fragments. The degraded fragments seen for example in renal failure rather than in acute heart conditions, may cause chronic cTnT elevations (10).

The application of age-specific reference limits for older population would help decision making and have clinical implications considering the high prevalence of older patients in emergency care as well as in other health care appointments. Troponin levels are often examined with admittance of an elderly person in an emergency room, and it is important to notice that it is quite likely that the person may have a troponin T level higher than the conventional cut-off limit of 14 ng/L also without an acute ischemic disease. In the oldest groups of our study population, the median cTnT concentrations exceeded this limit. The median cTnT concentrations exceeded this limit also when we examined over 64-year-old people with a history of a cardiovascular disease, even though none had acute symptoms at the time of the examination.

	n	Median concentration of cTnT (ng/L)	IQR	Median concentration of proBNP (ng/L)	IQR
Men					
64 to 69 years	138	9.0	6.9-12-1	64	34-118
70 to 74 years	85	10.7	8.3-13.4	75	47-121
74 to 79 years	49	14.6	10.7-19.4	115	79-186
Over 80 years	38	16.7	13.3-31.2	131	66-239
Women					
64 to 69 years	176	6.9	5.3-9.5	91	59-158
70 to 74 years	130	8.8	6.8-11.2	113	76-170
74 to 79 years	77	10.4	7.7-13.9	133	103-214
Over 80 years	76	15.3	10.9-21.7	219	125-355

Table 1. *Median concentrations and interquartile ranges (IQR) of cardiac troponin T (cTnT) and N-terminal natriuretic b-type propeptide (proBNP) in different age groups among the reference population*

	cTnT			**proBNP**		
	n	99% reference limit	95% CI for reference limit	*n*	97.5% reference limit	95% CI for reference limit
Men						
64 to 69 years	136	25	22-29	133	272	217-342
70 to 74 years	82	28	24-32	78	287	217-380
74 to 79 years	48	38	31-46	44	373	273-509
80 years and older	37	71	52-97	31	686	417-1130
Women						
64 to 69 years	174	18	17-20	168	341	285-409
70 to 74 years	124	22	19-24	122	377	312-455
74 to 79 years	75	26	23-31	73	471	366-607
80 years and older	74	52	42-63	67	794	603-1045

Table 2. *Reference limits and their 95% confidence intervals (CI) for cardiac troponin T (cTnT) and N-terminal natriuretic b-type propeptide (proBNP)*

Follow-up samples are still needed when an elderly person presents with acute cardiac symptoms, but it is still important to understand that their baseline cTnT level may be over the conventional cut-off limit unrelated to the acute symptoms. Our study shows that older population free of heart and kidney diseases have higher levels of cTnT and proBNP than general adult population and thus we suggest using separate reference limits for older population.

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Foto: Henrik Alfthan.

Blood sampling – can the phlebotomy process be automated?

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Many processes within the laboratories have been automated the last decade: Sample handling, aliquoting, transportation and storage, just to name a few. Even decision support tools to understand a mesh of complicated results are emerging. But phlebotomy itself is still in human hands – or?

There has for quite some years been attempts to automate parts of the phlebotomy process: A well-known aspect is the infrared vein finders that can be used to locate veins in patients difficult to puncture – e.g. children or patients with very fragile veins. This is however not an automation, but more an instrument to help the phlebotomist – and a good one!

Another issue is sample labelling: A number of instruments offer help to the phlebotomist labelling the tubes necessary for a given requisition. This not only reduces the workload and thereby the number of repetitive strain injuries, but also reduces the number of erroneously labelled tubes, the number of labels that cannot be read by the barcode reader, and the number of wrong tubes chosen for a given sample. Altogether, this makes perfect sense and helps us – but again, it is not automation of the phlebotomy.

Some years ago, our laboratory was involved in a project to develop a blood sampling robot – it was of course named Roblood**.** The project developed nicely and was for several years promising, until it suddenly wasn't anymore. There were huge psychological barriers, technical barriers – and not surprisingly financial barriers, because a company was needed to run the development process, but nobody was truly interested. And so it has been for years – until now.

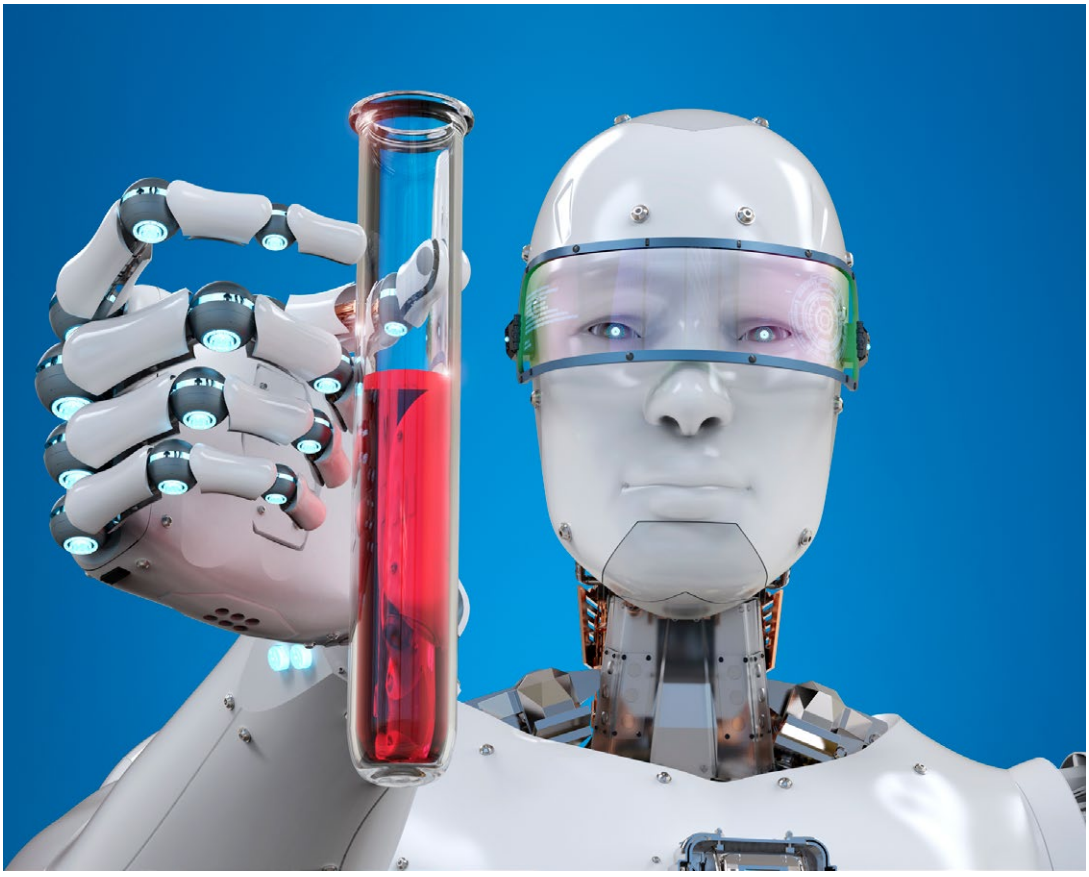
Now: this must not turn into a product commercial. But the Dept. of Clinical Biochemistry at Odense University Hospital has recently signed a contract ensuring access to an autonomous phlebotomy device – an instrument that right now is under scrutiny for CE-marking, which it is expected to pass at the end of this year. And so, in the beginning of 2025, we will hopefully be the first outside the Netherlands to draw the first blood samples with an automated device!

Briefly summarized, it uses infrared light to locate the veins, and an ultrasound probe thereafter draws a "vein map" enabling phlebotomy through a needle attached to the ultrasound probe. Pre-labelled tubes chosen through a LIS-connection are then filled, and finally, a band-aid is placed on the puncture site. Altogether, it more or less mimics the manual

phlebotomy process, so no surprises there. What *is* surprising is the apparent high percentage of successful punctures, even at individuals notoriously difficult to puncture. This is due to the ultrasound vein map and the decision that when a suitable vein is not available, a puncture is not performed. Results from studies in the Netherlands show that patients are indeed willing to be phlebotomized by a robot. And that the puncture success indeed seems high, even in patients that normally are difficult to puncture. Of note, the instrument is not yet CE-marked and it is therefore not released for clinical use, so all experiences are from the projects that has led to the CE-marking process.

Of course, some patients will always be problematic, and therefore, human phlebotomists must be present to assist when necessary. Also, not all patients are prepared for such an automated procedure, and some patients (e.g. children and in-house patients) will still need a manual phlebotomy – the plan is thus still to have a large contingency of phlebotomists available. What the automaton will guarantee is enough time slots for everybody, perhaps even longer opening hours if necessary, and at the same time a far more standardised puncture with less preanalytical variations and less repetitive strain injuries for the staff.

So perhaps, we here see yet another technological paradigm shift, where patients are willing and prepared to be handled by robots in order to avoid waiting – but of course only if the method is proven good enough to the usual high standards at our phlebotomy clinics. What will be next in line, nobody knows. Surgery? Nursing? Laboratory leaders? Exciting times lie ahead.



Summary of an evaluation organised by SKUP

SKUP
skup.org | 2024 | 136

Silje Bryn Ekehaug, on behalf of Scandinavian evaluation of laboratory equipment for point of care testing (SKUP), silje.ekehaug@noklus.no

LabPad Evolution

A system for measurement of CRP, (PT) INR, d-dimer and fibrinogen manufactured by Biosynex SA.

Background

The LabPad Evolution system (figure 1) is a handheld in vitro diagnostic device for the measurement of C-reactive protein (CRP), (PT) INR, d-dimer and fibrinogen. The product is intended for use by health care professionals. The measuring system is produced by Biosynex SA and was launched into the Scandinavian market in November 2022.

The Kmart CRP cassette is used with the LabPad Evolution for CRP measurement. The sample material for measurement of CRP is capillary whole blood and venous heparin anticoagulated whole blood and plasma. The SKUP evaluation was carried out from August to November 2023 at the request of Biosynex Nordic A/S.

The aim of the evaluation

The aim of the evaluation was to assess the analytical performance and user-friendliness of LabPad Evolution Ksmart CRP, when used by the intended users. The evaluation was performed by health care professionals in five primary health care centres (PHCCs).

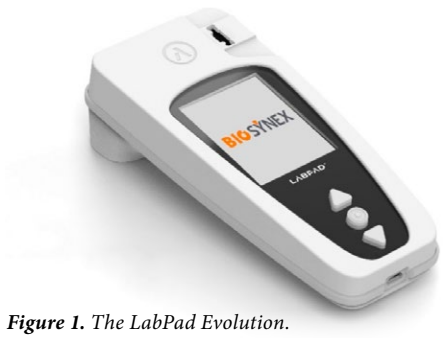


Figure 1. *The LabPad Evolution.*

Materials and methods

At the end of the evaluation, a total of 186 participants from the five PHCCs were enrolled. Participants with symptoms of infection where the general practitioner requested a CRP measurement, were included. Fresh capillary whole blood samples were collected from each of the participants and analysed in duplicate on LabPad Evolution. In addition, one venous sample was collected from each participant. The venous sample was analysed on a comparison method (cobas 8000, c 702) at a hospital laboratory.

The analytical performance and user-friendliness were assessed according to pre-set performance specifications. The analytical performance specification (APS) for precision was a repeatability (coefficient of variation, CV) ≤10 %. For accuracy the APS was ≥95 % of the results should be within the allowable deviation of ±2,0 mg/L at CRP concentration <10 mg/L and within ±15 % at CRP concentration ≥10 mg/L. The user-friendliness was assessed using a questionnaire covering four subareas with three given ratings; satisfactory, intermediate and unsatisfactory. The performance specification for the user-friendliness was an overall rating of "satisfactory".

Results

For precision, the CV achieved by intended users in PHCCs was between 18,6 and 24,9 % depending on the concentration level (table 1). The CV was higher than the APS for all concentration levels. The combined results from all five PHCCs showed an average small positive bias of 0,29 mg/L between LabPad Evolution Ksmart CRP and the comparison method.

For accuracy, 80,6 % of the results (141 out of 175) were within the limits for allowable deviation when used by intended users in the five PHCCs (figure 2).

The user-friendliness was rated as intermediate by the health care professionals.

Conclusion

The performance specifications for the evaluation was not fulfilled for repeatability, accuracy, and user-friendliness when evaluated by the intended users in primary health care.

The complete evaluation report and summaries published in Danish, Swedish and Norwegian are available at www.skup.org.

Table 1. *Repeatability (CV) of LabPad Evolution for CRP measured in capillary whole blood samples. Results achieved by intended users in PHCCs.*

Place	Level	CRP interval, mg/L	n*	Excluded results (statistical outliers)	Mean value CRP, mg/L	CV (90 % CI), %
	Low	0,6 – 18,5	101	8	4,4	24,9 (22,4 – 28,4)
PHCC1-5	Medium	20,0 – 59,0	48	0	36,0	18,6 (15,9 – 22,5)
	High	61,5 – 169,0	22	0	101,9	21,5 (17,2 – 28,9)

** The given number of results (n) were counted before the exclusion of statistical outliers. Mean and CV were calculated after the exclusion of statistical outliers. An account of the number of samples is given in the report.*

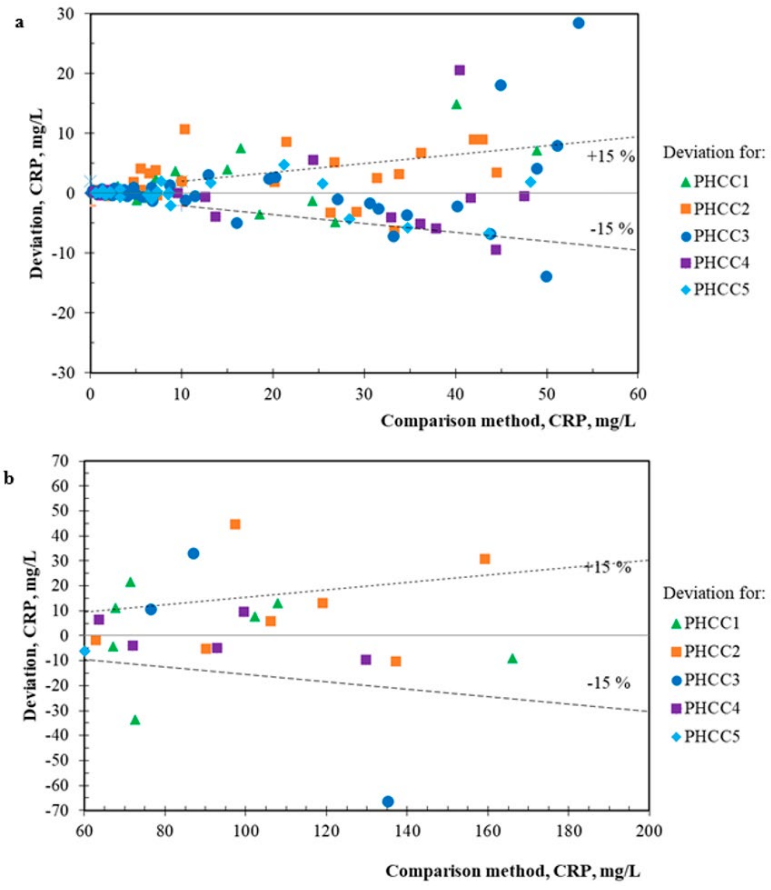


Figure 2. *Accuracy of CRP results on LabPad Evolution achieved by intended users. Low and medium CRP results are shown in figure 2a and high CRP results in figure 2b. The x-axis represents the mean CRP result of the comparison method. The y-axis represents the CRP deviation in mg/L of the first capillary whole blood measurement on LabPad Evolution from the mean result of the corresponding sample of the comparison method. The different PHCCs are illustrated with different symbols; ▲ (PHCC1), ■ (PHCC2), ● (PHCC 3), ■ (PHCC 4), ♦ (PHCC 5). The stippled lines represent the allowable deviation limits of ≤±2,0 mg/L for CRP concentrations <10 mg/L and ≤±15 % for CRP concentrations ≥10 mg/L. Number of results (n) = 175. An account of the number of samples is given in the report.*

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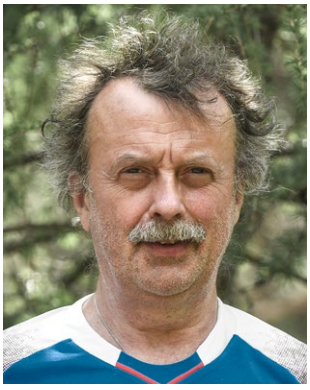

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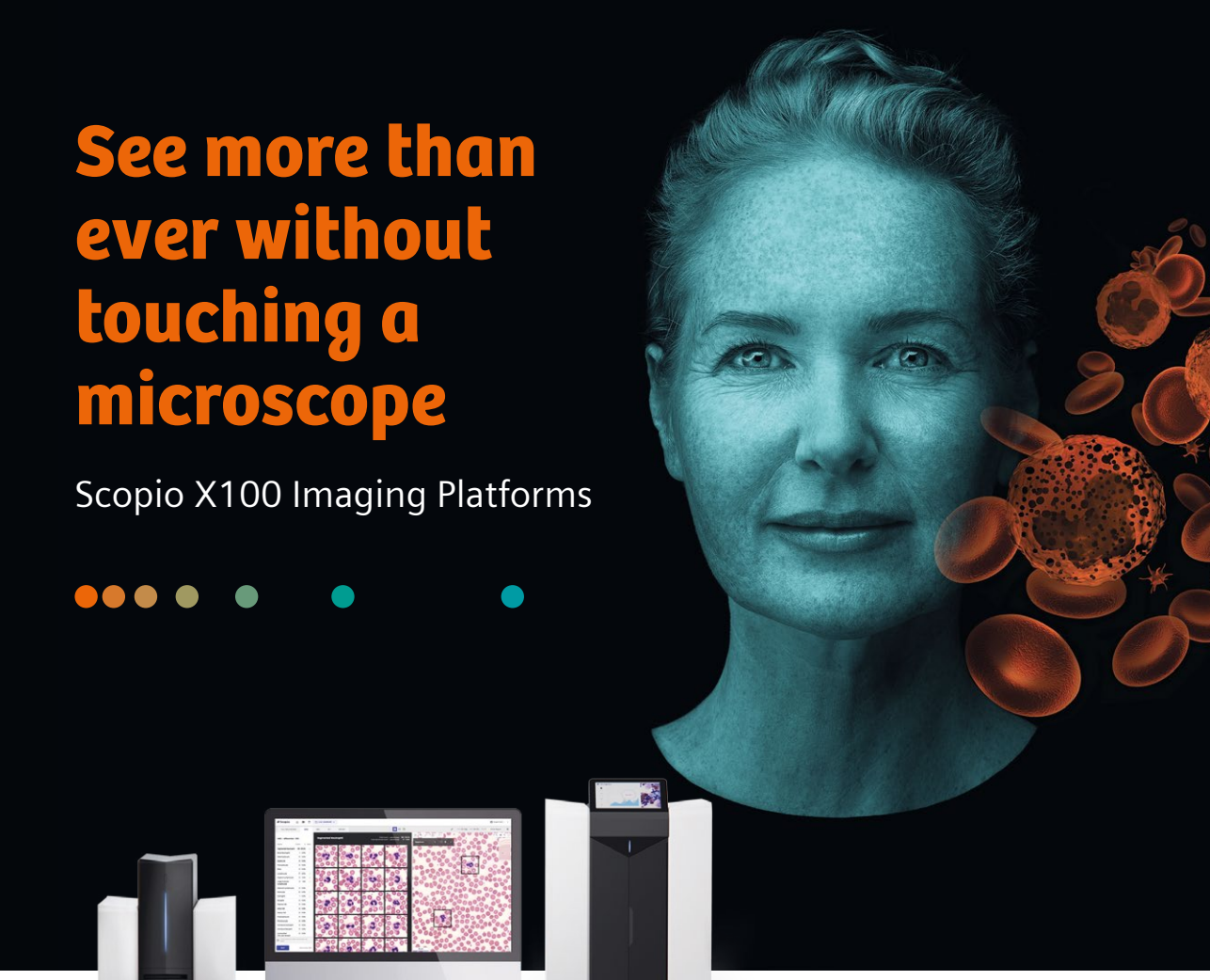

Full-Field Morphology is the first-of-its-kind solution to capture the entire slide digitally enabling fast access to a high degree of information and reduction in turnaround time for peripheral blood smears by up to 60%.[1]

1. Katz B-Z, et al. Evaluation of Scopio Labs X100 Full Field PBS: The first high-resolution full field viewing of peripheral blood specimens combined with artificial intelligence-based morphological analysis. Int J Lab Hematol. 2021;00:1–9. https://doi.org/10.1111/ijlh.13681 .This study was funded by Scopio Labs.

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