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numares insider

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2018

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Welcome to numares insider

Volker Pfahlert

Philipp Pagel

Winning a customer is the beginning of a long-term relationship rather than just "nailing that sale". At least that's what we believe at numares. That's why we are happy to support you throughout installation, assay 'development & validation' and production.

Keeping up communication with our customers is very important to us – through our sales people and service technicians, but also other departments and people in our company. Today, we are launching an additional communication channel:The customer journal "numares insider". A few times a year, we would like to use this publication as a vehicle for providing you with interesting background information, tips and tricks for the people who run tests on our instruments in everyday business and to keep you up to date on new developments at numares that may be of interest.

In this first issue, we are covering several topics. In the hands-on section, we explain what happens when NMR-probes collect dust or other types of contamination, as well as how to detect and fix this. Another very important topic that we are addressing in this issue is the discordance between NMR-particle concentration and the classic lipid panel. This phenomenon is at the heart of advanced lipid testing and thus a critical topic both for us and our customers.

We hope you will find this journal interesting– please let us know what you think and if there are any particular topics you would like us to cover in future issues. □

Volker Pfahlert, Chief Executive Officer
Philipp Pagel, Chief Medical Officer

HANDS ON

The Importance of Keeping your Probe Clean

Nuclear Magnetic Resonance (NMR) analysis is a highly detailed and specific measurement. Even the smallest contaminants can interfere with the calibration of an instrument and render invalid results.

It is critical to keep the probe, mounted in the instrument from the bottom, clean. Once loaded, the specimens descend into the magnet and into the probe, and are ready for analysis. Contaminants, like dust or a broken tube, will interfere with any measurements or can even stop the evaluation.

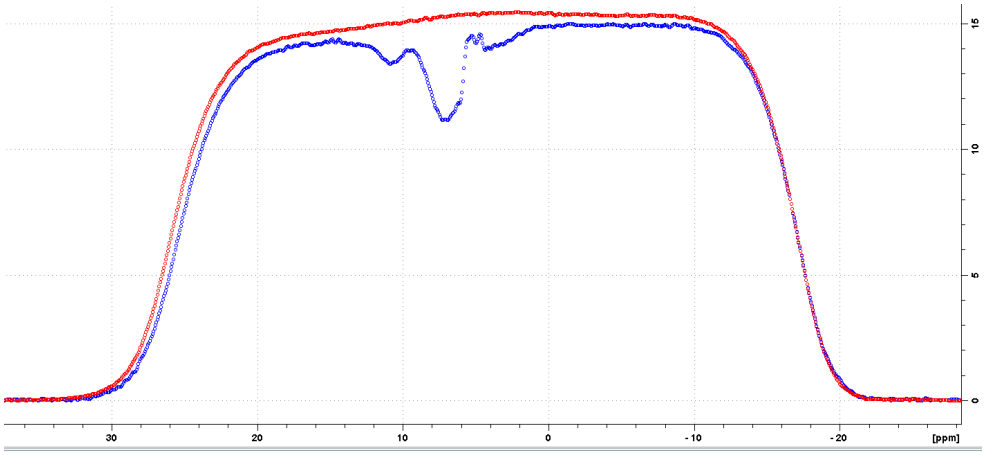
The gradient image, checked during monthly maintenance and in some versions of the software all specimens, will be off.

In summary, a dirty probe will result in an instrument that is out of specification. It will produce poor spectral images, which will result in error messages.

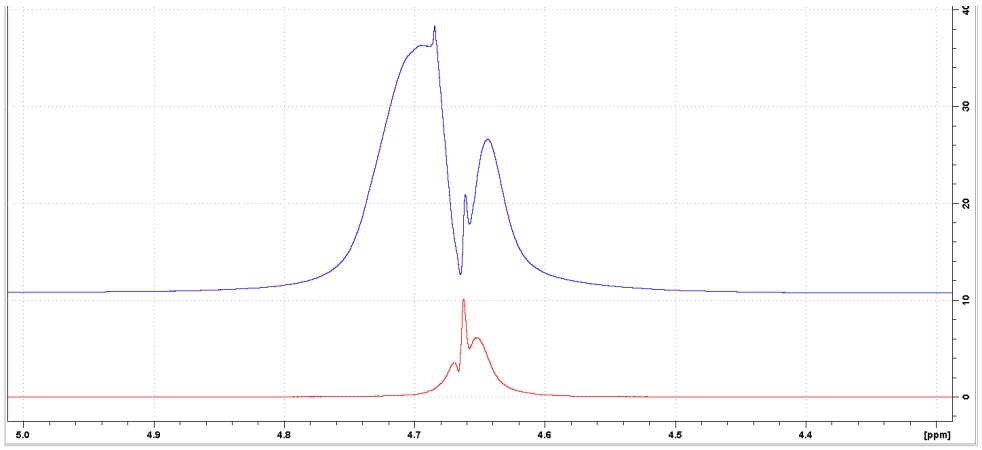
Consequently these errors will lead to a lack of reportable data for the physician. □

Michael Wiedelman, Technical Support and Sales US

See figures below for a correct (red) and incorrect (blue) gradient image:



Additionally, the water suppression statistics will be incorrect:



Some ways to keep the probe clean:

- Wiping down all specimen tubes before placing them in the rack
- Keeping the racks and the area around the instrument clean and dust free
- Ensuring a clean supply of compressed air
- Dirty or contaminated racks can be cleaned with water and some detergent

If assistance is needed, please contact:

technicalsupport@numares.com

INSIDE

Discordance of Lipoproteins – a Closer Look is Needed

Lipoproteins and Atherosclerosis

Lipoproteins facilitate the transport of lipids in the bloodstream. They are composed of a hydrophobic core and a hydrophilic outer layer. The outer surface comprises cholesterol, phospholipids and apolipoproteins, while the inner core consists of triglycerides and cholesterol ester (see Figure 1). Lipoproteins are usually classified according to their density and size. They are divided into five main classes from larger and less dense to smaller and denser: chylomicrons, very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL), low density lipoproteins (LDL) and high density lipoproteins (HDL).

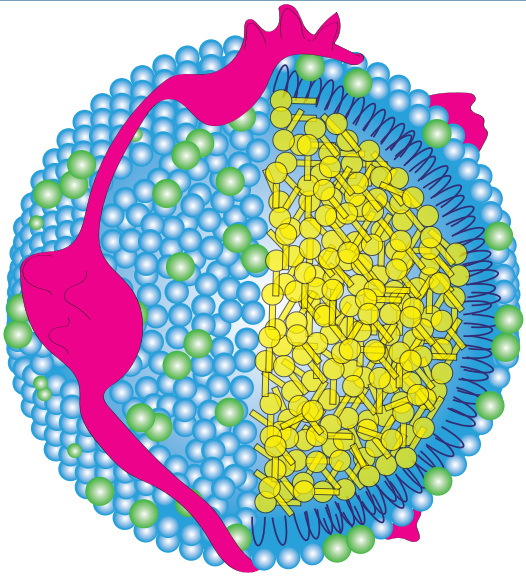


Figure 1: Structure of a lipoprotein (Stryer Biochemistry)

Chylomicrons are the largest and least dense lipoproteins. They are rich in triglycerides and relatively low in cholesterol. Chylomicrons are responsible for the transport of lipids from the intestine to the muscles and tissues. Next in size are the VLDL, they are secreted by the liver and are responsible for the transport of lipids to the inner organs. Similar to the chylomicrons, they are rich in triglycerides and low in protein and cholesterol. As they circulate through the blood, VLDL lose triglycerides and become smaller and denser, becoming IDL and finally LDL. LDL are mainly constituted of cholesterol (free and esterified) and phospholipids. The smallest and densest lipoproteins are HDL. Their main function is to take up cholesterol from the peripheral tissues and transport it back to the liver.

Lipoproteins are involved in the pathogenesis of atherosclerosis and its many consequences. Atherosclerosis is a disease that is characterized by the build-up of plaques on the inner arterial wall. These plaques consist of lipids, cholesterol, calcium and other substances circulating in the blood. Atherosclerosis is very common among the adult population. Almost everyone is affected by some form of atherosclerosis during the course of his life. In very severe cases, the artery becomes completely blocked, which results in coronary artery disease, stroke, peripheral artery disease or kidney problems. It is a major cause of death worldwide. Atherosclerosis starts early in life with small deposits on the inner arterial wall and continues over a person's entire life. Symptoms usually occur only at a very late stage of disease and, in many cases, when it is already too late. Early risk assessment and intervention could therefore prevent major complications of atherosclerosis. So what can we do? How do we know who is at risk? And how do we prevent major complications of atherosclerosis?

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Cardiovascular Disease (CVD) Risk Prediction

There are many risk factors and parameters that can tell us who is at an elevated risk for CVD. Common risk factors include age, gender, smoking, diabetes, body weight, and high cholesterol blood levels. Total cholesterol and the cholesterol content of LDL particles (LDL-C) have been established as standard laboratory parameters and measured in clinical routine to determine a patient's CVD risk. It is well known, for example, that high LDL-C is associated with a high risk for CVD. In order to reduce LDL-C and hence risk for future CVD, patients are usually treated with a lipid lowering therapy to a specific treatment goal. Unfortunately, it is not that simple: 50% of patients hospitalized for coronary artery disease (CAD) do not have elevated LDL-C [1]. So, there seems to be something else.

The different lipoproteins are not equally involved in the pathogenesis of atherosclerosis. Their contribution to total risk varies significantly among the different classes and subclasses. It is well understood today, that the most atherogenic lipoprotein particles are the LDL, while HDL seem to have a protective effect. And even among the LDL, you will find that there are bigger and smaller LDL particles (subclasses). The small, dense LDL are more atherogenic than large, buoyant LDL [2]. We cannot only measure LDL-C but also the concentration of LDL particles (LDL-P) and even further discriminate between concentration of small (SLDL-P) and large particles (LLDL-P). Like LDL-C, LDL-P also correlates with CVD risk. High LDL-P values (especially SLDL-P) lead to a high risk for CVD.

Concordance and Discordance

So now we have two lipid parameters (LDL-C and LDL-P) involved in CVD risk prediction. What else do we know about them? How are they related?

LDL-P and LDL-C are highly correlated and agree in most cases (=concordance), meaning that both parameters are either below the median (=low) or above the median (=high). However, in some cases they disagree (=discordance) and one of them is below the median while the other is above the median. Discordance is brought forward because the same amount of cholesterol can either be packed in a larger number of smaller LDL particles – or a smaller number of larger LDL particles (see Figure 2).

There are two forms of discordance: low LDL-C and high LDL-P and the other way around, meaning high LDL-C and low LDL-P. Discordance is often seen in patients with diabetes type II and metabolic syndrome (about 25% of these patients are affected by discordance). In case of discordance, CVD risk tracks with LDL-P not LDL-C (see Figure 3). This means that patients with high LDL-P and low LDL-C are at elevated risk and have a much higher risk than patients with high LDL-C and low LDL-P [3].

In patients affected by discordance high LDL-P and low LDL-C, the small, dense LDL which are the most atherogenic, are predominant. We can understand now, why CVD risk is better predicted by LDL-P, not LDL-C. LDL-C alone often underestimates the risk in patients affected by discordance.

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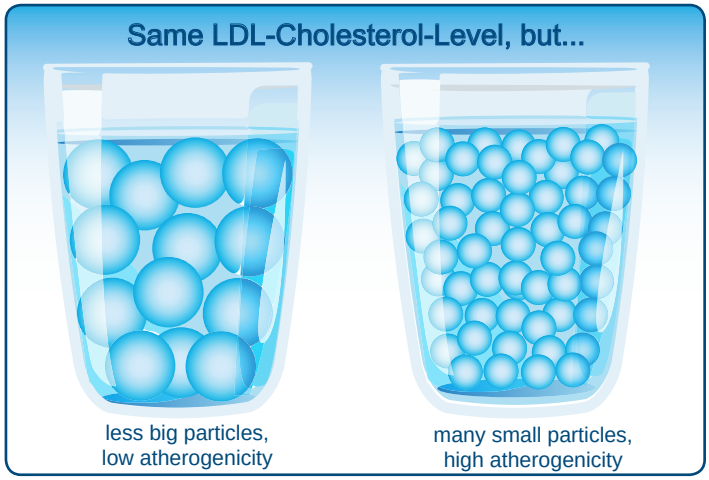

Figure 2: Different LDL-P leads to the same LDL-C

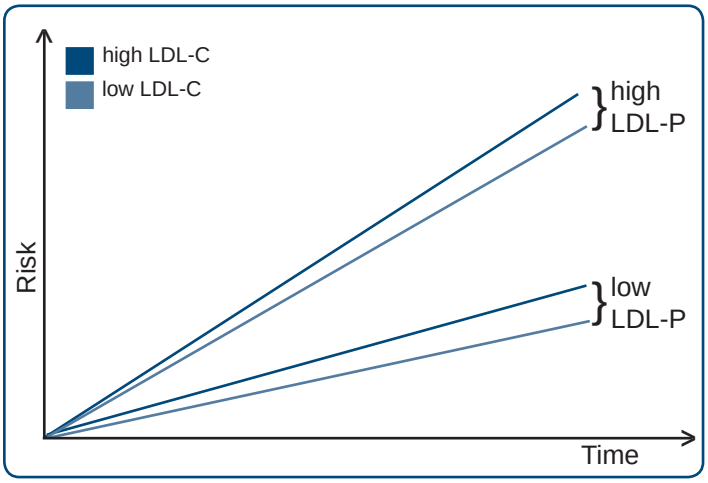

Figure 3: CVD risk tracks with LDL-P not LDL-C

How We Measure LDL-P

There are basically two methods to determine the concentration of LDL particles. Either direct using NMR spectroscopy or indirect through the immunologic determination of apolipoprotein B (ApoB). Each LDL particle contains exactly one molecule of ApoB, therefore the concentration of ApoB is basically the same as of LDL-P. NMR spectroscopy uses a magnetic field to capture all organic substances contained in a sample and yields a signal in the NMR spectrum. The position and shape of the signals are substance specific, and signal intensity is directly proportional to the concentration of the substance. For lipoproteins, this means that the position of the signal is different for different classes of lipoproteins (see Figure 4). Algorithms are then used to decompose and calculate the concentrations of the lipoprotein classes and subclasses.

numares' *AXINON® lipoFIT®-S100** is a CE-marked IVD-test, based on NMR spectroscopy that can process more than 300 samples in 24 hours and requires minimal sample preparation. It produces highly reproducible and standardized results due to numares' proprietary *Magnetic Group Signaling (MGS®)* technology. The test delivers 24 parameters from just one sample, including LDL-P and LDL-C.

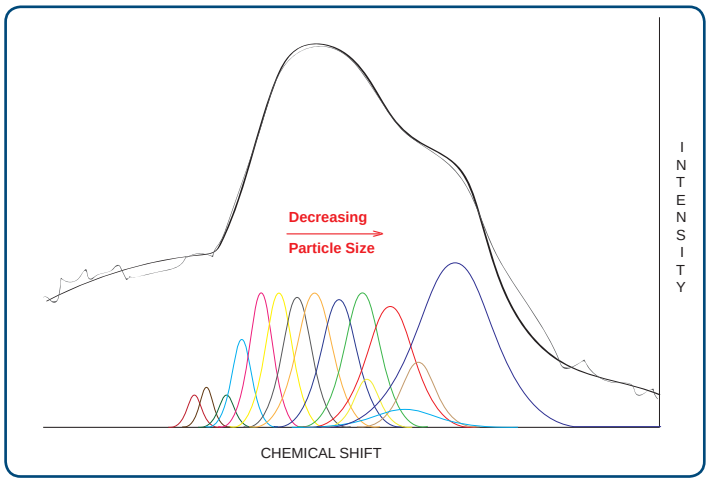

Figure 4: Region of an NMR spectrum containing signals of different lipoproteins

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LDL-P and Treatment of High Risk Patients

In patients with a high risk for developing CVD, LDL-P should always be an essential part in diagnosis when deciding on appropriate treatment. Especially for those who are most commonly affected by discordance, such as patients with type II diabetes mellitus or chronic kidney disease, CVD risk can easily be underestimated by LDL-C alone and optimal treatment can only be ensured by a more elaborate assessment. □

Doris Zeugner, Product Management

Literature

1. Sachdeva, A., et al., Lipid levels in patients hospitalized with coronary artery disease: an analysis of 136,905 hospitalizations in Get With The Guidelines. Am Heart J, 2009. 157(1): 111-117 e2.

2. Mikhailidis, D.P., et al., "European panel on low density lipoprotein (LDL) subclasses": a statement on the pathophysiology, atherogenicity and clinical significance of LDL subclasses. Curr Vasc Pharmacol, 2011. 9(5): 533-71.

3. Mora, S., J.E. Buring, and P.M. Ridker, Discordance of low-density lipoprotein (LDL) cholesterol with alternative LDL-related measures and future coronary events. Circulation, 2014. 129(5): 553-61.

NEWS

numares HEALTH

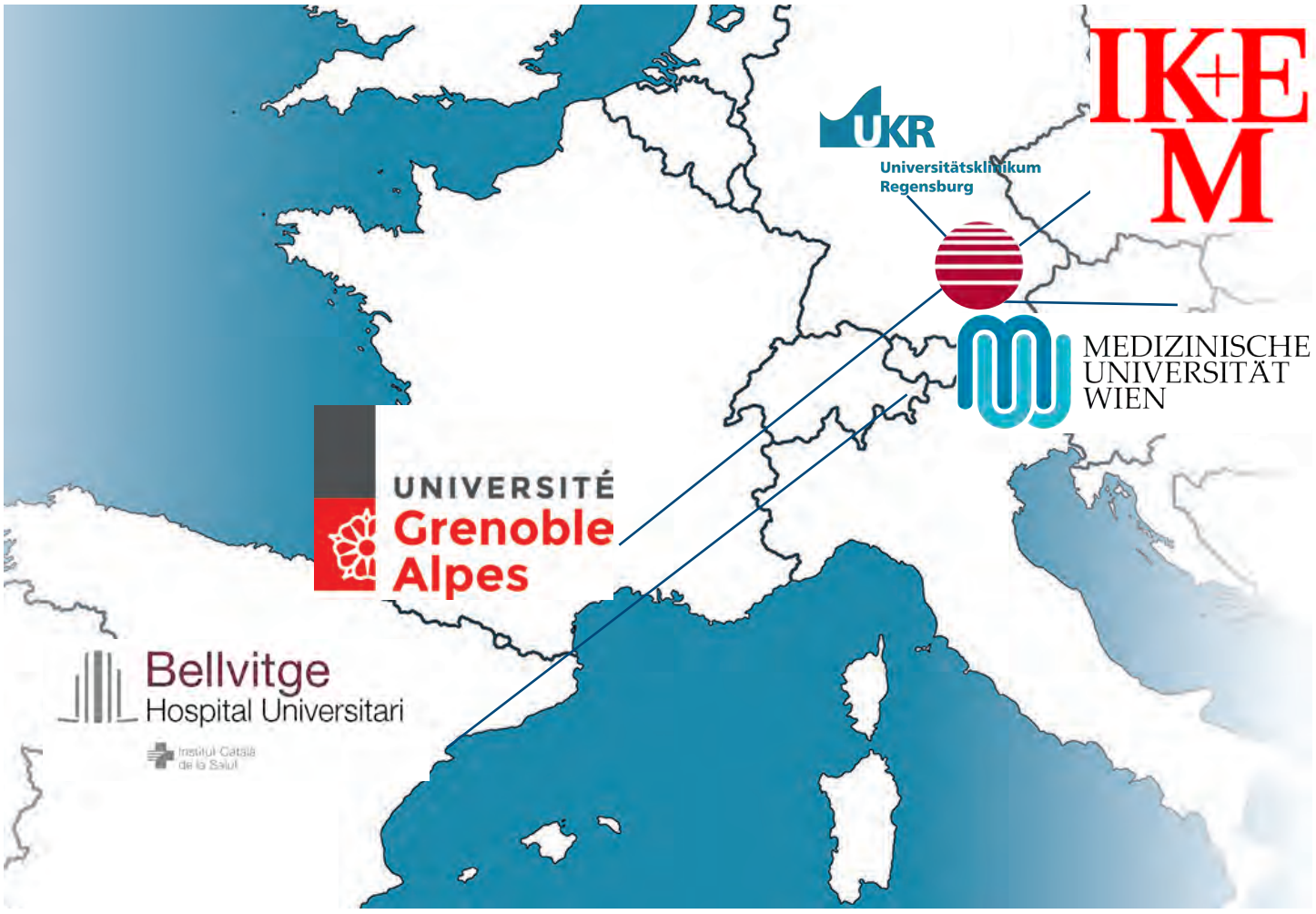
numares' New Multicenter Study PARASOL:

Metabolic Constellations across Europe

5 European sites, 4 metabolic biomarkers and 1 aim: Support a physician's diagnosis to potentially reduce the number of unpleasant kidney biopsies: The pan-European multicenter study PARASOL utilizes numares' proprietary *Magnetic Group Signaling (MGS®)* technology based on nuclear magnetic resonance (NMR) spectroscopy. PARASOL was preceded by the UMBRELLA study, in which the initial mathematical model for the presented test was developed.

The prospective PARASOL study will enroll at least 1,000 patients across the continent. Metabolic constellations are evaluated to detect the risk of acute allograft rejection in spot urine samples. This is achieved with numares' *AXINON® renalTX-SCORE®-U100** which is a non-invasive, CE-marked in-vitro diagnostic test (IVD) for the diagnosis of kidney transplant rejection. First results of this study are expected in 4Q2018. □

Simone Mark, Clinical Development
Julia Hertlein, Marketing



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EVENTS

numares @ AACC Annual Scientific Meeting & Clinical Lab Expo

Thanks for visiting numares at this great event! For us, it is a loved tradition: numares participated at the largest global scientific conference and tradeshow in the field of laboratory medicine. The annual meeting of the American Association for Clinical Chemistry (AACC) took place in Chicago from July 29 to August 2. More than 20,000 visitors informed themselves about the latest science and technology developments.

numares' team, Jodi, Claus, Philipp, Torsten and Mike, enjoyed great conversations with our customers. Moreover, we gave an overview about our future pipeline in the fields of cardiology, transplantation medicine, nephrology, oncology and neurology.

We hope to meet you again at AACC 2019. The booth is already booked…

numares team: Torsten, Philipp, Claus, Jodi and Mike (from left to right)

Congress of The Transplantation Society (TTS)

The Transplantation Society (TTS) held its 27th International Congress in Madrid, Spain in July. Our cooperation partners Prof. Dr. Bernhard Banas and Dr. Miriam Banas (Department of Nephrology, University Hospital Regensburg) presented the results of *AXINON® renalTX-SCORE®-U100** test in clinical use. In their talk "Non-invasive diagnostic of renal allograft rejection via urine metabolites using NMR-spectroscopy" the approach to detect a rejection by a urinary metabolite constellation was explained. *AXINON® renalTX-SCORE®-U100** is the first non-invasive test for the diagnostics of kidney transplant rejection. Interested visitors gathered further information about developments in transplantation science, clinical routines and the improvement of patient outcomes at our numares booth. □

Julia Hertlein, Marketing

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