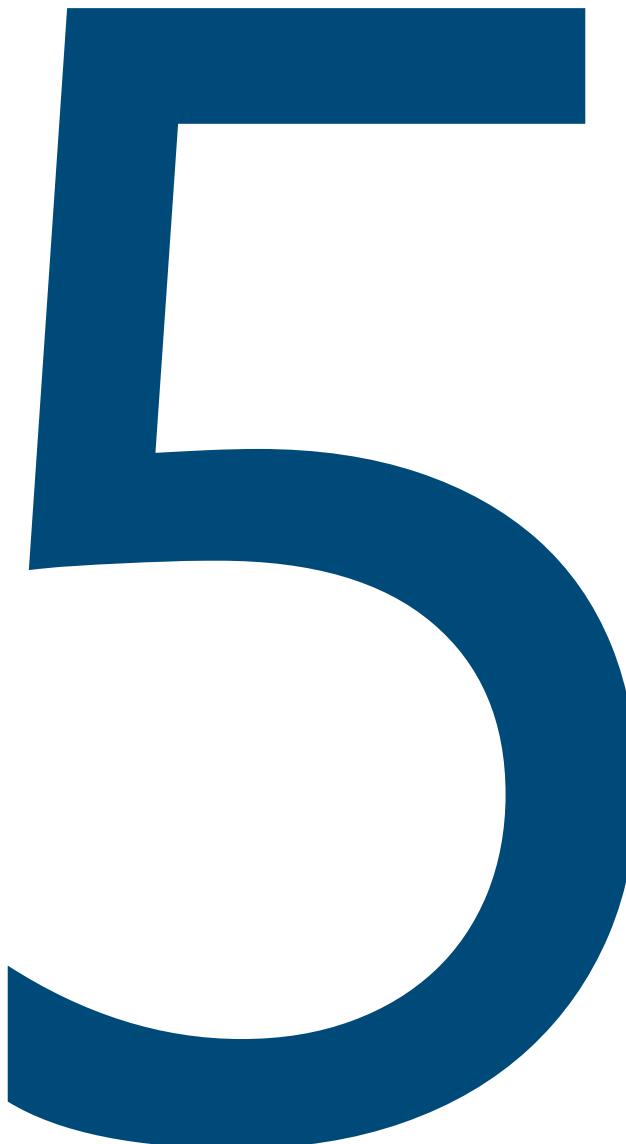


numares insider

2020



HANDS ON

Video Tutorial: How to Exchange
the NMR Pincer

INSIDE

Kidney Function Measurement:
Set and Done or Still
Room for Improvement?

NEWS

Winton Gibbons New President
of *numares GROUP Corp.*

Welcome to *numares insider*



Volker Pfahlert



Winton Gibbons

In this issue, we highlight a special clinical field and medical condition that could benefit significantly from improved diagnostic information: kidney function assessment.

As we write this, the world is still “on hold” due to the ongoing pandemic. However, at *numares* we are still working hard in the new normal. Like everyone else, Zoom is enabling us to stay in touch visually and viscerally with each other, and stay in touch with our customers and other collaborators. This has allowed us to keep pursuing our goal to bring state-of-the-art NMR-based diagnostics to the market, in order to provide valuable clinical insights.

In this issue, we highlight a special clinical field and medical condition that could benefit significantly from improved diagnostic information: kidney function assessment. The leading article highlights survey research that *numares* undertook to ascertain concerns that still exist in quantifying kidney function, and the implications of solving those. Based on these results, we developed an NMR-based GFR serum test to overcome the current weaknesses.

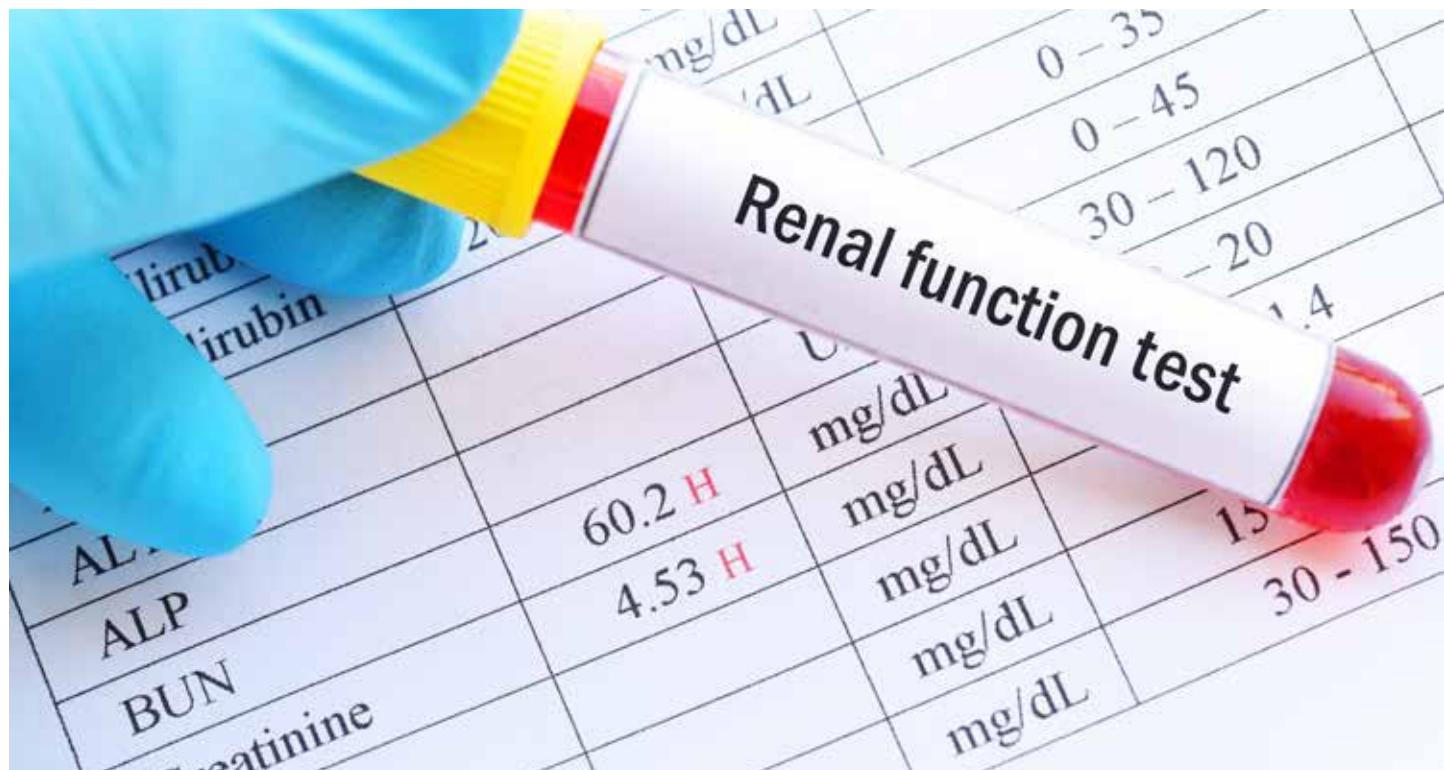
From the discussions associated with kidney function assessment, the *numares insider* moves on to topics related to *numares* itself and NMR instrumentation. In a new section, we would like to give you an impression of the work and the daily challenges of the department of Spectral Lipoprotein Analysis and Data Processing. Further departments will follow in the upcoming issues. Next, we provide an overview of the role of the superconducting magnet in NMR spectroscopy. Finally, we conclude with a technical instruction on changing an NMR pincer - derived from our online tutorials that support our clients in the required maintenance procedures of our AXION® System.

We hope you all stay healthy and safe, even as you navigate living and working in the current environment.

Volker Pfahlert, Chief Executive Officer

Winton Gibbons, President of numares GROUP Corp.

Measurement of Kidney Function – Set and Done or Still Room for Improvement?



It's common knowledge that our kidneys are critical for many different vital functions. These include, for example, the maintenance of acid-base balance, regulation of fluid balance, blood pressure, sodium, potassium and other electrolytes, clearance of toxins and many more. On the other hand, the kidney gets easily affected by various conditions like diabetes, hypertension and diet or by treatments like contrast media, some antibiotics or anti-tumor drugs. Thus, it's not surprising that the determination of kidney function is frequently assessed by physicians in the context of many different medical circumstances.

For this purpose, the determination of creatinine in serum has served as an indicator for renal function for decades and still today the marker is heavily used in

clinical routine. As *numares* decided to develop a new test for kidney function assessment, the question arose how the market is structured, what the thinking and considerations behind clinical decisions really is and to which extent the measurement of kidney function in the market does already fulfill all requirements or if there is still room for improvement.

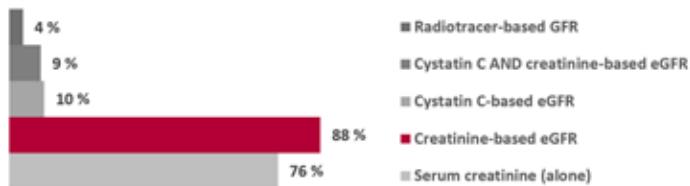
Gain representative data from a survey

To approach these questions, 204 physicians were interviewed with the help of "Squerix Global Insights". In order to illuminate the topic from different angles, roughly 50 doctors each from four most relevant indications in the context of kidney

function assessment (nephrologists, endocrinologists, cardiologists, PCPs) were included. To ensure that conclusions drawn from the survey are representative for the respective group, the participants originated from different parts all over the US, spent on average 95 % of their time in clinical practice and had 21 years mean professional experience. Beyond, the mean percentage of the patients with some kind of renal impairment seen by these doctors was 68 % and more than 91 % of patients had a creatinine and/or GFR value available, which indicates that all participants have also empirical knowledge on kidney function assessment.

Use of current clinical methods

As a first step to understand thinking and behavior of the different groups, the doctors' experience with existing methods in the outpatient setting was surveyed. This revealed that 88 %/76 % of all physicians frequently or always use creatinine-based eGFR/serum creatinine when assessing kidney function. In contrast, more precise methods like cystatin C determination or radiotracer-based measured GFR are used rarely.



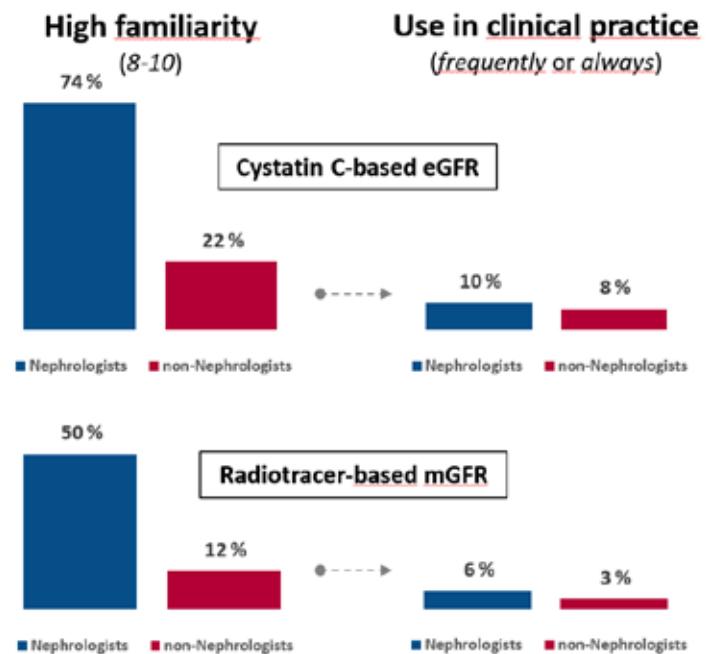
Creatinine-based eGFR is the most frequently used method to determine GFR, whilst the more precise methods cystatin C or radiotracer are rarely used.

However surprisingly, 70 % of all participants see the need for a more accurate GFR diagnostics. So, on one hand there is a need for a more precise measurement, on the other hand doctors don't use existing methods designed for that purpose.

In order to understand this apparent contradiction one needs to look more differentiated: the first thing

to notice is that mainly two groups split up in their behavior: nephrologists vs. "non-nephrologists" (endocrinologists, cardiologists, PCPs). While only 4 % of nephrologists state that creatinine-based eGFR is good enough to support all their clinical decision making, roughly one quarter of the non-nephrologists had that opinion. One explanation of this can be seen in the fact that 77 % of nephrologists' patients are CKD stage 3 or higher (= eGFR < 59 mL/min/1.73) while non-nephrologists' patients consist only to 33 % of this group.

Anyway, this still doesn't explain why nephrologists also use the more precise methods cystatin C or radiotracer (10 % and 6 %, respectively) only as little as non-nephrologists (8 % and 6 %, respectively) although many more nephrologists are highly familiar with both methods (nephrologists 74 %/50 % vs. non-nephrologists 22 %/12 %). First thing that jumps to mind is of course costs. Surprisingly, that was not the main reason for not using cystatin C or tracer-based methods. In the case of radiotracer, 80 % of the



Nephrologists are very familiar with mGFR and cystatin C. Nevertheless they do not use those methods more often in clinical practice.

nephrologists agreed that even though tracer-based GFR measurements are more accurate for assessing kidney function, the time-consuming nature and impracticality of the process prevents them from utilizing that approach.

Regarding cystatin C, nephrologists stated that this method was either not easily accessible (52 %) or that the clinical benefit over creatinine did not justify the higher costs (48 %). So, the lack of availability can be interpreted in several different ways: from the possibility that cystatin C is not listed in the standard lab ordering panel to a lack of insurance or payer coverage or even a too narrow indication of recommendation in guidelines can lead to this answer, which will need further follow-up clarification.

Taken together these statements together with 27 % of nephrologists claiming that cystatin C-based eGFR provides no clinical advantage, it's quite obvious that current clinical methods don't fully meet market requirements.

More accurate, easy-to-access GFR diagnostics needed

In order to understand this market need even better we asked for which medical condition the nephrologists perceive the biggest usefulness of a more accurate GFR. According to the nephrologists' opinion, patients with malnutrition/underweight (82 %), limb amputation (72 %), liver dysfunction, post-AKI surveillance and elevated BMI (each 62 %) will benefit most. Additionally, also in the context of drug treatments like contrast media (62 %), chemotherapy, ACE inhibitors/ARBs (60 %) or metformin (56 %) a more accurate GFR meets with much interest.

Summarizing the market for GFR determination, as expected, the nephrologists clearly have the lead in this field and physicians of other indications orient themselves via clinical guideline how to handle related situations. However, the market apparently

shows a gap between the need of a more precise GFR measurement and a lack of availability of a convenient and more precise method. Especially in the context of use cases with known problems of creatinine determination, the interest in a more accurate blood-based GFR test is very high.

On this basis, *numares* decided to develop a NMR-based GFR test which utilizes metabolite constellations to overcome the weaknesses of creatinine and combine it with the convenience of a simple blood test. The final test called "*AXINON® Clearance Check**" will be available at the beginning of 2021. □

Torsten Winkler, Product Management



AXINON® Clearance Check* will be available in early 2021.

The serum-based test uses several biomarkers, combined in a metabolite constellation, providing a GFR_{NMR} result to assess kidney function.

Introducing *numares* Departments

Spectral Lipoprotein Analysis & Data Processing

In this new section of the *numares insider* we ask *numares* employees to give an insight into their daily work. In this issue senior data analyst Kilian Bärwinkel answers questions on what data processing and algorithms need to fulfill to ensure smooth diagnostic processing with NMR.

ni: Kilian, which tasks does the department "Spectral Lipoprotein Analysis and Data Processing" perform within the product development of diagnostic products?

Our department develops the algorithms that prepare the measured NMR spectra in a standardized way for the analyses - this process is called processing. In the subsequent quality assurance, the suitability of each spectrum for an analysis in the AXINON® System is checked. After all, the spectra are the "feed" for our diagnostic tests. The algorithms ensure that the results provided by the AXINON® System are globally comparable, for example, between two instruments, at different locations or over a longer period of time. In addition, our algorithms check for irregularities that may have occurred during preparation or for deviations during measurement.

ni: In other words, you implement a wide range of requirements so that a diagnostic test can be used in everyday clinical practice.

Exactly. During the development of the AXINON® LDL-p test* (for determining cardiovascular risk based on LDL particle count, editor's note), our department was involved in increasing the sample throughput of the system while improving the stability and reliability of data processing. To this end, our team further developed the algorithms for the above mentioned processing and quality assurance, and analyzed the generated data. From these, parameters such as



precision, comparability of results with reference methods and failure rates were determined, which are used in conjunction with our internal expertise to assess the performance of the system. When all acceptance criteria and market requirements such as sample throughput and usability have been met, the test needs to be validated before it can be used - if this validation is passed, the product is ready for the market.

ni: What are the challenges in data processing and analysis of lipoproteins?

numares tests are used in laboratories with a focus on high throughput. Therefore the laboratory application of the test, e.g. sample preparation, must be as standardized as possible. This is ensured by using the AXINON® kits. With only one pipetting step the sample preparation can be fully automated. Data processing should also be carried out without any interaction by the laboratory personnel.

Therefore, robust, quality-assured algorithms have to be used, which accompany the complete process fully automatically, from the analysis of the samples, through processing, to the results. At the same time,

however, the user must be reliably warned in case of known problems, for example, when the pH value of the sample changes significantly. A particular challenge is the analysis of lipoproteins: they form broad, strongly superimposed signals that are broken down into individual components in the analysis process. Here, we pay special attention to ensure that the results are reliably calculated and reported even if there are deviations in the spectra. *numares* products therefore always implement a multi-level quality assurance, which ensures the correct preparation of the samples, a measurement and data processing according to the *numares* quality standards and the global comparability of the results. This level of quality pays off: In contrast to uncalibrated systems the test results in our system consistently remained the same on average even after longer periods of time, as shown in a long-term study of LDL-p.

ni: What concepts/projects are you working on for future products?

A current project is concerned with the further development of data processing and quality assurance

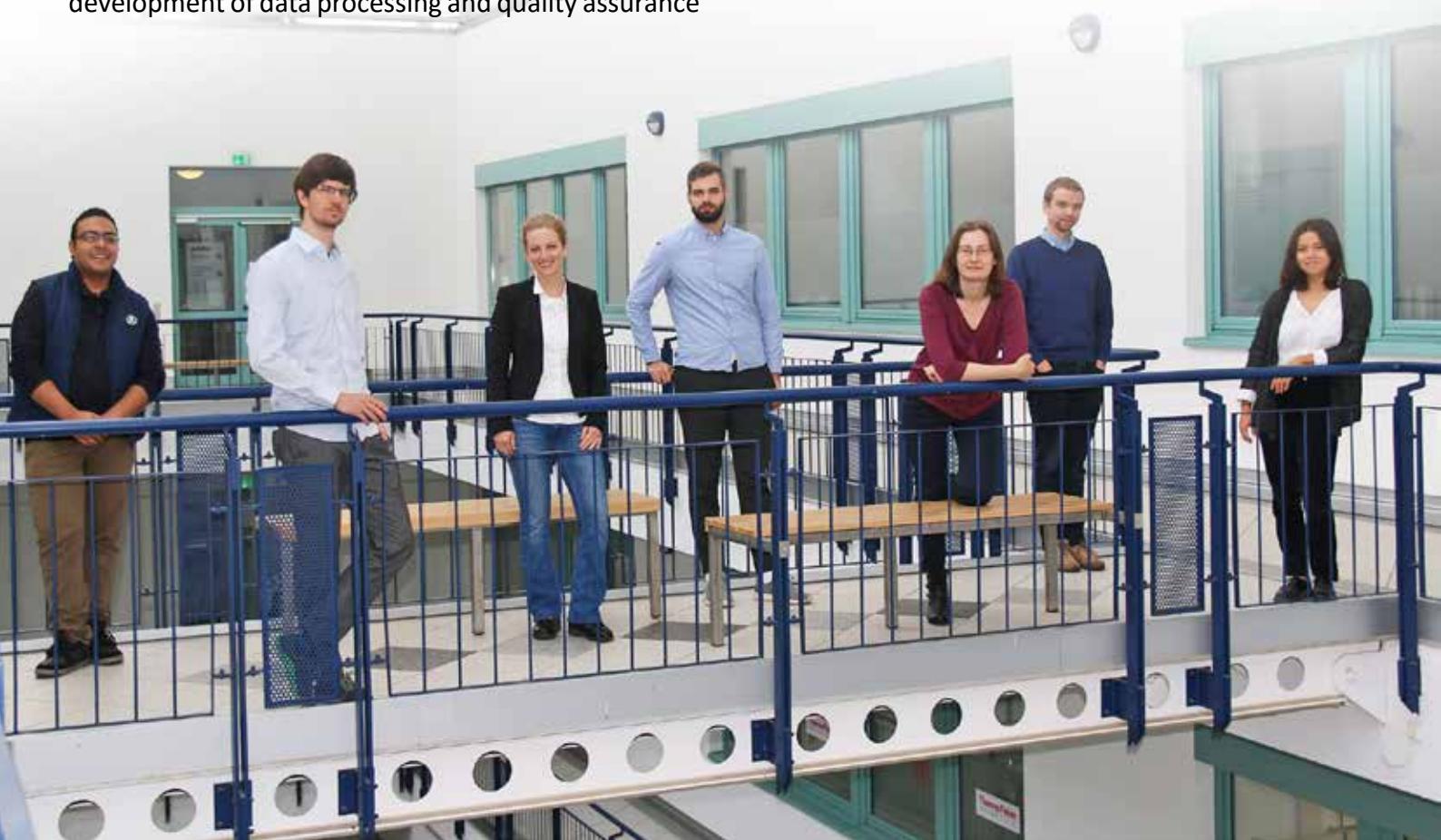
for urine. The goal is to establish uniform data processing for a wider range of clinical use cases by increasing the stability of data processing in relation to the biological variance of patient samples. It is not uncommon in special use cases that small amounts of proteins or blood are present in urine, which significantly changes the resulting spectrum. Our algorithms must be able to handle this.

Furthermore, during all projects we continuously expand the technical infrastructure of our processes in order to enable lean development processes with short reaction times using a uniform and high-performance development environment based on the *AXINON® System*. □

Kilian Bärwinkel, Spectral Lipoprotein Analysis & Data Processing

Christiane Proll, Marketing

* For Research Use only in the United States. *numares'* products are not yet available for sale within the United States; they have not yet been approved or cleared by the U.S. Food and Drug Administration.



NMR series:

Why Do We Need a Magnet?

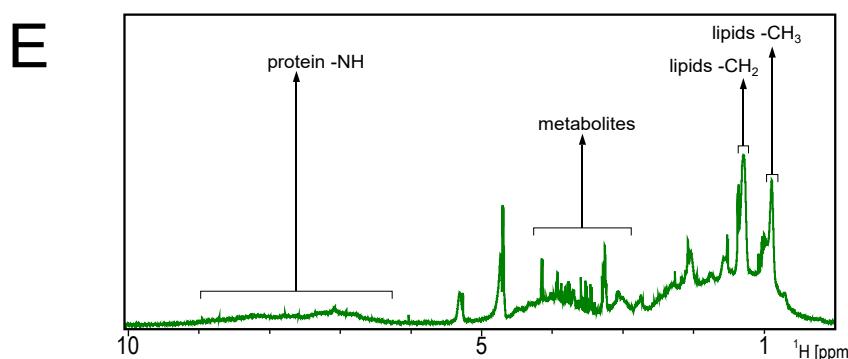
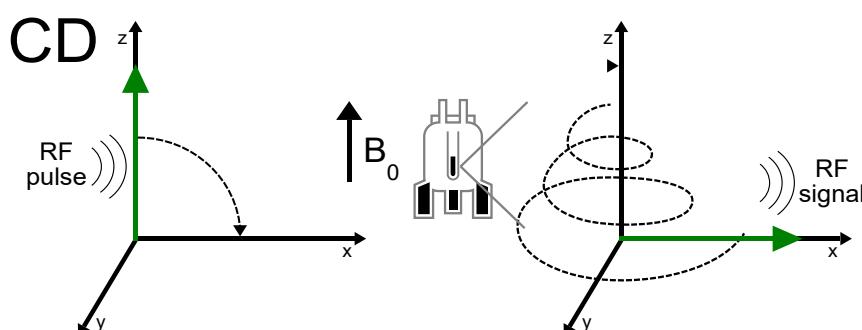
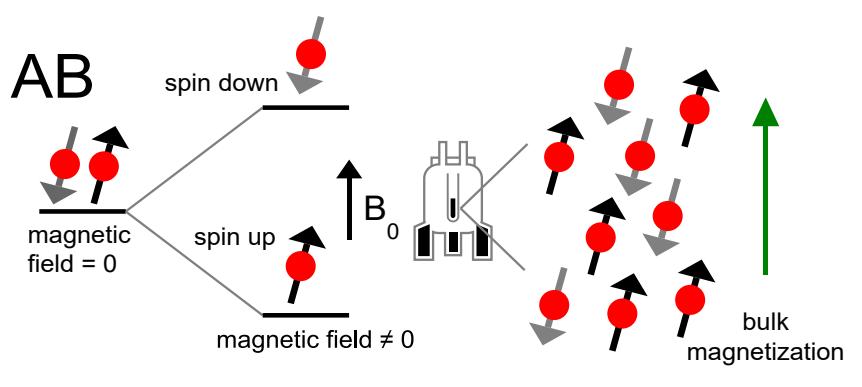
The superconducting magnet is the piece of the NMR lab that catches most of the attention. With its big vessel and three feet stand, it is certainly not a common piece in a medical diagnostic laboratory.

But why is a superconducting magnet needed to perform an NMR experiment?

The nucleus of a hydrogen atom has a “spin” associated with it. That means that the nucleus acts

a little like a small magnet. Without a magnetic field, those tiny magnets have no preferred orientation and NMR experiments would not be possible.

In the presence of a magnetic field, the spin can align either in direction of the magnetic field (spin up) or against it (spin down). There is a small energetic advantage to the spins being up, and this energy difference can be exploited to perform NMR spectroscopy.



A) The stronger the magnetic field is, the bigger is the energy gap between the two states. This leads to a better sensitivity and increased signal-to-noise ratio. That is why such big magnets are needed for NMR spectroscopy.

B) Due to the energetic advantage of the spins up, there will be a slightly larger number of spins pointing up out of the many present in an NMR tube. The sum of all individual spins results in the “bulk magnetization”, which is pointing up as a result.

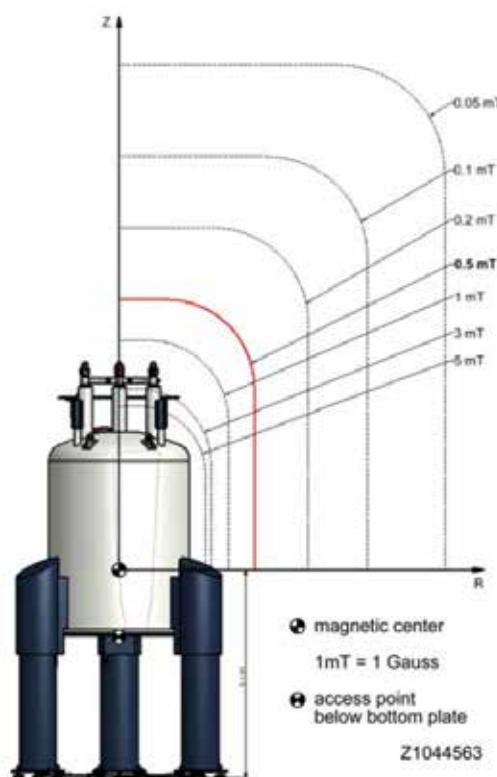
C) At the beginning of an NMR experiment, the bulk magnetization is tilted from its equilibrium state using a radio frequency pulse.

D) After that, the bulk magnetization will start to precess around the direction of the magnetic field. That is, the base of the magnetization stays in the same place, while the tip traces a circle, just like the wobbling of a spinning top.

The precession of the bulk magnetization generates the RF signal that is processed into an NMR spectrum.

E) The precession frequencies of an individual proton depends on its chemical environment, e.g. aliphatic protons like in the CH₃ and CH₂ groups of lipids have a different frequency than the amide protons in proteins. Thus, different chemical groups can be distinguished in an NMR spectrum based on the position in the spectrum. The larger the magnetic field is, the better the resolution in an NMR spectrum. Also for this reason strong magnetic fields are needed for NMR spectroscopy.

Magnetic fields used in NMR spectroscopy are at least 5 orders of magnitude stronger than the earth's magnetic field. Therefore, some precaution has to



Fringe Field Plot for a Bruker's 600 MHz/54 mm Ultra Long Hold Ascend Magnet

be taken to avoid health related risks and damage to valuables. First of all, identify the 0.5 mT line.

This defines a border to an area in which the magnetic field could affect implanted devices and is often marked with a yellow and black line. For an AXINON® 600 MHz NMR Spectrometer, the 0.5 mT line falls into 0.70 m radius from the magnetic center.



In addition, pay attention to:



- Place the permanent workplace outside the 5 Gauss line
- Place oxygen sensors in the room in case liquid gases evaporate and displace the oxygen
- Keep people with pacemakers and metal implants away from the identified area
- Keep disks, credit cards and electronic device away from the identified area
- Not use ferromagnetic tools or item within the identified area

For more information about safety operation with magnetic field, please refer to paragraph 2.4.6 Technical Risks of the user manual of the magnet or contact us or Bruker. □ Michele Salvi, Technical Support

numares' Video Tutorial Series:

How to Change the NMR Pincer*

**Only for trained personnel. Also refer to Bruker SampleJet User Manual.*



New pincers and o-rings can be purchased via the Bruker shop (<https://bruker-labscape.store/>): USC Spare Parts Kit for SampleJet, catalog no. Z106 364.



Prepare a new pincer by pulling the o-ring over the pincer's sleeves.



Make sure that the o-ring is placed in the second indentation of the pincer's sleeves.



To access the gripper arm in the SampleJet, push "Load rack" and select any rack number of options 1 through 5 on the SampleJet Touch Display.



The gripper arm will move to a neutral position at the back of the SampleJet.



To access the gripper arm, ensure the cover of the SampleJet is pushed upwards.



Remove the old pincer by slowly turning while simultaneously pulling it off.

Push the new pincer into the gripper arm and turn the pincer slowly until it clicks into place.



Pull down the cover of the SampleJet.



The pincer is now ready to use.

Find more helpful video tutorials on *numares*' YouTube channel...



#numares@Social Media

Welcome to the social media world of *numares*! By following the LinkedIn (<https://www.linkedin.com/company/numares-ag/>) profile of *numares*, you will get a continuous flow of news around our products, developments and the company itself. Here is an excerpt from the latest news:



A new metabolite panel as a chance for improved prostate cancer diagnostics. Castration-resistant prostate cancer (CRPC) is defined as disease progression despite treatment. A new urinary metabolite constellation could differentiate between patients who respond to the treatment and those who develop CRPC. The same metabolites might also be able to discriminate between indolent and aggressive PCa.

numares' Marouane Kdadra, PhD candidate of the TransPot program, presented his latest research results at the TransPot Collaborative Symposium: <https://lnkd.in/dG-tFm2>

The symposium was a great opportunity to get insights into current research projects around integrated prostate cancer research across the European Union. □

„Development of diagnostic tests based on NMR metabolomics using machine learning“ was the contribution of Dr. Sindy Neumann, head of the biostatistics department at *numares AG*, to the workshop „Artificial Intelligence in Health“.

Dr. Neumann gave an interesting insight into the challenges of developing diagnostic tests, using the wealth of information deriving from NMR and metabolomics data and applying machine learning to obtain the right „metabolite constellation“ for diagnostic applications.

The virtual workshop discussed challenges and potentials with representatives from research institutions and companies from Regensburg. □

Lipoproteins may play a role in the antidepressant actions of minocycline, which has shown therapeutic promise in pre-clinical animal models and early phase clinical trials for a variety of psychiatric disorders.

Read article at <https://lnkd.in/ehW5uEK> by Shi Yu Chan et al. in Translational Psychiatry of the Nature Research (Publishing), who investigate the underlying mechanisms and psychological and biochemical effects of this psychotropic agent.

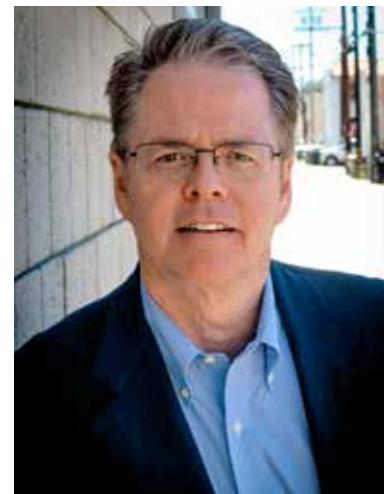
We are happy to have contributed to these results with our advanced NMR lipoprotein analysis. □



@AgNumares
@numares AG

@numares NMR diagnostics
@numaresAG

numares Announces Winton Gibbons as New President of US Subsidiary



numares appointed Winton Gibbons as new president of its US subsidiary, numares Group Corp., effective of June 1st, 2020. Mr. Gibbons will further strengthen commercialization of numares' products, and help expand the existing network of collaboration partners and investors.

Winton Gibbons brings to *numares* almost 30 years of experience related to life science businesses, particularly diagnostics. He has extensive experience in business development, strategy, and new product innovation, as well as in financial services and management consulting. As head of *numares Group Corp.*, he will be responsible for further commercializing the company's in vitro diagnostic products, growing collaborations, and expanding investors.

"We are very excited to have Winton Gibbons joining us," says Dr. Volker Pfahlert, Chief Executive Officer of *numares*. *"His large pool of experiences in the IVD sector will help us unlock even more possibilities in the US market to support numares in its North American expansion. His in-depth knowledge and relevant experience in developing early- and mid-stage in vitro diagnostic and life science firms will be invaluable to numares."*

German diagnostics company *numares* has its main market in the United States, providing a unique diagnostics approach – the "*numares* model," a distinctive nuclear magnetic resonance (NMR) technology to identify metabolite constellations for diagnostic purposes. Just recently, *numares* and

US-based Mayo Clinic Laboratories announced their collaboration to develop new diagnostic tests.

"I am excited to lead numares in the US. In a relatively short time, numares has built a strong track record as a provider of a unique diagnostic approach, and is now focused on some very exciting new products," commented Mr. Gibbons. *"I look forward to building the market for the company's innovative product pipeline, some of which should be filed with the FDA by year end."*

In recent years, Mr. Gibbons has consulted for innovative clinical diagnostic and life science companies, focusing on market assessment, business development, and strategy. Prior to that he was Senior Vice President of corporate development for Agena Bioscience, following his position as CEO and President of Siloam Biosciences, where he evaluated and implemented strategic options for the company, secured bridge financing, and managed investment banking relationships. This followed his senior management roles in business development for Nanosphere, and strategic marketing for Biosite. Leading up to this, Mr. Gibbons spent eight years at William Blair, a global investment banking & wealth management firm, where he was a Principal, sell-side Stock Analyst, and Healthcare Equity Research Group Head. Early in his career, he was a consultant and manager for McKinsey & Company, after which he worked for Boehringer Mannheim and Merck. He has also served on several industry and academic advisory boards. Mr. Gibbons holds an MBA from the University of Chicago, and a degree in chemistry from Duke University. □

Christiane Proll, Public Relations

numares is going to participate at the upcoming virtual meetings & conferences

Due to the threat of the ongoing coronavirus pandemic, many congresses and trade fairs have switched to new dates and digital platforms. We will be part of it and invite you to get in contact with us on the dates below.

If you want to contact us independently from any event, please get in contact with our US Sales Director Sean Keohane (sean.keohane@numares.com) to arrange an individual appointment via Zoom. Thank you for your comprehension and stay healthy!



virtual.MEDICA

November 16-19, Düsseldorf, Germany

<https://virtual.medica.de/>



National Lipid Association

Scientific Lessons

December 10-12 - Virtual Conference

<https://www.lipid.org/sessions>



American Association for Clinical Chemistry (AACC)

Annual Scientific Meeting

December 13-17 - Virtual Event

<https://meeting.aacc.org/>



American College of Physicians

Internal Medicine Meeting 2021: Virtual Experience

April 29 - May 1, Orlando, FL

<https://www.acponline.org/>

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