

THE FIRST P₂M ROUEN INTERNATIONAL SYMPOSIUM

ROUEN SCHOOL OF HEALTH SCIENCES
UFR SANTÉ ROUEN

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P₂M

PATHWAYS PRECISION MEDICINE



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ROUEN NORMANDIE FRANCE

Pathways to **PRECISION MEDICINE**

FROM RARE TO COMMON DISEASES

Chair : Prof. Soumeia Bekri
Co-chair : Dr. Abdellah Tebani

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Historical perspectives of individualized Medicine

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Since the late 1990s, the term "Personalized Medicine" has been coined to enable collaborations between different stakeholders in and outside research units. It has since then become a flourishing field under various names such as Individualized Medicine, Precision Medicine or 4P-Medicine. As a concept, it constitutes an imaginary framework of expectations and claims for a better, patient-centered and efficient health care system. In my talk I would like to shed light on past framings of individualized treatment and research, the role of pharmacogenetics and of some key figures such as Archibald E. Garrod and Werner Kalow. Instead of tracing back the history of Personalized Medicine to a supposed beginning, I want to consider research concepts centered upon the key category of "(bio-)chemical individuality" and "human variability" as a cultural framework of visions, expectations and normative claims.



Societal and Ethical Challenges of Precision Medicine

Catherine BOURGAIN

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Precision medicine has the ambition to promote a new medical practice. Medicine is made more efficient through the systematic use of detailed descriptions of the molecular identity of individuals. These promises of a medicine of the future, made more precise and adapted to everyone through scientific and technological progress, have important effects. Public policies combining support for certain types of biomedical research and innovations and new drug regulations are being implemented on their behalf. This concerns in particular the significant public and private investments required to develop the major genome sequencing programs. A variety of clinical practices already fit into this precision medicine category. They all mobilize different technologies to make a diagnosis, decide on a treatment, specify a disease prognosis or predict its occurrence. While genomics is essential, other forms of molecular description are also involved: transcriptomics, proteomics, epigenomics. In practice, the clinical applications of precision medicine differ significantly from the discourses and promises mentioned. Most of them existed before the introduction of the term and have been transformed by the new technological developments. In this presentation we will discuss this gap between discourses and practices of precision medicine and evaluate the ethical and social issues at stake.



The continuum from mendelian to complex diseases

Joseph NADEAU

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Precision medicine promises to revolutionize healthcare by using DNA content to personalize diagnosis and management of health and disease. While DNA information may suffice for some simple genetic conditions, the underlying premise is currently unreliable in most circumstances. Each person is a singular story, based on unique inherited factors, environmental exposures and life-style choices. For most genetic conditions, modifier genes, gene-gene, gene-environment and gene-age interactions, transgenerational epigenetic inheritance, and 'noisy' genes (variance differences without mean effects) complicate reliable mapping of genotype to phenotype. But we may be at a watershed where a deeper understanding of inheritance and systems genetics will emerge from high-throughput, low-cost genome sequencing, phenotyping, genetic engineering and computing. I will focus on evidence for these genetic phenomena that complicate inheritance and discuss the ways that they can be used to improve precision medicine.



The Role of Biomarkers in Precision Medicine: Opportunities and Challenges

Abdel B. HALIM

Biomarkers and Companion Diagnostics Taiho Oncology, NJ, USA

Incredibly high failure rate in the pharmaceutical industry has been positioning biomarkers and precision medicine in the frontline as optimistic rescuers. Successful development and implementation of biomarkers and companion diagnostic strategies can likely mark the difference between winners and losers in this crowded space. To achieve this ambitious goal, some prerequisites should be fulfilled, principally, embracing an effective biomarker strategy as early as possible during the drug development phase and implementation of the right processes. This presentation will highlight the following points;

- Where we stand with the initiative after two decades of the first CDx approval
- Attributes for robust and successful drug-diagnostic co-development
- Some critical but overlooked challenges facing CDx; Case study demonstration



Biobanking in Precision Medicine

Olli CARPEN

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Precision medicine will remain an empty concept, unless sufficiently large-scale disease-related sample sets are collected and analysed across the world, and the information fluently translated to the health care system. Especially, longitudinal phenotype information obtained from electronic hospital records, when combined with biological specimens, will provide an essential toolkit for understanding individual variation within disease entities. These databases in combination with artificial intelligence tools and user interphases, allow comparison of an individual's disease profile to a reference group, and provide evidence-based predictions of disease outcome and optimal

treatments. To achieve this goal, hospital-integrated biobanks, connected with comprehensive electronic health records, provide an elementary platform. I will describe the Finnish nationwide hospital biobank network's "consent all comers" approach for bringing tools for early recognition, successful targeted treatments, and effective preventive strategies to a variety of diseases. Finally, I will provide examples of the possibilities, challenges and achievements along our road towards precision medicine ecosystem.



Laboratory Medicine as a Key Driver in Precision Medicine

Nicolas VUILLEUMIER

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SWITZERLAND

Since the mid of the 20th century, laboratory medicine has been playing an ever growing role in providing -through biomarkers results- critical medical information allowing physicians to assess patients' diagnosis, prognosis, therapeutic response, as well as producing meaningful preventive or predictive information directly impacting patients' routine management. Being genuinely biomarker-driven, the precision medicine paradigm dedicated to improving diagnostic accuracy by considering both patient and the disease characteristics to optimize patients' therapeutic response and safety, has the same goal than routine laboratory medicine, which can be summarized as: "get the right results/diagnosis for the right patient, at the right time, to provide the right treatment". The major difference resides in the volume and complexity of biomarker-derived data needing to be integrated in precision medicine. Among the numerous challenges precision medicine will face, building accurate medical decision tools based upon the intrinsic and cumulative inaccuracy and imprecision plaguing any biomarker results could even be perceived as a paradox, especially because biomarker-derived data are believed to be the oil of precision medicine. As "n=1" trials are likely to become the standard of precision medicine studies, defining the amount of change requested for a given algorithm to drive a clinical/therapeutic action for a given patient will become even more crucial. Deviations from baseline individual values are likely to become more meaningful than any deviation from a population-based interval reference range or cut-off points. Clinical integration and viability of such paradigm shift will require clear-cut operating instructions which will have to be based upon on the knowledge of the intrinsic total variability of these algorithms.

This presentation will present how laboratory medicine expertise in quantifying and minimizing biomarkers results inaccuracy through the continuous operational optimization (processes standardization/harmonization, automation/consolidation, quality insurance policies) could be a key structuring player to transform raw biomarker-derived data into high-quality combustible to fuel the rocket of precision medicine, thereby maximizing the chances of transforming the precision medicine initiative into a successful moon shot.



The Role of Drug Monitoring in Precision Medicine

Jürgen BROCKMÖLLER

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Therapeutic drug monitoring (TDM) is one of the oldest approaches in precision medicine. This presentation aims to give an overview on achievements, limitations and future perspectives of TDM. What is TDM? In its narrow definition, it is drug concentration monitoring (TDcM) in body fluids and therapy (drug dose) adjustments according to that. In its broad definition, it is any therapeutic drug effect monitoring (TDeM) including all indicators of therapeutic and adverse drug effects to be considered for an individually optimized drug therapy. TDcM started to become part of practical medicine around 1970. As illustrated with immuno-suppressant drugs, anti-infective drugs and psychotropic drugs, it is immediately evident that TDcM can identify massive overdosing or underdosing, for instance due to dosing errors, drug drug interactions, genomic variation, or noncompliance. However, TDcM is apparently of limited value only in prediction of nonresponse to drug treatment. For instance, roughly 50% of patients do not sufficiently respond to psychotropic drugs in spite of drug blood concentrations mostly within the ranges considered to be effective. Reasons behind that may include still not fully understood disease heterogeneity and wide variation in the target pathways. One additional reason for those limitations of TDcM may be that we measure at the wrong place. For instance, immunosuppressant drugs should be measured within the immune cells, antibiotics at the centre of tissue infections, psychotropics within the brain. In our study on personalized immunosuppression, we compared intracellular TDcM with conventional TDcM in 160 patients after liver transplantation. Disappointingly, both, intracellular and conventional TDcM were not very good in prediction of rejections (therapy failure) and infections (adverse drug effects). The situation is similar in other areas of TDcM: It is apparently difficult to prove the value of a basically very convincing concept in clinical trials. That is due to different factors including statistical power issues and complex study design issues including feasibility issues with frequent enough monitoring in long term drug treatments. In our study on personalized immunosuppression we also investigated graft-derived cell-free DNA as a non-invasive early rejection and graft damage marker. Cell-free DNA-based biomarkers may indeed be superior to conventional markers in organ transplantation, but even much greater are the results and expectations in cell-free DNA-based biomarkers for drug monitoring in cancer therapy. One of the big hopes and reasons behind TDM is the burden from adverse drug effects. Death from adverse drug reactions may still rank in the 6th place of all causes of death following heart disease, cancer, stroke, lung disease and accidents. Apparently, TDeM would be the most appropriate approach to reduce that burden. Approaches include clinical biochemistry and hematology monitoring, blood pressure, heart rate, ecg monitoring and even monitoring for disturbances in coordination and cognitive abilities. Although these simple biomarkers of adverse drug effects are generally available (many of them at a low to negligible price) people die from adverse drug effects because physicians sometimes simply forget looking at and considering these markers. Several of such markers are already now available in the smartwatches and in many types of diseases this will become the drug monitoring of the future. Both, with TDeM and with TDcM, any presentation has to include thinking about the appropriate informatics infrastructure and quantitative pharmacology approaches. Most ingenious principles of TDcM based dose adjustments were already developed by Lewis Sheiner and colleagues 40 years ago, but still most TDcM is applied and interpreted in a very conventional fashion. Increasing availability of hospital information systems may bring indeed many new perspectives for TDcM and TDeM.



Data Sciences and Predictive Analytics in Precision Medicine

Abdellah TEBANI

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Everyone likes the concept of gazing into a crystal ball to learn what will happen in the future. The history of medicine of the Middle Ages taught us that healthcare was centered on mystical seers who deliver medical advices. With the increase in health data, health professionals have new kinds of technology to collect, analyze, and use health information. So, our modern era science has, luckily, replaced the crystal ball. Science can look into the future to the extent of events that have happened in the past. Gaining new insights from old data requires the complicated analysis of many interacting factors in medicine and health care far beyond human cognitive abilities, but current computers and the large amount of available data (big data) can do it almost effortlessly. Data sciences is an interdisciplinary field about processes and systems to extract knowledge or insights from data in various forms, either structured or unstructured using computing, data mining, statistics, machine learning or other artificial intelligence techniques. It involves developing techniques to efficiently process and analyze data to produce summative results that can then be used to improve health outcomes. The purpose of the data analyses is no longer simply answering existing questions, but also unveiling novel ones and generating new hypotheses. Predictive analytics is the area of data mining concerned with forecasting probabilities and trends. This is enabled by the use of high quality labeled big data, enhanced computing power and extended storage capacities. These data-driven innovations impact deeply clinicians predominantly through the automation of patterned-based tasks such as rapid, accurate image interpretation. Improving hospital workflows has the potential to enhance safety reducing medical errors and optimizing clinical pathways for better quality and cost effectiveness. These technologies may also allow better patient participation in promoting their own health. The real-world clinical implementation of these technologies has not yet become a mainstream and more prospective clinical validations through randomized clinical trials are needed. The limitations including talent gap, data standardization, privacy, safety and to some extent, lack of transparency in the algorithms are the key practical issues for both patients and health professionals. Clinicians and healthcare providers are thrilled and notice the potential that these deep changes can bring into healthcare practice. However, many are still frustrated and concerned about the patient–doctor relationship that could be eroded. Thus, promoting literacy in all these data-related aspects should be encouraged in medical education, biomedical research, and public health training. This will prepare well informed and strongly trained professionals who are poised to evolve in a competitive data rich healthcare ecosystem. This talk will present the basics of predictive analytics tools and their current and potential applications. It will also dissect major flaws and challenges for effective implementation.



Radiomics: transforming standard imaging into mineable data related for diagnostic and theragnostic applications

Philippe LAMBIN

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The rise of radiomics, the high-throughput mining of quantitative image features from (standard-of-care) medical imaging for knowledge extraction and application within clinical decision support systems (animation: <https://youtu.be/Tqg80GEVPoY>) to improve diagnostic, prognostic, and predictive accuracy, has significant and substantial implications for the medical community (1, 2, 5). Radiomic analysis exploits sophisticated image analysis tools and the exponential growth of medical imaging data to develop and validate powerful image-based signatures/models. We will describe the process of radiomics, its pitfalls, challenges, opportunities, and its capacity to improve clinical decision making (presently primarily in the care of patients with cancer, however, all imaged patients may benefit from quantitative radiology) (5,8). Finally, the field of radiomics is emerging rapidly; however, the field lacks standardized evaluation of both the scientific integrity and the clinical significance of the numerous published radiomics investigations resulting from this growth. There is a clear and present need for rigorous evaluation criteria and reporting guidelines in order for radiomics to mature as a discipline (see www.radiomics.world). Certain author's proposed that radiomics could be used as a "virtual biopsy". It could be the case in the sense that several reports demonstrated that biological features of tumours such as EGFR mutations, HPV status and even hypoxia could be quantified by radiomics (6). There are however two main differences: a) Radiomics is based on the whole tumour in contrast to a biopsy taken most often randomly in an heterogeneous tumour and b) the radiomics values is a continuous variable in contrast to molecular biology assays which are often dichotomized (e.g. mt vs wt). Interestingly, certain radiomics signatures e.g. a proliferation radiomics signature, works as well with cone beam CT which opens the field of "4D-Radiomics" (4, 7). The next step is however a "totalomisc" approach in which radiomics signatures will be used in a multifactorial Decision Support System for both diagnostic or theragnostic questions (3, 9, 10).



References:

1. Lambin, P. et al. Radiomics: extracting more information from medical images using advanced feature analysis. *Eur J Cancer* 48, 441-6 (2012).
2. Aerts, H. et al. Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach. *Nat. Comm.* 5 (2014).
3. Lambin P. et al. Radiomics: the bridge between medical imaging and personalized medicine. *Nat Rev Clin Oncol* 2017. Dec;14(12):749-762.
4. van Timmeren JE et al. Survival prediction of non-small cell lung cancer patients using radiomics analyses of cone-beam CT images. *Radiother Oncol.* 2017 May 12.
5. Lambin, P. et al. . Decision support systems for personalized and participative radiation oncology. *Adv Drug Deliv Rev.* 2016 Jan 14.
6. Grossmann P et al. Defining the biological basis of radiomic phenotypes in lung cancer. *Elife.* 2017 Jul 21;6. pii: e23421. doi: 10.7554/eLife.23421. [Epub ahead of print]
7. van Timmeren JE, Leijenaar RTH, van Elmpst W, Reymen B, Lambin P. Feature selection methodology for longitudinal cone-beam CT radiomics. *Acta Oncol.* 2017 Aug 22;1-7. doi:10.1080/0284186X.2017.1350285. [Epub ahead of print]
8. Larue RTHM, Van De Voorde L, van Timmeren JE, Leijenaar RTH, Berbée M, Sosef MN, Schreurs WMJ, van Elmpst W, Lambin P. 4DCT imaging to assess radiomics feature stability: An investigation for thoracic cancers. *Radiother Oncol.* 2017 Aug 7. pii: S0167-8140(17)32482-9. doi: 10.1016/j.radonc.2017.07.023.
9. Lambin P. et al.. Predicting outcomes in radiation oncology-multifactorial decision support systems. *Nature Reviews Clinical Oncology.* 2013 Jan;10(1):27-40.
10. van Wijk Y, Vanneste BGL, Jochems A, Walsh S, Oberije CJ, Pinkawa M, Ramaekers BLT, Vega A, Lambin P. Development of an isotoxic decision support system integrating genetic markers of toxicity for the implantation of a rectum spacer. *Acta Oncol.* 2018 Jun 28;1-7.



The Patient's Journey in Intensive Care

Peter LAUSSEN

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Critical care units are dynamic, complex and resource intense environments, where humans directly interface with technology. Decisions are time-sensitive and often occur in circumstances where clinicians need to quickly aggregate and integrate data from multiple sources. In turn there can be variability in practice and uncertainty in management, whether it be related to the patient disease and diagnosis, the patient physiologic state and unpredictable responses to management, and to the ability of clinical teams to interpret data correctly. In addition, there are numerous competing pressures inherent to any ICU environment around work flow, communication, distraction and resource utilization.

The continuous physiologic data streaming from devices and monitors are time-series data, data in motion. They are characterized by a number of features: huge in volume and velocity, signals are variable in frequency and subject to considerable artifacts. No question that these data are essential for supporting decision at the bedside, but when it comes to modelling for the purpose of real-time (bedside) predictive analyses, the ability to capture, label and integrate these data is limited. The data is messy; hard to manage, store and retrieve.

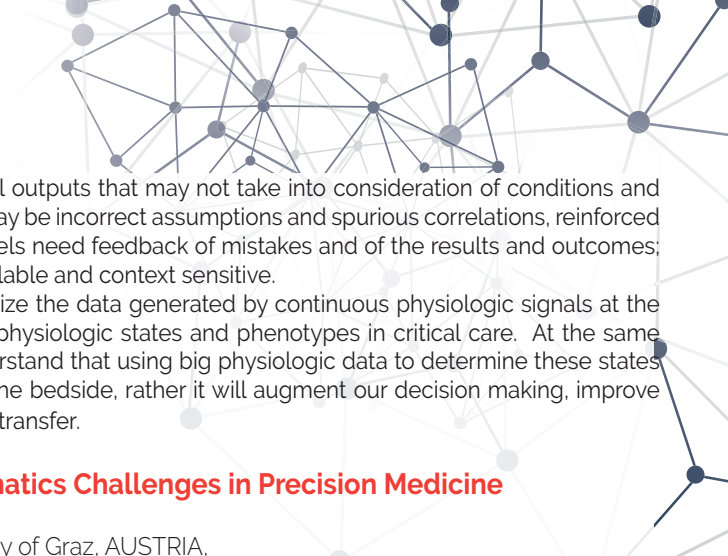
The problem of volume has placed constraints around data storage and retrieval, and there are bottlenecks as the data is input/output (I/O) bound. In our department, we have built and deployed a bespoke data management platform to facilitate collection, file indexing, compression and decompression (see www.lausсенlabs.ca). As an indication of the scale of continuous physiologic data that is measured and can be collected, and depending on the complexity of disease and treatment, there are routinely 500+ signals per hour and between 70-150 million physiologic data points per day generated in the 42 beds of our paediatric intensive care unit. Over 700,000 hours and 2 trillion data points from over 4000 patients is currently stored in the database.

Data Analysis

There are broad categories for using these data in critical care. Some of these include: 1) Describing the physiologic phenotype and individualized physiology according to age, disease, treatment and time, 2.) Understand the physiologic state, such as risk for low oxygen delivery, hemodynamic instability, effectiveness of mechanical ventilation, risk for neurologic injury, and metabolic state, 3.) Develop early warning systems and the risk for an event within a physiologic state through recognizing patterns in the data, such as risk for sepsis or cardiac arrest, 4.) Track the trajectory of a patient in response to treatment protocols, and direct specific interventions according to a change in the expected trajectory, 5.) Develop decision support and business analytic tools to ensure the efficiencies of care against validated outcome metrics, such as length of stay and risk for readmission, 6.) Enhanced signal processing and waveform analysis such as to diagnose changes in heart rhythm and uncover previously hidden signals that may be embedded within composite waveforms, and 7.) Develop new insights into the underlying physiology, tease out sub-populations of patients that may respond to a particular treatment, and develop prognostic and predictive enrichment strategies that can lead to individualized and precise critical care management.

The promise and problem with physiologic data

There is a disconnect between how we make decisions and the trust we might otherwise have in a model or algorithm. Models can be opaque, containing weighted features, components and simplifications with blind spots related to the inputs and the priorities and judgement of their



creators. They are mathematical outputs that may not take into consideration of conditions and behaviours. The risk therefore may be incorrect assumptions and spurious correlations, reinforced and contaminated by bias. Models need feedback of mistakes and of the results and outcomes; they need to be explainable, scalable and context sensitive.

It is nevertheless possible to utilize the data generated by continuous physiologic signals at the bedside to help us understand physiologic states and phenotypes in critical care. At the same time, it is important to also understand that using big physiologic data to determine these states will not replace the clinician at the bedside, rather it will augment our decision making, improve communication and information transfer.



Clinical Informatics Challenges in Precision Medicine

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Information technology has transformed our digital footprints into an important commodity. Non-linear machine learning modelling approaches are increasingly addressing the challenge presented by unstructured, noisy and incomplete data. There is evidence that data from social network posts and biosensors can be used for health-related predictions. However, we also leave our digital footprints in electronic health records (EHRs), which constitute a main topic of interest in clinical informatics. Precision medicine means tailoring health care assets and services to the individual patient. This requires, frequently, the stratification of patients by phenotypical features, lifestyle characteristics as well as features from health care processes like medication or therapies. Harvesting meaningful and interoperable information from raw texts in EHRs is often unavoidable, which poses challenges to human language engineering tools and resources. Clinical language is overly compact and context-dependent, often misspelt or mistyped, and uses idiosyncratic expressions that vary between languages, dialects, professional groups and clinical disciplines. Thus, the success of information extraction requires not only robust and context-sensitive methods but also sources of real clinical language such as custom dictionaries and annotated corpora. Much of these resources are underrepresented for languages other than English. The target representation matters as well. Ideally, it should follow standards and clearly distinguish between the meaning of a term and its context, e.g. negation, uncertainty, temporal reference.

A current effort is described, in which information extraction is used in the context of the Austrian biomarker research centre CBmed. Text analytics software processes large amounts of discharge summaries and annotates them with codes of the clinical terminology standard SNOMED CT, which not only allows representing subtle distinctions in meaning but also aggregations along different semantic axes. Manual creation of dictionaries constitutes a major bottleneck, but it can increasingly be supported by deep learning approaches, e.g. for the resolution of ambiguous short forms.



The Human Protein Atlas - implications for human biology, drug development and precision medicine

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The Human Protein Atlas (HPA) is a Swedish-based program with the aim to map of all the human proteins in cells, tissues and organs using integration of various omics technologies, including genomics, transcriptomics, antibody-based imaging, mass spectrometry-based proteomics and systems biology. The version 17 (www.proteinatlas.org) consists of three separate parts, each focusing on a particular aspect of the genome-wide analysis of the human proteins; (1) the Tissue Atlas showing the distribution of the proteins across all major tissues and organs in the human body, (2) the Cell Atlas showing the subcellular localization of proteins in single cells, and the new Pathology Atlas showing the impact of protein levels for survival of patients with cancer. The Human Protein Atlas program has already contributed to several thousands of publications in the field of human biology and disease and it was recently selected by the organization ELIXIR as a European core resource, due to its fundamental importance for a wider life science community. All the data in the knowledge resource is open access to allow scientists both in academia and industry to freely access the data for exploration of the human proteome.

Key publications

1. Uhlen et al (2015) Science 347: 1260419
2. Uhlen et al (2016) Mol Systems Biol., 12: 862
3. Uhlen et al (2016) Nature Methods, 13: 823-7
4. Thul et al (2017) Science 356 (6340): eaal3321
5. Uhlen et al (2017) Science 357 (6352): eaan2507



A multi-omic approach reveals a new type of inherited errors of vitamin B12 metabolism

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Vitamin B12 (B12, cobalamin (Cbl)) is a water-soluble vitamin that requires complex mechanisms for its assimilation, blood transport and intracellular metabolism. In mammalian cells, only two enzymes depend on vitamin B12: L- methylmalonyl - CoA mutase (EC 5.4.99.2) in the mitochondrion and methionine synthase (EC 2.1.1.13), in the cytoplasm. Inherited defects result produce a wide spectrum of clinical manifestations that includes cardiometabolic decompensation, megaloblastic anemia and neurological manifestations, and a metabolic profile that includes the accumulation of homocysteine (HCy) and /or methylmalonic acid (MMA). More than a dozen of genes are involved in the intracellular metabolism of B12, corresponding to several disease groups named in cblA to cblJ. The most common of these diseases, called cblC, is recessive, with identical or composite mutations of the two alleles of MMACHC gene. We have found a new type of cblC that we named epi-cblC in an infant deceased from a severe form of cblC, which paradoxically only showed a mutation in the heterozygous state. By carrying out the genome wide study of methylome we have identified an epimutation on one allele of MMACHC in 3 generations and in the sperm of the father of the index case. To date, most epimutations reported in humans are somatic and are erased in germ cells. The epimutation turns off the expression of the non-mutated allele of the MMACHC gene. MMACHC belongs to a trio of genes. It is flanked by two genes CCDC163P

and PRDX1, which are transcribed in opposite sense. The secondary epimutation results from a PRDX1 mutation that forces MMACHC antisense transcription and produces an H3K36me3 mark at the CCDC163P and MMACHC common promoter. We found 7 other cases of epi-cblC in Europe and USA and we identified more than forty gene trios with the same configuration on the whole genome. The 8 cases of epi-cblC illustrate the need to look for an epimutation in gene trios with similar configuration, when patients present typical manifestations of a rare recessive disease despite the presence of a heterozygous mutation.



The genome, the metabolome and beyond

Ron WEVERS

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Traditionally the diagnosis of metabolic disorders relies on targeted analyses of metabolite groups like amino acids and organic acids usually in body fluids. Although more or less non-invasive this approach delivers only a narrow view on the repertoire of metabolites and pathways present in cells and tissues. As such it is not comprehensive and not very cost effective. The study of metabolism at the «-omics» level, so-called untargeted metabolomics, performs better. It holds a promise to have a profound impact on medical practice. The metabolome is largely determined by what has been encoded by the genome while being modified by diet, environmental factors and by the gut microbiome. The metabolic profile provides a quantifiable readout of the metabolic pathways. At the center of metabolomics, is the concept that a person's metabolic state provides a close representation of that individual's overall health status. Genetic defects will derange the normal physiological state and often lead to disease. A substantial part of our genome is devoted to maintain the required metabolic pathways in our body. Metabolic diseases can present at any age and in many different clinical forms making life difficult for health care professionals to find the correct diagnosis. Here untargeted metabolomics can be of help. Modern analytical techniques like NMR and LC-MS provide a holistic overview of the metabolome and can pinpoint a molecular derangement of human metabolism at an unprecedented precision and accuracy. This will further improve when the intracellular metabolome (I like to call this the "forgotten metabolome") is taken into account by applying untargeted metabolomics on cell homogenates. Untargeted metabolomics techniques will teach us as yet unknown biomarkers for many known IEMs thus improving our understanding of their pathophysiology and providing targets for improving therapeutic strategies. Exploring the human body fluid metabolome has already shown how little we know. Surprisingly significant numbers of unknown "features" pop up deriving from molecular species that cannot yet be annotated with the help of available public databases. The lecture will show approaches to unravel the molecular identity of the metabolites behind such "unknowns", also called Features of Unknown Significance (FUS). This is a major challenge that calls for international collaboration between metabolic labs. Answers can be provided by using the structural information from NMR spectra, MSn spectra and infrared spectra. This can be done in Nijmegen by the collaboration between the Felix laboratory and the Translational Metabolic Laboratory. Solving the identity of as yet unknown disease biomarkers will provide a deeper understanding of the disease mechanism in individual patients. We have coined the novel untargeted metabolomics approach to IEMs as Next Generation Metabolite Screening (NGMS). Using metabolomics in parallel with whole exome sequencing will enable a higher diagnostic yield. Glycomics- and lipidomics techniques can add further essential diagnostic information.

SATELLITE EVENT SHIRE

Child-Adult Transition in patients with an inborn error of metabolism



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François MAILLOT

Tours University Hospital, Tours, FRANCE

The transition process from pediatric to adult care is always a challenge especially for chronic diseases with childhood onset, such as inborn errors of metabolism. The tremendous advances in diagnosis and treatment of these diseases have markedly improved their prognosis and their management. Thus, numerous patients with IEM who reach adult age need to be managed by a non-paediatric professional. The objective of this satellite event is to present updated guidelines to smoothly manage a successful transition of these patients'. Complementary perspectives of a pediatrician and an internist will be interactively discussed.

SATELLITE EVENT PerkinElmer

Newborn screening of inborn errors of metabolism

This satellite event will concern neonatal screening for inborn errors of metabolism with a presentation of the latest advances worldwide of newborn screening for Lysosomal Storage Disorders using Tandem Mass Spectrometry. A French perspective will also be presented regarding national screening programs.



Enzo RANIERI

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The impact of tandem mass spectrometry (MS/MS) on biochemical genetic testing for metabolic disorders is considerable. The use of MS/MS in expanded newborn screening for inborn errors of metabolism by determination of amino acids and acylcarnitines is now routinely implemented into newborn screening programmes world-wide. It was introduced into the South Australian Neonatal Screening Programme in 1999. To date, advancement in MS/MS instrument performance has greatly improved the sensitivity enabling the detection of metabolites to levels of less than 1nmol/L. This increase in sensitivity and specificity provides the capacity for the determination of additional metabolites as intermediates of biochemical reactions. The simplicity and accuracy of the use of MS/MS makes it amenable for use in newborn screening. This has enabled the inclusion of the screening for Lysosomal Storage Disorders (LSD) with superior performance characteristics of large dynamic range and lower end assay sensitivity that is able to distinguish between unaffected and confirmed true positive LSD cases. In addition, the use of 2nd tier MS/MS metabolite assays has resulted in a significant reduction in the false positive rate and provided the necessary confirmatory diagnostic test for the LSDs.



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In France, five diseases are subjected to a systematic newborn screening (NBS): phenylketonuria, congenital hypothyroidism, congenital adrenal hyperplasia, cystic fibrosis and sickle cell disease. For the latter, the focus is on populations of Afro-Caribbean origin. In general, these diseases meet Wilson's criteria: relatively frequent, severe, detectable and treatable. The NBS of deafness has been added in France from 2014. In June 2011, the "Haute Autorité de Santé" (HAS) published recommendations for an extension of neonatal screening to an additional metabolic disease, MCAD deficiency (expected frequency: 1/15000 births), using tandem mass spectrometry (MS/MS) technique. The French NBS organization has been modified in 2018. Thus, NBS Regional Centres (CRDN) have been identified and the global organization has been revisited.

The MS/MS implementation will make it possible to identify many other inherited metabolic diseases, including intermediate metabolic diseases, such as aminoacidopathies or organic aciduria, but also lysosomal diseases, some of which could benefit from early treatment. In a close future, NGS (next generation sequencing) can be implemented in the NBS practice, regarding long QT syndromes or spinal muscular atrophy for instance.

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