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Nota dell'Editore: i riassunti sono stati riprodotti senza alcuna revisione dal materiale direttamente fornito dagli autori.

SS01- Cyber security in Medicina di laboratorio

SS01 - 01

Risposta e Strategie di Mitigazione per l'Attacco Ransomware all'Azienda USL di Modena

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Introduzione
Questo abstract esamina le misure adottate dall'Azienda USL di Modena dopo l'attacco ransomware del 28 novembre 2023. L'ente, situato in Emilia-Romagna, Italia, con oltre 5.400 dipendenti, serve una popolazione di 690.000 abitanti. I crescenti attacchi ransomware bloccano l'accesso ai dati essenziali fino al pagamento di un riscatto e colpiscono frequentemente le strutture sanitarie, compromettendo la sicurezza dei dati dei pazienti e l'efficienza dei servizi, con gravi conseguenze per la salute pubblica. (1), (2).

Individuazione e risposta all'incidente. Il 28 novembre 2023, alle ore 22:00, una segnalazione relativa a problemi di accesso al Radiology Information System/Picture Achieving and Communication System (RIS/PACS) del dipartimento di radiologia ha permesso di rilevare l'attacco ransomware in corso. I tecnici informatici dell'azienda, insieme ai tecnici esperti di risposta agli incidenti di cybersecurity sono intervenuti per limitare la diffusione del malware.
Per mantenere l'operatività, l'ente ha adottato misure quali l'uso di documentazione cartacea, la gestione manuale dei braccialetti di identificazione dei pazienti e l'impiego di sistemi di videoscrittura su PC. L'attacco ha interessato varie strutture a causa dell'intensa integrazione delle reti aziendali, incluse l'Azienda USL, l'Azienda Ospedaliero - Universitaria e l'Ospedale di Sassuolo Spa, tutte interconnesse nella rete sanitaria di Modena. Il giorno successivo, il supporto è giunto dalla Computer Security Incident Response Team (CSIRT) dell'Agenzia per la Cybersicurezza Nazionale (ACN). È stato costituito un team di tecnici delle aziende colpite, esperti di cybersecurity e membri del CSIRT, operanti secondo le direttive dell'ACN. La riattivazione ha privilegiato i sistemi centrali e quelli critici per i processi clinici e automatizzati, seguendo rigide procedure di sicurezza e minimizzando i tempi di ripristino. Contestualmente, i sistemi sono stati esaminati ai fini della ricostruzione della catena di eventi dell'incidente e alla raccolta delle evidenze necessarie all'analisi forense. Su un portale del dark web, una gang di ransomware ha rivendicato l'esfiltrazione di 1.202.175 file (954,7 GB) dall'Azienda USL di Modena, richiedendo un riscatto di 3 milioni di euro. L'organizzazione criminale ha poi pubblicato i dati. Durante l'incidente, la cittadinanza è stata aggiornata tramite comunicati stampa, e le azioni criminali sono state denunciate alle autorità competenti e al Garante per la Privacy.

Conclusioni
L'attacco ransomware ai sistemi sanitari di Modena evidenzia la crescente minaccia globale degli attacchi informatici. Le indagini proseguono, ma l'evento ha accentuato il rischio in un contesto moderno, sottolineando l'importanza di sviluppare sistemi di sicurezza avanzati per proteggere i cittadini e i loro dati sensibili.

Ringraziamenti
Tutti gli autori hanno contribuito in egual misura a questo lavoro. Gli autori non dichiarano conflitti di interesse.
Esprimiamo la nostra sincera gratitudine a tutti coloro che hanno partecipato alla mitigazione dell'impatto e al ripristino dei nostri servizi sanitari.

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SS01 - 02

Management of a laboratory during a cyberattack

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Cyberattacks on healthcare facilities are increasing exponentially and can result in a kaleidoscope of serious consequences, potentially impacting patient care, compromising sensitive medical data and disrupting essential healthcare operations. Operating a laboratory during a cyberattack is particularly challenging as it requires a combination of preparedness, resilience and rapid response. Some steps can be identified to mitigate the impact of a cyberattack on laboratory operations. First, the laboratory needs to develop a cybersecurity incident response plan that includes a number of well-documented activities outlining the steps to take in the event of such an incident. This plan should include employee roles and responsibilities, communication protocols, and steps to contain and mitigate the attack. All employees must then be trained in cybersecurity best practices and know how to recognize and respond to potential threats. Regular training can help to reinforce good cybersecurity habits. The proactive implementation of strong security measures such as firewalls, intrusion detection systems, anti-virus software and data encryption would then allow the laboratory's systems and data to be protected. Critical data and systems must be regularly backed up to offline or cloud storage to ensure that important data can be restored at any time. Continuous monitoring of laboratory systems for unusual activity or anomalies can draw timely attention to a potential cyberattack (early detection can help minimize the impact of the attack). Contingency plans also need to be developed for maintaining essential laboratory operations, mostly based on manual processes or alternative systems that can be used when primary systems are compromised. Rapid resumption of service by available staff may be required to cope with the exponentially increasing burden of manual sample processing and alternative transmission of test results to

requesting physicians (i.e., by fax). The availability of emergency modules for requesting laboratory tests (preferably with unique identification number and barcode) and for the transmission of test results by paper sheet must be prepared before the crisis occurs. Open communication channels with employees, stakeholders and relevant authorities must be ensured to communicate the situation, any impact on laboratory operations and measures to counter the attack. Last but not least, once the cyber-attack has been dealt with, a thorough review of the incident must be conducted to draw lessons learned and identify areas where the lab's cybersecurity posture can be improved. The policies could be updated accordingly to be better prepared for possible future incidents.

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SS02- Laboratorio 4.0: sfide del futuro

SS02 - 01

Secrets of successful publication of a scientific article in high-ranking journals: Data analysis

Over the past decade, immunological studies have advanced significantly in single-cell technologies, generating extensive datasets with multiple parameters. As a result, new and sophisticated data analysis methods have been developed to facilitate precise investigation. One of the main challenges has been identifying the primary phenotypes present, which allows for an efficient and meaningful profiling of the tissue and assessing whether their frequencies correlate with clinical outcomes. Dimensionality reduction techniques such as principal component analysis (PCA), t-distributed stochastic neighbor embedding (t-SNE), and uniform manifold approximation and projection (UMAP) aid in data visualization but do not explicitly identify and categorize cells into subpopulations1. Additionally, not all subpopulations are visually distinct when high-dimensional data is rendered in only two dimensions. Therefore, non-parametric clustering methods like Phenograph and FlowSOM have been introduced to enable researchers to robustly identify subpopulations in high-dimensional single-cell data. Furthermore, new supervised learning methods, such as PENCIL, enable the prediction of subpopulations associated with clinical outcomes. Single-cell data allow the exploration of dynamic processes such as differentiation, disease progression, or vaccine efficacy. As a result, trajectory inference methods have been developed to map out the developmental and temporal changes that cells experience. Here, we demonstrate how the application of state-of-the-art data analysis methods can lead to insights into how disease-modifying therapies (DMTs) administered to patients with multiple sclerosis (MS) impact immune responses to SARS-CoV-2 and vaccine efficacy2,3,4. Despite numerous publications in the field, there is still limited detailed data on the phenotypic, functional, and metabolic characteristics of antigen (Ag)-specific cells following the third dose of the mRNA vaccine. Using flow cytometry and 45-parameter mass cytometry, we comprehensively investigate the phenotype, function, and single-cell metabolic profile of SARS-CoV-2-specific T and B cells up to 8 months after the third mRNA vaccine dose in a cohort of 94 MS patients treated with various DMTs, including cladribine, dimethyl fumarate, fingolimod, interferon, natalizumab, teriflunomide, rituximab, and ocrelizumab2. By applying a high-dimensional data analysis approach, we found that almost all patients exhibit a functional immune response to SARS-CoV-2. Significantly, fingolimod- and natalizumab-treated patients exhibit distinct metabolic profiles in their antigen-specific T and B cell responses, contrasting with those observed in patients receiving other MS treatments. Lastly, employing PENCIL, a novel supervised learning approach for predictive analysis, we pinpointed SARS-CoV-2-specific Ag+ T and B cells linked to symptomatic infection following the third vaccine dose2.

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SS02 - 02

La sfida del Laboratorio nella determinazione delle Nuove Sostanze d'Abuso: lo Stato dell'Arte

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Le nuove sostanze psicoattive (NPS) sono un gruppo di composti di origine naturale e/o sintetica che imitano gli effetti delle droghe "classiche" sottoposte a vincoli legislativi e che comportano rischi sanitari e sociali simili, se non peggiori. Hanno un mercato altamente dinamico e resiliente, caratterizzato da un elevato turnover di sostanze economiche, disponibili e sostituibili (1, 2), la cui diffusione è facilitata dal crescente utilizzo di Internet nonché delle piattaforme di social media e di altre applicazioni di comunicazione crittografate (1, 3, 5). Nel mondo, alla fine del 2023, sono state identificate circa 1.200 NPS immesse sul mercato negli ultimi 15 anni (3). Se in Nord America i nuovi oppioidi (fentanili), le benzodiazepine e la xilazina sono elementi consolidati, in Africa Occidentale, si osserva una maggiore diffusione di farmaci contraffatti a base di tramadolo, mentre in Cina si ha un aumento dell'uso di cannabinoidi sintetici comunemente presenti anche in Europa e negli Stati Uniti (1, 3). Un'indagine europea del 2020 ha rilevato che il consumo di NPS è più elevato tra i giovani rispetto alla popolazione generale e che tra i ragazzi di età compresa tra 15 e 16 anni è in aumento il consumo una tantum in particolar modo di cannabinoidi sintetici (dal 1,1% al 5,2%)

e di catinoni sintetici (dal 0,2% al 2,5%) (1,3).
In Italia, il Sistema Nazionale di Allerta Precoce (SNAP) riporta tra le NPS maggiormente in uso sul nostro territorio i cannabinoidi sintetici, i catinoni sintetici, ma anche gli oppioidi sintetici, le fenetilammine, gli analoghi della ketamina, le piperazine e le triptamine (2, 5).
In tale contesto, preoccupa la crescente combinazione tra le droghe illecite e le NPS perché gli utenti, in questi casi, potrebbero essere inconsapevolmente esposti a sostanze estremamente più potenti di quelle che credono di assumere e che aumentano il rischio di overdose anche fatali (1, 3, 5). La determinazione delle NPS rappresenta una sfida cruciale e complessa per i laboratori di analisi cliniche e tossicologiche. I metodi di screening (immunochimici/immunoenzimatici), utilizzati per la loro rapidità ed economicità, sono sempre più spesso affiancati da tecniche di cromatografia liquida (LC) o gas cromatografia (GC) accoppiate alla spettrometria di massa (GC-MS, LC-MS o LC-MS/MS) che consentono di ottenere spettri specifici per ogni singola molecola presente in una miscela complessa, aumentando notevolmente la selettività e l'affidabilità dei risultati e riducendo al contempo i tempi di analisi e le interferenze tra gli analiti e la matrice nella quale si trovano. Le sfide future includono l'adattamento delle metodologie analitiche per far fronte alla crescente diversità delle NPS, la miniaturizzazione e l'automazione delle tecniche analitiche al fine di essere di supporto al clinico in situazioni di emergenza, nonchè implementare il network di expertise e conoscenze necessarie a formare il personale e rendere più fruibili le tecnologie atte a contrastare un fenomeno in espansione e che, interessando soprattutto le generazioni più giovani, potrà rappresentare un serio problema di natura socio-sanitaria.

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SS03- Il Ruolo dell'Intelligenza Artificiale nel Laboratorio Clinico: sfide ed opportunità

SS03 - 01

Prerequisites for A.I. modelling or application – Expectations vs. Reality

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Artificial Intelligence (AI) has changed the way we live, maybe even without us noticing (1). These innovations are being adopted more slowly in healthcare due to strict regulations like the General Data Protection Regulation or the In Vitro Diagnostic Medical Device Regulation, and several others. However, especially in diagnostic processes using image recognition, AI is increasingly being implemented, with radiology leading the field with the most FDA approved software solutions (2).
With the recent hype of large language models such as ChatGPT, Claude, Gemini and others, expectations on revolutionizing healthcare are high. But there are many obstacles along the way from conception to implementation. At the beginning, and maybe most importantly, a large amount of high quality and "FAIR" data is needed (3). This data should be accurate, reliable, and representative of the real-world scenario for the intended use and ideally should be labelled correctly (e.g. with the correct diagnosis).
Due to the afore-mentioned data protection regulations, but also because of the data being distributed across many different IT-systems and its quality mostly relying on the correct input by medical personnel, the task of gathering the data is probably the most burdensome and the most common reason for failure. After approval by ethical committees, and data collection, the data then needs to be cleaned and pre-processed to remove duplicates, inconsistencies, and irrelevant information, while also handling missing information. Thereafter, this data can be used to adapt a pre-existing model to the intended tasks (fine-tuning), which requires a certain technical infrastructure, such as secure and fast storage solutions, reliable and secure network solutions with the necessary bandwidth if cloud services are being used, as well as an adequate software and programming environment.
Even with all of these prerequisites in place, data scientists or technically advanced IT personnel are needed to handle the data processing and fine-tuning of the selected model, who sadly are part of "a scarce breed" (4). Of course, healthcare facilities do not necessarily need to train their own models or finetune pre-existing ones and may purchase commercially available solutions, but these, similarly to the above-mentioned prerequisites, come with a certain price tag and considering the current financial situation of healthcare systems in many countries, the path to functioning AI-based clinical decision support systems (CDSS) is quite a long and cumbersome one.

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SS03 - 02

Esperienza del GdS SIBioC nello sviluppo e validazione di un modello multicentrico basato su parametri ematologici per lo screening della sepsi

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Sepsis is a condition characterized by an abnormal reaction to infection: its early identification is critical for improving patient outcomes. Laboratory medicine is essential in detecting biomarker alterations before clinical signs and symptoms appear. In the last decade, the role of Monocyte Distribution Width (MDW) as a screening sepsis biomarker has emerged. However, MDW has low sensitivity and positive predictive value compared to other biomarkers.
Machine Learning (ML) approaches can improve the performance of traditional biomarkers by integrating several factors and, therefore, enhancing sepsis detection accuracy. Making ML models work in clinical practice, on the other hand, can be challenging. Indeed, even widely used commercially available models have been shown to generalize poorly. We performed a multi-centric study to construct and externally validate ML models for early identification and screening of sepsis using MDW and other Complete Blood Count parameters. Five patient cohorts (5344 patients) from five different Italian hospitals were used to develop six ML models. The cohorts were selected to evaluate the models' performance in various settings, including the emergency department and ICU, using different diagnostic criteria (Sepsis-2 vs Sepsis 3), inclusion criteria, and data availability. To ensure generalizability and robustness in these markedly different settings, the developed ML models adopt advanced techniques inspired by controllable AI, namely: cautious classification, which allows the ML models to avoid making predictions; and explainable AI, which provides clinicians and health operators with helpful information about how the models work.
The developed models achieved good diagnostic performance on internal validation (AUC between 0.91 and 0.98) and consistent generalization performance across external validation datasets (AUC between 0.75 and 0.95), outperforming baseline biomarkers and cutting-edge ML models for sepsis detection. Controllable AI approaches were also employed to boost performance and provide a basic, understandable set of diagnostic guidelines. Our findings show how controllable AI techniques based on CBC and MDW may be useful for early identification of sepsis, as well as how the suggested methodology can be used to create ML models that are more transportable and generalizable to different clinical settings.

SS04- Casi Clinici

SS04 - CO01

Sinergie e compliance tra laboratori centrali e presidi di Ps per l'implementazione di POCT: la nostra esperienza

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A quasi due anni dalla pandemia da SarsCov stiamo assistendo ad un profondo cambiamento nel settore sanitario, soprattutto nel modo in cui viene erogata l'assistenza al paziente, per un approccio alla cura mirato e orientato alla riduzione del tempo di degenza e dell'annesso impatto economico.
La progettazione relativa ai fondi del PNRR (MISSIONE 6C1) ha posto al centro lo sviluppo e il potenziamento degli ospedali e di tutti gli assetti territoriali, spostando l'attenzione dei professionisti verso una nuova modalità di presa in carico, con risvolti positivi sulla mitigazione dell'uso improprio e sul sovraffollamento delle strutture già fortemente oberate. In tale scenario la Medicina di Laboratorio assume un ruolo centrale anche nell'implementazione e sviluppo di sistemi decentrati POCT, campo nel quale l'ASST Bergamo EST è stata precursore sin dai primi anni 2000.
In un percorso volto a cogliere le nuove necessità cliniche, analitiche e di personale si è proceduto nel Marzo 2024 alla creazione di un'innovativa isola POCT nel presidio Ospedaliero SS. Capitanio e Gerosa di Lovere. Dopo aver attivato un benchmarking con le realtà vicine e con altre regioni (Presidio di Sassuolo), si sono individuate le strumentazioni più idonee e poi si è riunita la commissione HTA (studio di congruità e budget) e un comitato multidisciplinare (farmacia, laboratorio, U.O.) per dettare i confini del progetto e il target dello stesso (accettazione, esecuzione e refertazione dell'esamistica decentrata) e stesura condivisa di protocolli operativi.
Alle strumentazioni da tempo già presenti e interconnesse, sono stati affiancati cinque strumenti analitici (emocromo, PT e PTT, 13 principali analiti di chimica clinica, marker cardiaci e infiammatori) organizzati in uno spazio dedicato ed ergonomico, utilizzabili dal personale infermieristico e con un pannello test concordato con il Comitato Multidisciplinare. L'implementazione, preceduta da una serie di incontri volti a rimarcare l'importanza della fase preanalitica e del corretto utilizzo dei dispositivi di prelievo, si è conclusa con l'installazione di software e strumenti a Febbraio 2024 e con la formazione su campo di circa 25 infermieri operanti nel sopracitato PS oltre che dei tecnici di laboratorio dei presidi di afferenza.
Dopo le perplessità iniziali da parte del personale medico \infermieristico ad oggi possiamo dirci soddisfatti della scelta poiché sia i questionari di gradimento compilati dagli utilizzatori che la mappatura dei processi da middleware stanno dimostrando in pieno la lungimiranza del progetto di delocalizzazione dell'azienda, da sempre orientata alla continua crescita e al miglioramento professionale.

SS04 - CC03

Occasional diagnosis of multiple sclerosis in a young patient

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In February 2024, a 17-year-old woman, following a motorvehicle accident, underwent brain Magnetic Resonance Imaging (MRI) which detected numerous periventricular lesions in the corpus callosum as well as juxtacorticals lesions typical of Multiple Sclerosis (MS). She was seen at the Multiple Sclerosis Center of the Neurosciences Department of the University of Naples, and clinical history and neurological examination were normal. The results of blood chemistry analyses carried out at the Department of Laboratory and Transfusion Medicine of the University of Naples were all within the normal range, as were the main Cerebrospinal Fluid Analysis (CSF) parameters, including absence of red blood cells, normal leukocytes, glucose and protein levels. However, the k index (ratio between CSF/serum kappa free light chains and CSF/ serum albumin) was 15.9, much higher than the proposed cut-off level (6.1)[1], suggesting intrathecal immunoglobulin synthesis, while the serum /liquor isoelectrofocusing for Oligoclonal Bands (OB) detection, currently employed for MS diagnosis, was negative. A group of MS experts has recently developed a consensus statement[2] recommending the introduction of the k index in the forthcoming revision of MS diagnostic criteria as an additional tool to measure intrathecal immunoglobulin synthesis. The high k index observed in this patient confirmed the suspected diagnosis of MS, but given her young age, disease-modifying therapy (DMT) was not recommended, and MRI follow-up is ongoing. This case is very unique for the occasional finding of MS-like brain lesions, due to MRI performed for other indications. This allowed the patient to be classified as having MS thanks to the concomitant findings at the k index, despite the complete absence of symptoms. Furthermore, this clinical case highlights the high diagnostic sensitivity of the k index for MS, which was markedly high even in the absence of OB. In this case, the early diagnostic classification will allow the young patient to be monitored
with stringent clinical/laboratory follow-up to highlight the possible evolution of the pathology and, consequently, a timely administration of suitable therapy. Hegen et al. MSJ 2023, 29, 169-812. Hegen et al. MSJ 2023, 29, 182-95

SS04 - CC04

TSH testing in amniotic fluid for monitoring of dyshormonogenetic fetal goiter: a case report

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Fetal goiter is a rare condition characterized by increased fetal thyroid gland volume as a sign of hypothyroidism and, if severe, can lead to cardiac failure, hydrops and intrauterine death. Fetal goiter can be treated by administration of levothyroxine in amniotic fluid (AF), umbilical vein or muscle. Current evidences show an efficacy of about 70% of intra-amniotic therapy. Fetal blood (FB) sampling is associated with 5% of complications and amniocentesis is considered a safer procedure (<1% complications).
Although AF sampling poses fewer risks, a well-established, analytically validated, assay for AF TSH monitoring should be warranted. In this case report, we evaluate AF TSH measured on an automated chemiluminescent immunoassay (Alinity i Abbott) in a hypothyroid fetus with goiter. A 25-years-old hypothyroid woman treated with levothyroxine and with a history of multiple miscarriages was referred to the Fetal Therapy Unit at 20.4 gestation weeks for a suspected fetal goiter, confirmed by ultrasound. TSH assayed on FB resulted >100 mU/L and intraamniotic injection of 100 µg of levothyroxine was performed. Treatment was repeated weekly from week 22 to 27. FB and AF sampling was performed at week 25, with TSH results of 24.2 and 5.6 mU/L, respectively. AF TSH levels at 27, 29 and 33 weeks were 2.9, 1.2 and 1.8 mU/L respectively. The decreasing values probably reflected the efficacy of therapy, with a subsequent rise few weeks after stopping therapy. In absence of hydrops, AF sampling was not repeated further to reduce prematurity risk. A liveborn weighing 3020g was delivered at 38 weeks, with blood TSH >100 mU/L and negative thyroid autoimmune screening treated with levothyroxine which normalized thyroid function in 4 days. Intrauterine treatment of fetal goiter is fundamental to prevent complications. The possibility of monitoring the dysfunction with minimal risk by measuring AF TSH is important. However, some limitations cannot be ignored: a) TSH commercial assays need to be analytically validated to avoid matrix effects when used on AF; b) physiological or pathological confounders influencing AF TSH levels should be investigated; c) clinical studies are needed to assess the actual power of the test in clinical decision-making.

SS04 - CC05

Gaucher syndrome: A new intronic mutation in the GBA gene creates a cryptic splicing site

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Gaucher disease (GD) is a lysosomal storage disorder characterized by toxic accumulation of glucocerebroside lipids in multiple organs. It is an autosomal recessive inborn error of metabolism, mainly due to mutations in the GBA1 gene encoding acid β-glucosidase, a lysosomal membrane protein. A 47-year-old patient came to our attention with a diagnosis of GD, carried out at 4 years based on the beta glucosidase enzyme activity test. The patient's medical history showed a severe course of the disease: marked hepatosplenomegaly and thrombocytopenia, subsequent partial liver resection and splenectomy, delayed physical and motor development, severe bone involvement and needfor orthopedic surgery. Moreover, the patient has been on enzyme replacement therapy since the age of 20, with an improvement of his clinical condition. Patient underwent molecular investigation using a NGS method to define his genotype. Genetic analysis showed the presence, in heterozygosis, of two variants in the GBA1 gene: c.626G>C, (p.Arg209Pro), already described in literature as being associated with GD, and c.1225-14_1225-11 delinsAGT, not reported in literature and classified, according to ACMG criteria, as a variant of uncertain clinical significance (VUS). The in-silico analysis, using 'AlamutVisual' software, of the c.1225-14_1225-11 delinsAGT variant revealed the possible formation of a cryptic splicing site, with a retention of 11 intronic bases. Subsequently, the mRNA analysis confirmed the formation of the predicted cryptic splicing site. The alteration produces a frameshift and introduces a premature stop codon (p. Asp409SerfsTer19).
Therefore, this variant can be reclassified as pathogenic. The mRNA analysis enabled the definitive reclassification of the c.1225-14_1225-11 delinsAGT variant as pathogenic and led to defining the patient's genotype, which is associated with a very severe form of Gaucher disease. The identification of the causative variants of disease allowed a proper genetic counselling and the cascade screening in the patient's family members. Finally, the study highlighted the relevant role of a molecular biology laboratory able to carry out functional studies of VUS for the correct attribution of pathogenicity.

SS04 - CC06

Dalbavancin Pharmacokinetics in a 18-Month-Old Child Undergoing Extracorporeal Membrane Oxygenation

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Introduction: Extracorporeal membrane oxygenation (ECMO) is a life-saving support for patients with severe respiratory or cardiac failure. ECMO significantly affects the pharmacokinetics (PK) of administered drugs, leading to drug sequestration by the ECMO circuit, increased volume of distribution (Vd), and altered drug clearance (CL). For antimicrobial agents, maintaining drug levels within the therapeutic range is crucial. This necessity is especially pronounced in patients undergoing ECMO, as it can significantly influence the attainment of therapeutic levels, and thus drug regimen should be individualized through Therapeutic Drug Monitoring (TDM). We describe the PK profile of dalbavancin in an 18-month-old child during ECMO and after ECMO discontinuation.
Methods:
The PK study was based on a sparse sampling strategy at random time-points to better fit in the clinical pediatric setting. Dalbavancin concentrations in plasma were measured using a validated microsampling-based liquid chromatography-tandem mass spectrometry (LC-MS/MS) method with deuterated internal standard, and calibration curve from 0.66 to 400.00 mg/L. The PK parameters of dalbavancin were estimated using a non-compartmental analysis (NCA) approach performed in PKanalix 2023R1 from the available concentration–time data. Data handling and graphical summaries were performed using R version 4.3.2. Results: The non-compartmental PK analysis reveals a significant impact of ECMO on dalbavancin clearance (CL), estimated to be 2.13 times higher during ECMO than after ECMO discontinuation and accounting for a reduction of 52.32% in terminal half-life (79.13 vs 165.98 h). Conclusion: The case that we describe shows PK alteration in dalbavancin disposition under ECMO whichmay potentially lead earlier than expected to a suboptimal drug exposure, unable to guarantee the suggested PK/ PD efficacy threshold of dalbavancin over time. Our data support the role of TDM of dalbavancin in patients undergoing ECMO.

SS04 - CC07

Why is my patient not responding to drug treatment?

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Employment of therapeutic drug monitoring (TDM) in clinical practice may guide clinicians in the individualisation of antipsychotic treatment of patients with severe mental disorders. TDM is indicated in case of poor drug response at therapeutic doses, evaluation of therapy adherence, tolerability issues, and drug-drug interactions and may be particularly valuable in the therapeutic management of specific populations, such as children and adolescents.
We present here the case of an adolescent of 13 years old not responding to Risperidone treatment despite the increase of drug dose. Risperidone was introduced at a drug dose of 0.5 mg bid. Subsequently, many variations of posology were necessary, due to behavioral and mood instability of the patient. The maximum dose reached was 2 mg bid, without apparent clinical benefit. A first trough blood sample was collected 3 days after reaching the dose of 2 mg bid, exactly a month after the beginning of the therapy. Risperidone concentration was under the limit of quantification of the method set at 3 ng/mL. Clinician decided to maintain the dose, repeating the blood measuring a week later: the blood sample sent to the laboratory confirmed subtherapeutic drug concentrations. Renal (serum creatinine 0.60 + 0.03 mg/dL) and hepatic function (AST 17 + 0.5 U/L; ALT 19 + 1.5U/L) of the patient were normal and the patient was not concomitantly administered agents affecting risperidone exposure.
By investigating the possible reasons of the underexposure to the drug it was found out that the patient decided to chew the tablet in the mouth due to purported swallowing difficulties. This practice should not be a reason for limiting bioavailability if the chewed drug suspension was completely swallowed, even if the solubility of risperidone is particularly poor in salivary fluids and the short residence time in oral cavity would not allow oromucosal absorption.
After introducing inspection of the mouth following the drug intake and total swallowing of the drug suspension was verified, risperidone plasma concentration resulted in high plasma level (42 ng/mL), which required dose reduction.
Weekly TDM with additional dose adjustments brought to plasma concentrations in the range 7.5-18.1 ng/mL
TDM was applied to help clinician in patient treatment.

SS04 - CC08

Endogenous Digitalis-Like Factors In Pregnancy

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Introduction. Endogenous digitalis-like factors (ELDF) are molecules with a steroid structure that inhibit the functioning of the Na/K-ATPase pump[1]. The biological consequences of this inhibition are primarily the accumulation of Na+ and secondarily of Ca++ in the cytosol. Humans secrete high quantities of EDLF in three clinical conditions characterized by hypervolemia, two of which are pathological (heart and renal failure) and one physiological (pregnancy). The aim seems to be the stimulation of diuresis by EDLFs to counteract volume excess but the accumulation of intracellular Ca++ also determines an increase in arrhythmogenesis which in turn rises cardiac excitability[2]. Clinical case description In a 42-year-old woman at 33 weeks of pregnancy we observed the onset of an incessant ectopic atrial tachycardia, not responsive to beta-blockers, which caused a rapid deterioration of cardiac function (the ejection fraction decreased to 39% at 36 weeks). The blood digoxinemia was 0.16 µg/L despite the patient not taking digitalis therapy. The data allowed us to hypothesize the presence in the blood of EDLF type marinobufagenin (produced by the adrenal gland and placenta) and/or ouabain (secreted by the adrenal gland and hypothalamus)[3]. The administration of flecainide, a Na+ channel blocker effectively stopped the arrhythmia. Thanks to the restoration of sinus rhythm, a normal systolic function was recovered at 38 weeks. The patient completed her pregnancy at full term, in excellent hemodynamic compensation, giving birth to a healthy and normal weight baby girl.
Materials and methods. Drug monitoring for digoxin was conducted with immuneturbidimetric method by Beckman Coulter OSR6404-AU400 platform and flecainide by LC-MS/MS with Chromsystems kit. Pregnancy was under echocardiographic control.
Conclusion. The determination of digoxinemia has made it possible to highlight the presence (but not to measure the actual concentration) of EDLF and guide cardiac therapy, however this is an improper use of the test (not sensitive and not specific for EDLF). The development of specific and sensitive assays specifically designed to identify and measure ELDFs represents a challenge for laboratory medicine and path the way for new avenues of clinical research.

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SP01- European Federation Laboratory Medicine - SIBioC-Medicina di Laboratorio

SP01- 01
Direct-to-consumer laboratory testing (DTCT): Challenges and implications

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In paternalistic medicine, the attending physician determines the indication of medical tests only by the medical need and the rules of marketplace, the major triggers of decisions outside of healthcare, should have only negligible influence. Recently, technological progress, the self-empowerment of patients (a.k.a. “4P-medicine”), and the widespread experiences with Covid self-testing are strong triggers for Direct-To-Consumer Testing (DTCT). In DTCT, the consumer himself initiates and pays for the testing which is performed either by the consumer himself or self-collected samples are analyzed in nonmedical or medical laboratories, the latter is named DAT (direct access testing). The clear differentiation between the setting of the testing can be obscured but will affect the quality of the test results and therefore their potential use for medical decision making or for “lifestyle modification”. Healthcare is highly regulated and numerous laws, regulations and restrictions are being enforced by the authorities to protect the patients. Aggressive marketing including promises to optimize the own health by IVD testing draws much attention of the consumers to DTCT. It is not obvious whether the increased interest and demand in DTCT testing might have beneficial effects on laboratory testing in healthcare – or whether DTCT might be a burden for healthcare or even the society as a whole. The intended use of IVD testing should be claimed when offering an IVD test but in DTCT this description should not contain the term healthcare. Vendors of DTCT tests achieve this by either using confusion, by negligence, or by false claims. The user of DTCT is hardly aware of the shortcomings of DTCT. Reasons for the often-inferior quality are the selection of unsuited tests, non-scientific methods for testing (such as sink testing or bogus/quacksalver technologies), unsuited preanalytics, lack of quality control, and poor interpretation of the test results not considering the medical history and pretest probabilities.
DTCT has a higher rate of false positive results which often trigger extensive medical studies to calm down the scared consumer. One can assume that the resources spent for DTCT (from the consumer as well as from the national healthcare budget for the follow-up procedures) are not always used efficiently and that the medicalization by DTCT challenges the optimized use of the limited resources in healthcare.Data protection is often hampered in DTCT and the customers are not aware of the obvious risks of this for themselves and – in particular in genetic testing – even for their families. Medical health records even might become worthless if hampered by unreliable DTCT data. In summary, ethical risks of DTCT are manyfold such as by overmedicalization, wasting healthcare resources, infiltration of medical records by bogus data, and hampering the trust of patients and healthcare professionals in real laboratory test results.

SS05- Etica

SS05 - 01
Etica e Intelligenza Artificiale

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Artificial Intelligence (AI) has revolutionized and transformed the medical field, changing how healthcare is delivered and managed. AI can be involved in many different tasks. Among others, AI systems can analyze vast amounts of medical data with unprecedented speed and accuracy, offering remarkable opportunities in healthcare, especially valuable from an ethical perspective. For instance, AI can bridge gaps by providing critical assistance and prevention programs in regions with limited resources and a shortage of trained professionals, ensuring more equitable access to healthcare. AI also holds promise in research, potentially reducing the time needed to develop new treatments and advancing cutting-edge surgical techniques.
However, the application of AI comes with relevant risks, making it essential to ensure its responsible and ethical use, particularly in healthcare and other areas where AI directly impacts human lives.
Among others, a significant risk is related to informed consent and data protection. Users are often unaware of their interactions with AI tools and may not know how their personal data is used or shared with third parties.
Additionally, there is a dangerous misconception that AI outputs are neutral and flawless, contrasting with the acknowledged fallibility of human beings. While automation is captivating, it's crucial to remember that AI can contain and propagate errors and biases. These biases, absorbed and amplified by AI algorithms, can become entrenched, exacerbating existing inequalities. Moreover, the issue of bias in AI is further complicated by AI opacity (non-explainability).
Given the risks and benefits of AI, it is imperative to maintain a critical perspective and encourage its ethical, responsible, and inclusive use. This approach is vital to ensure that the advantages of AI, particularly in healthcare, benefit everyone rather than just a select few.

SS05 - 02
The Coalition for Advancing Research Assessment (CoARA): first outcomes of a global initiative for a systemic change of research assessment

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There is a broad consensus among research communities worldwide that the existing tools of academic rewards and recognition criteria, such as h-indexes or the weight of publisher prestige, in particular if determined on the basic of indicators such as the journal impact factor, have ceased to accurately reflect what we most value in, and need from, research. A wide range of innovative, born-digital scholarship such as databases, visualisations, software development, or contributions to research infrastructures, are still invisible from formal research administration and assessment. Therefore it is essential that a qualitative-centered approach and not a quantitative one, characterizes research assessment activities. Besides, beyond focussing solely on the end

products of research it is also clear that it is the integrity and transparency of research processes that lead to truly innovative, open and high-quality research. Building on progress made so far (DORA, Leiden Manifesto, Hong Kong Principles), over 700 research organisations, funders, assessment authorities, professional societies, and their associations have agreed on a common direction and principles for reforming the assessment of research, researchers and research organisations, outlined in the Agreement on Reforming Research Assessment (ARRA). They commit to a common vision, which is that the assessment of research, researchers and research organisations recognises the diverse outputs, practices and activities that maximise the quality and impact of research. This requires basing assessment primarily on qualitative judgement, for which peer-review is central, supported by responsible use of quantitative indicators. Based on these principles and committements a Coalition for Reforming Research Assessment (COARA) has been implemented offering a platform for member organisations for collaboration and mutual learning that, initially born in Europe, is now expangin globally. CoARA, founded in December 2022 currently supports 13 Working Groups and 16 National Chapters to facilitate exchange and develop resources that member organisations can rely on, for their reform journeys. Working groups, jointly collaborated by several Institutions who joined CoARA, cover a variety of topic of relevance for research assessement, e.g, are "Ethics and Research Integrity Policy in Responsible Research Assessment for Data and Artificial Intelligence" , "Towards an Inclusive Evaluation of Research", "Supporting the alignment of research assessment systems with CoARA in biomedical disciplines through administrative reforms and governance".

SS06 Governance della Diagnostica Decentrata nella Medicina del Territorio: sinergie fra POCT e Laboratorio di riferimento

SS06 - 01

Requisiti necessari per l'implementazione di una rete diagnostica di emergenza urgenza sul territorio: suggerimenti per un capitolato

Marilena Fantacci

L'Azienda UslSudEst copre un territorio di 13 Distretti Zona/Società della Salute e di una Assistenza Ospedaliera dalla presenza di 13 Stabilimenti Ospedalieri nelle province di Siena, Arezzo e Grosseto.
Per raggiungere l'obiettivo aziendale di diminuire gli accessi impropri dei pazienti al Pronto Soccorso con l'ospedalizzazione, di anticipare sul territorio il trattamento in emergenza/urgenza e di sfruttare al meglio le risorse umane disponibili, si è valutato l'utilizzo di emogasanalisi portatili Point Of Care Testing (POCT), strumenti in grado di fornire dei risultati sia dei gas del sangue che dei metaboliti di base in meno di un minuto utilizzando delle CARD a temperatura ambiente. Tali strumenti operano tramite una tecnologia POCT connessa via Wi-Fi o Bluetooth al sistema informativo di emergenza/urgenza (EMUR), senza richiedere l'esecuzione di operazioni manuali per la connessione, ai fini di una rapida comunicazione del dato tra operatori in missione e la centrale del 118. Sulla base della geolocalizzazione delle sedi del 118 e di una analisi dei fabbisogni, si sono consegnati 51 apparecchi alle auto mediche e a quelle demedicalizzate ("India").
Nella fase di attuazione dell'iniziativa, si è riscontrata una criticità relativa alla mancanza di una definizione delle modalità tecniche di esecuzione nel capitolato di gara, che riportava solo gli obiettivi generali, con conseguente rallentamento dei processi, superabile con l'inclusione di una figura professionale del settore informatico nella commissione di stesura.
Si è rivelata risolutoria la collaborazione tra il dipartimento ICT aziendale, che ha garantito la connessione tra reti ed il rispetto della legislazione in materia di privacy, l'ente responsabile della gestione delle procedure di gara, ed il fornitore, che si è reso disponibile ad adattare i sistemi alla tipicità territoriale.
L'informatizzazione dei processi POCT ha consentito di: a) governare l'intero processo emogasanalitico da parte del Laboratorio Analisi, b) minimizzare le possibili fonti di errore per la sicurezza del paziente e garantire la massima sicurezza dell'operatore in tutte le fasi del processo analitico, dal campionamento alla manutenzione, c) garantire la tracciabilità dell'intero processo dalla richiesta, alla refertazione, al Fascicolo Sanitario d) migliorare la gestione e l'outcome del paziente critico attraverso la riduzione del Turn-around-time (TAT), e e) aspirare ad un accreditamento secondo le normative vigenti.

SS06 - 02

Comparative Analysis of organizing Point-of-Care Networks in Wales (UK), France, Switzerland, and Norway

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Background: Point-of-care (POC) networks are critical in enhancing healthcare delivery by providing timely diagnostics and treatment options directly to patients, especially in rural and underserved areas. This study aims to compare the POC networks in four European countries—Wales, France, Switzerland, and Norway—to identify best practices and areas for improvement.ACCESSIBILITY:Wales: POC networks are integrated with the National Health Service (NHS), ensuring broad accessibility. However, rural areas face challenges due to lack of health facilities. France: A centralized healthcare system allows regional customization of POC services. Accessibility is generally high, but there are strong disparities between urban and rural regions.Switzerland: A robust POC network supported by a well-funded healthcare system. High accessibility is facilitated by strong public-private partnerships. Norway: Extensive coverage due to government initiatives targeting rural healthcare. Telemedicine is widely used to enhance accessibility in remote areas. INFRASTRUCTURE:Wales: Infrastructure is improving, with recent investments in mobile POC units. However, there is a need for further development in digital health records integration. Dr Annette Thomas, POCT National Lead wrote.: "Building on the success of the informal network, one of the key actions in the National Pathology Programme Statement of intent, published in 2019, was to establish a more formal structured arrangement to deliver Point of Care Testing services in NHS Wales. A National Strategy Group of mPOCT clinical

leads and POCT Managers from each Hub Board, stakeholders and government representatives was established with the aim of setting the strategy and standards, with the existing National POCT Delivery Group supporting the delivery of the service." France: widespread availability of POC devices in primary care settings is needed. Continuous innovation in telehealth and mobile health units.Switzerland: Highly developed infrastructure with seamless integration of digital health records and POC devices. Strong emphasis on data security and patient privacy.Norway: Comprehensive infrastructure supported by government funding. Advanced telehealth services and POC units are standard in both urban and rural areas. TECHNOLOGICAL INTEGRATION: Wales: Efforts are underway to improve technological integration. Current systems are fragmented, impacting efficiency.France: High level of technological integration, supported by national e-health initiatives. Strong focus on interoperability and data sharing. Switzerland: Leading in technological integration with extensive use of electronic health records (EHRs) and common regulatory rules. Norway: Advanced technological integration, with widespread use of EHRs and telemedicine platforms.
CONCLUSION: Switzerland and Norway lead in terms of infrastructure, technological integration, and patient outcomes, with Norway excelling in rural healthcare delivery. France has a robust regulatory system in public health, ensuring high standards of care and patient safety through stringent policies and oversight, while Wales is improving through recent investments and reforms. Lessons from these countries highlight the importance of government support, technological integration, and tailored approaches to rural healthcare in developing robust POC networks. Future research should focus on longitudinal studies to assess the impact of ongoing reforms and innovations in POC networks across these countries.

SS07 Nuovi biomarcatori emergenti nella pratica clinica

SS07 - 01

Applicazioni diagnostiche e predittivo-prognostiche di suPAR

Matteo Vidali

Il recettore solubile dell'attivatore del plasminogeno di tipo urochinasico (suPAR) rappresenta la forma solubile del recettore dell'attivatore del plasminogeno di tipo urochinasico. Esso è rilasciato in circolo dopo il taglio del frammento di glicosil-fosfatidil-inositolo che lo ancora alla membrana di cellule del sistema immunitario, cellule endoteliali e cellule muscolari lisce. suPAR rappresenta un marker aspecifico di attivazione della risposta immunitaria e infiammatoria.
Numerose evidenze suggeriscono un ruolo di suPAR in differenti condizioni patologiche. A questo proposito, suPAR è stato associato a patologie renali e cardiovascolari, sepsi e altre malattie infettive, malattie gastrointestinali e polmonari, malattie dermatologiche, reumatiche, ematologiche, oncologiche e diabete (1). È interessante sottolineare che numerosi autori hanno dimostrato un ruolo di suPAR come predittore indipendente di severità di malattia, riammissione ospedaliera e mortalità a breve o lungo termine (7, 30 e 90 giorni) in diverse popolazioni di pazienti e in differenti ambiti clinici (2). Inoltre, negli anni più recenti si sono accumulate sempre più evidenze relativamente al valore predittivo negativo di suPAR nell'esclusione di esiti clinici sfavorevoli.
In pazienti con COVID-19 una recente meta-analisi ha dimostrato un ruolo di suPAR nel predire il rischio di sviluppare complicanze severe (3). A seguito dello studio SAVE-MORE, che ha evidenziato come il trattamento precoce con anakinra, guidato dai livelli di suPAR, in pazienti ospedalizzati con forme di COVID-19 moderato o grave, riduca significativamente il rischio di peggioramento del quadro clinico al giorno 28, l'Agenzia Italiana per il Farmaco (AIFA) ha approvato l'inclusione di anakinra nell'elenco 648/96 per il trattamento degli adulti ricoverati con COVID-19 e suPAR ≥6ng/ ml. La necessità della misurazione dei livelli di SUPAR, ai fini della prescrivibilità di anakinra in pazienti con COVID-19, ha indotto una minoranza di laboratori a implementare il test. Ad eccezione di questo ultimo setting, tuttavia, suPAR rimane un test scarsamente conosciuto dai laboratoristi e sottoutilizzato, a dispetto delle numerose evidenze e della disponibilità da alcuni anni del test sulle principali strumentazioni automatizzate di chimica-clinica.
suPAR in differenti setting, in particolare nell'urgenza-emergenza, può rappresentare un valido strumento per identificare quei pazienti che necessitano uno stretto monitoraggio, o un atteggiamento terapeutico più aggressivo, perché a maggior rischio di evoluzione sfavorevole.
È auspicabile la progettazione di studi aggiuntivi, ben disegnati, al fine di valutare in differenti contesti l'efficacia diagnostica e prognostica di suPAR.

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SS07 - 02

Unlocking the Future of mTBI Management: Innovative Biomarkers and Value-Based Approaches

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Mild traumatic brain injury (mTBI) is a prevalent concern, both in clinical-surgical contexts (neurology, neurosurgery and emergency room) and in sports-related and military contexts, due to its subtle clinical presentation and potential long-term consequences [1]. Laboratory biomarkers have emerged as crucial tools in diagnosing, prognosis, and managing mTBI. This abstract synthesizes findings from recent publications and evaluates the introduction of innovative diagnostic technologies to provide an overview of the current state of mTBI biomarkers, highlighting their clinical utility, challenges, and the role of value-based medicine in optimizing outcomes.
Recent studies emphasize the importance of the neurofilament light (NfL) chain, tau protein, S100 calcium-binding protein B (S100B), glial fibrillary acidic protein (GFAP), and ubiquitin carboxy-terminal hydrolase

L1 (UCH-L1) as potential biomarkers for mTBI. NfL and tau proteins indicate axonal damage, while S100B and GFAP are markers of glial injury and blood-brain barrier disruption. UCH-L1, an enzyme expressed in neurons, has shown promise as a biomarker for neuronal injury. Elevated levels of these biomarkers in cerebrospinal fluid (CSF) and blood correlate with the severity of brain injury and provide critical information on neural damage.

The utility of these biomarkers in sports settings is significant, given the high incidence of mTBI among athletes [2]. Biomarker analysis can aid in timely diagnosis, reducing the risk of repeated injuries and facilitating appropriate management decisions. NfL and UCH-L1, for instance, have shown promise in monitoring recovery and predicting long-term outcomes, which is essential for safe return-to-play decisions. However, clinical application faces challenges like variability in biomarker levels due to individual differences (age, sex, genetics) and timing of sample collection. Standardization of assays and normative data is crucial to enhance reliability and utility.

The Abbott i-STATTM TBI Plasma Test, approved by the FDA and CE-marked, is a significant advancement in mTBI management [2]. This technology quantifies GFAP and UCH-L1 levels in peripheral blood, providing a rapid, reliable tool for diagnosing mTBI in emergency settings. Studies indicate that this test can reduce unnecessary CT scans, decrease radiation exposure and shorten patient management time in emergency departments. The ALERT-TBI trial reported a sensitivity of 95.8% and a negative predictive value of 99.3%, suggesting a substantial reduction in CT scans among mTBI patients with negative biomarker results.

Incorporating value-based medicine into mTBI management is essential for optimizing outcomes. Value-based medicine focuses on achieving the best health outcomes relative to costs, ensuring medical practices benefit patients [3]. In mTBI, this approach emphasizes the judicious use of biomarkers to guide decisions, reduce unnecessary interventions, and allocate resources efficiently. Integrating biomarker data with clinical assessments and neuroimaging findings allows for personalized, cost-effective care.

Health technology assessment (HTA) plays a crucial role by systematically evaluating the medical, social, economic, and ethical implications of health technologies [4]. The new EU HTA regulation, from January 2025, aims to ensure inclusion, transparency, and predictability in evaluating health technologies, thereby improving access to innovative diagnostics [4], like the Abbott i-STATTM TBI Plasma Test. HTA helps in assessing the value of these biomarkers in clinical practice.

Furthermore, integrating biomarker data with clinical assessments and neuroimaging is crucial for comprehensive mTBI evaluation. This multimodal approach improves diagnostic accuracy and stratifies patients based on long-term sequelae risk.

In conclusion, laboratory biomarkers are promising for advancing mTBI diagnosis and management, particularly in sports-related contexts. The Abbott i-STATTM TBI Plasma Test exemplifies how innovative technology can enhance clinical practice by reducing unnecessary imaging and improving patient flow in emergency settings. Incorporating value-based medicine and HTA principles can further enhance these biomarkers' impact by ensuring effective and efficient clinical practices. Continued research is needed to address current limitations and validate clinical applicability. By enhancing our understanding and utilization of mTBI biomarkers within a value-based framework, we can improve patient outcomes and ensure safer practices in sports and other high-risk activities.

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SS08- Ematologia Digitalizzata e Intelligenza Artificiale

SS08 - 01

The role of the new analytical research parameters of the haematology analyzers BC 6800 plus (Mindray), DxH 900 (Beckman Coulter) and XN-2000 (Sysmex) in the differential diagnosis of peripheral lymphocytosis

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Background and Aim.
The presence of lymphocytosis in peripheral blood, even in asymptomatic individuals, is a frequent occurrence in clinical practice. This poses a challenge for laboratory professionals who must differentiate between morphologically reactive lymphocytes of benign origin and atypical lymphocytes indicative of lymphoproliferative disease. Modern automated hematology analyzers offer various research parameters that describe the activity status of the blood cells in detail. These parameters are available without additional reagents and have the same turnaround time (TAT) as the complete blood count (CBC).
The aim of this study was to evaluate the diagnostic utility of these parameters in differentiating between reactive and chronic clonal lymphocytosis.

Materials and Methods.
The retrospective study analysed traditional and research parameters of 823 subjects admitted to the emergency room with lymphocytosis. The analysis was performed with different platforms: 230 subjects with the BC 6800 plus (Mindray), 255 with the DxH 900 (Beckman Coulter) and 338 with the XN-2000 (Sysmex). Predictors of clonal disease vs reactive lymphocytosis were evaluated by multivariate logistic regression. Multivariate models were built considering only non-collinear predictors found significantly associated at the univariate analysis.
Results. [Mindray]: the multivariate model included NEU# ($p=0.019$), MON% ($p<0.001$), RDW-SD ($p=0.003$), HFC ($p<0.001$) and LY-Y ($p=0.012$) [Nagelkerke r2=0.735]; the percentage of corrected predictions increased from 56.1% for the model without predictors to 90.1% for the multivariate model. [Sysmex]: the multivariate model included RBC ($p<0.001$), Ht ($p=0.009$), MCHC ($p=0.001$), LYM% ($p<0.001$), BAS% ($p<0.001$) and LY-WY ($p<0.001$) [Nagelkerke r2=0.628]; the percentage of corrected predictions increased from 60.2% for the model without predictors to 83.1% for the multivariate model. [Beckman]: the multivariate model included Hb ($p<0.001$), MCH ($p=0.001$), NEU% ($p=0.002$), MN-SU-LI ($p<0.001$), SD-SU-LI ($p=0.012$), MN-SA-LI ($p=0.019$), MN-SU-MO ($p<0.001$) and SD-LMALS-NRBC ($p=0.001$) [Nagelkerke r2=0.733]; the percentage of corrected predictions increased from 50.4% for the model without predictors to 90.1% for the multivariate model.

Conclusion.
The multivariate logistic regression models for each analysis platform showed significant improvements in predictive accuracy. For the BC 6800 plus (Mindray), the multivariate model increased the percentage of correct predictions from 56.1% to 90.1%, for the XN-2000 (Sysmex) the prediction accuracy increased from 60.2% to 83.1% and for the DxH 900 (Beckman) the accuracy of the model improved from 50.4% to 90.1%.
The study shows that modern automated hematology analyzers can significantly improve diagnostic accuracy in distinguishing between reactive and chronic clonal lymphocytosis in patients with lymphocytosis. By incorporating various research parameters, these analyzers provide detailed insights into the activity status of blood cells without the need for additional reagents and with the same turnaround time as CBC.

SS08 - CO02
Peripheral blood smear performance: results from the External Quality Assessment of Lombardy Region

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Introduction. Analysis of the peripheral blood (PB) smear is the final step of the complete blood cell count analysis. Since, in most cases, it is carried out by a single operator, it could cause errors that can have a significant impact on the patient's diagnosis. The Regional Reference Center for the Quality of the Laboratories of the Lombardy Region (Center) manages External Quality assessment (EQA) program for cellular morphology on PB smear with the aim to verify the inter-laboratory reproducibility and the correlation to a clinical condition. Aim of this study was the evaluation of the results and the possible sources of error.

Methods.
In 2023, 4 PB smears and 400 digitalized images of 4 May-Grunwald Giemsa stained smears, were sent to 143 laboratories. Participants were asked to do the differenzial cell count and to indicate any morphological anomalies found for each cell series, the clinical condition most frequently associated with the morphological anomalies and any in-depth tests that would be useful to recommend.
Laboratories qualitative performances were evaluated by comparison with the expected outcome assigned by a consensus group of experts. For the statistical analysis were used the absolute values of the different cell populations.Results. The coefficient of variation (CV) was analysed for each exercise and for all cell populations including immature and atypical cells. The CV varies from 3% (Lymphocytes) to 101,2% (Monocytes). For Blast CV varies from 18,3% to 89,9%. Percentage of laboratories that committed serious errors in morphological recognition varied from 10,2% (Elliptocytosis) to 25,9% (Acute Mieloid Leukemia). Percentage of laboratories that committed serious errors in indicating the diagnostic suspicion varied from 2.1% (virosis) to 56,7% (slide without morphological alterations).
Discussion. The results were in agreement with the literature data. CV increase exponentially at lower cell concentrations, especially for Neutrophils. The correctness of the answers depended on the type of cell involved, the complexity of the case or the skills of the

operator. It still necessary to do a lot of work, but our results confirm that EQA schemes can be a valid educational tool to improve
skills in blood morphology.

SS09- Gammopatie monoclonali di significato renale: gestione multidisciplinare di una patologia multiorgano

SS09 - 01

Monoclonal gammopathies of renal significance: clinical overview of the structural and functional damage of the kidney

Antonello Pani

Monoclonal Gammopathies of Renal Significance (MGRS) are a complex group of disorders characterized by the production of aberrant monoclonal proteins that interact directly or indirectly with kidney structures, causing tissue damage (1). Unlike neoplastic forms, kidney damage in MGRS does not correlate with clone mass or circulating monoclonal protein levels, conferring unique pre-neoplastic or non-neoplastic properties to the responsible clones. Direct damage can be demonstrated by documenting monoclonal restriction of deposits on immunofluorescence (IF)/immunohistochemistry (IHC) renal biopsy. Indirect damage is more complex to define as the monoclonal protein is not directly observed in the tissue. The clinical manifestations of MGRS essentially depend on the segment of the nephron affected by the pathogenetic process. Glomerular involvement is characterized by proteinuria of variable extent (from sub-nephrotic proteinuria to full-blown nephrotic syndrome) sometimes in association with microhematuria (especially in the presence of glomerular lesions with endocapillary or extracapillary proliferative aspects). Decline in renal function may be observed, with clinical features ranging from chronic kidney disease to rapidly evolving renal failure. In the presence of a main tubular localization of the direct or indirect damage secondary to the M protein, the clinical picture is characterized by the finding of elements suggestive of tubular dysfunction: low urinary specific gravity, normoglycemic glycosuria, hyperphosphaturia with consequent hypophosphatemia, tubular proteinuria, aminoaciduria, hyperuricosuria and urinary bicarbonate loss. Therefore, a diagnosis of MGRS should be considered in any patient with clinical manifestations suggestive of renal disease (encompassing the full spectrum of nephrological clinical syndromes) associated with the presence of an M protein (2,3,). Clinical suspicion of MGRS increases in the absence of other conditions clinics potentially responsible for kidney damage (diabetes mellitus, hypertension and atherosclerosis). The diagnosis of MGRS is based on two fundamentally important phases: 1) the identification of the circulating M protein 2) the demonstration of a causal correlation between the circulating M protein and the observed renal anomaly, the fundamental diagnostic tool of which is the biopsy renal. In MGRS, evaluation of the haematological response to treatment is crucial because the renal response depends on the haematological response. In the absence of a circulating monoclonal component and without identification of the cell clone, GFR and proteinuria may be the only parameters used to evaluate disease activity. It is important to note that the renal response is usually delayed: in the work published by Leung et al a minimum duration of 12 months of hematological response was required before the onset of renal response was observed in patients with AL amyloidosis (4).

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SS09 - 02

Il laboratorio clinico nella valutazione e monitoraggio del paziente con gammopatie monoclonale di significato renale

Alberto Dolci

Monoclonal gammopathy of renal significance (MGRS) is a clonal proliferative disorder that produces a nephrotoxic monoclonal (M) immunoglobulin and does not meet haematological criteria for treatment of a specific malignancy. The nephrotoxic activity of the noxious M-immunoglobulin, often synthesized by a dangerous small B-cell–derived clone, is independent from the clonal mass. Despite kidney biopsy is essential to make diagnosis of MGRS, once an MGRS-associated lesion has been confirmed, the presence of serum or urine M-protein pathophysiologically linked to MGRS should be defined. Serum protein electrophoresis (SPE), quantitative, rapid and easy to perform on automated analyzers. is the first test performed. However, its poor sensitivity is an issue in searching for the MGRS related M-protein, often small, reflecting the low tumor burden, and made up of free light chains, difficult to find when comigrate with other proteins. Urine protein electrophoresis (UPE) is less sensitive than SPE for M-protein detection, but in a 24 h urine specimen, provided total protein assay, permits quantitation of Bence Jones protein and albumin needed for diagnosis, risk stratification and response assessment of MGRS. Serum and urine immunofixation (IFE) is more sensitive and specific than SPE and UPE, and is performed to detect and type M-protein as well as in treatment monitoring to define a complete response. Every laboratory should be aware of the analytical sensitivity and limitations of all the techniques used to find M protein in MGRS diagnosed patients. Serum κ and λ free light chain (sFLC) assays and κ to λ ratio estimation can increase the sensitivity of M-protein detection even more, except for MGRS associated with an intact M-protein. However, sFLC are cleared by the kidney, and that affects their serum concentration in patients with renal failure, since the moderate stages. To measure sFLC concentration, two major assays and some other are available, and their results cannot be compared. Moreover, the effects of

renal impairment differ between the different assays. Thus, the same assay must be used to monitor a patient with MGRS from the diagnosis to treatment monitoring. In MGRS patients, laboratory should perform all available tests to reach the highest sensitivity in detecting the M-protein inducing disease. However, despite all laboratory efforts, a MGRS without detectable circulating M-protein may occur, tipically the proliferative glomerulonephritis with monoclonal immunoglobulin deposits. Novel techniques, such as mass spectrometry, greatly improving the sensitivity of M-protein detection are now available and will be discussed in a dedicated speech.

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SS10- Nuove sfide in Tossicologia Clinica e Forense

SS10 - 01

The bioanalysis of New Psychoactive Substances in biological matrices in the field of laboratory medicine

Annagiulia Di Trana

The most recent data reported over 1200 compounds detected all over the World, divided into different pharmacological classes exerting similar effects to those provoked by the classical drugs of abuse. Indeed, the NPS market is fluctuant and adaptable to the general socio-economic conditions, with a variable panel of new substances emerging and others disappearing from year to year, increasing the phenomenon complexity. Over the last two years, the European Drug Agency (EUDA) reported record quantities of NPS seized in Europe, especially cathinone stimulants and ketamine. Accordingly, the NPS related risks for the public health have also grown during the last decade, with threats increased by the continual flow of new, potent products, distributed on ever easier ways to buy and use the NPS. In this scenario, the laboratory medicine plays a crucial role in containing the NPS related issues and to identifying the new emerging molecules on the illegal markets. Therefore, the development of new approaches is fundamental, based on multi-method and multi-analytical techniques analyses to identify and characterize the unknown compounds in the biological matrices. Considering the classical systematic toxicological analyses, new comprehensive extraction protocols should be implemented for the biological samples pretreatment in order to extract a larger panel of molecules with different physicochemical properties. To this concern, the pharmaco-toxicology laboratory of the National Center of Addiction and Doping of the National Institute of Health developed different analytical methods in high-pressure liquid chromatography coupled to High-resolution mass spectrometry (HPLC-HRMS/MS) and gas chromatography coupled to tandem mass spectrometry (GC-MS/MS) to characterize, detect and quantify drugs of abuse, NPS or their adulterant in biological matrices. In particular, a suspected opioid related death, occurred in Italy, raised the attention of the EUDA which requested to further investigate the fatality. A semi-unknown approach was applied to the analytical investigation of the available biological matrices through a comprehensive HPLC-HRMS/MS screening method. Therefore, the analytical screening of whole blood and urine revealed the presence heroin biomarkers and xylazine, a veterinary drug used as an opioid adulterant. Then, a quantitative method for xylazine was developed and validated in HPLC-HRMS/MS to confirm the analytical results and evaluate the possible role of xylazine in the determinism of death [1]. A similar approach was applied in the detection of levamisole in biological matrices which was identified as the principal cause of extensive ulcers on the limbs of a cocaine user. Whereas, a multi-analytical approach was applied to study the excretion profile in different biological matrices, and the metabolism of the semi-synthetic cannabinoid hexahydrocannabinol and cathinones, such as ✔-PVP[2]. In particular, the NPS and metabolites were quantified in GC-MS/MS, while the unknown metabolites identification was conducted by HPLC-HRMS/MS unknown method analysis supported by the Compound Discoverer™ assisted data-mining for the structure elucidation.

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SS10 - 02

In silico and in vitro metabolism studies for the identification of novel psychoactive substances’ biomarkers

Jeremy Carlier

Novel psychoactive substances (NPS) have flooded the illicit drug market for almost two decades as alternatives or adulterants for traditional drugs of abuse, in an attempt to reduce manufacturing and processing costs and evade legal controls and analytical detection. NPS pose an important threat to public health as they have caused thousands of intoxications and deaths worldwide with societal and legislative implications. The turnover also is high: new NPS regularly emerge on the drug market to replace newly banned substances or produce ever-more-potent psychotropic drugs.

Little to no pharmacological data are available on NPS when they first surface on the market, which is a concerning matter since users are unaware of the potential risks associated with their consumption. From an analytical point of view, in toxicology, the topic is also problematic: the methods must be constantly updated to adapt to the market dynamics, but NPS are often challenging to detect as they may be active at trace concentrations in biological matrices and may undergo

substantial metabolic degradation. Assessing NPS pharmacokinetics is therefore essential to be able to document consumption in clinical and forensic casework. Particularly, the metabolic profiling of NPS is a major step to identify specific metabolite biomarkers of consumption that may be more easily detected than the corresponding parent drug.
Clinical studies with NPS are time-consuming and hardly feasible due to health, ethical, and legal considerations. Positive biological samples from authentic cases of NPS consumption may also be difficult to obtain due to the high turnover rate and analytical challenges. Researchers have therefore relied on in silico, in vitro, and in vivo prediction tools to simulate NPS human metabolism. In silico models typically identify the molecules' functional groups and predict the sites of metabolism and the metabolic transformations based on machine-learning algorithms. In vitro models usually include incubations with recombinant enzymes or animal or human liver microsomes or human hepatocytes to simulate metabolism at the liver, the main site of metabolization in humans. Undeniably, in silico and in vitro models provide quick results, which is essential to keep up with the NPS market dynamics. However, they cannot totally account for interindividual variations and all in vivo post-metabolism processes such as reabsorption, extrahepatic metabolism, enterohepatic circulation, and elimination. In vivo animal models with controlled drug administrations to rats, mice, or zebrafish have been used to circumvent these difficulties. However, they are more time-consuming, and inter-species variations may be a problematic limitation.
Only through comprehensive research and adaptative methodologies can we hope to stay ahead of the evolving NPS landscape, ensuring public safety and informed legislative responses. Continuous advancements in metabolite prediction through various models are essential to provide suitable biomarkers of consumption to update analytical methods in clinical and forensic toxicology, despite their inherent limitations.

SS10 - 03

Tecniche di laboratorio applicate alla caratterizzazione degli effetti farmacologici delle Nuove Sostanze Psicoattive nel Sistema Nervoso Centrale

Pasqualina Castaldo, Agnese Secondo

Le nuove sostanze psicoattive (NPS) rappresentano una sfida emergente nel campo della farmacologia e della tossicologia a causa degli effetti tossici a carico del SNC e cardiovascolare, tra cui: agitazione, euforia, stimolazione del SNC, coma ed ipertensione. Nonostante la larga diffusione di queste sostanze, pochi studi sono stati condotti sui loro effetti farmacologici ma sembrano mostrare una maggiore potenza e neurotossicità, rispetto alle NPS di prima generazione.
I pochi studi disponibili si sono concentrati sulla caratterizzazione della vitalità cellulare utilizzando metodologie consolidate come la misurazione dei livelli di MTT, rilascio di LDH e produzione citoplasmatica delle specie radicali dell'ossigeno (ROS); utilizzando come modello cellulare dopaminergico in vitro le SHSY5Y differenziate con acido retinoico (RA). Questi studi hanno evidenziato che le NPS inducono tossicità attivando meccanismi di tipo necrotico e/o apoptotico. In accordo con questi dati, l'esposizione delle cellule SHSY5Y, a concentrazioni sub-tossiche di mefedrone determina un aumento dei livelli di ROS mitocondriali. Inoltre, studi di microscopia elettronica suggeriscono che il metilone determina un'alterazione della struttura della matrice e delle creste mitocondriali.
Alcuni studi hanno evidenziato la capacità di alcune NPS di interferire con l'attività elettrica dei neuroni catecolaminergici causandone alterazioni nell'attività e danno neuronale, suggerendo che possano interferire con i sistemi recettoriali coinvolti nella omeostasi ionica. Allo scopo di chiarire tale aspetto sono state identificate metodologie in grado di evidenziare alterazioni dei principali sistemi di controllo dell'eccitabilità neuronale. In particolare, è stata utilizzata la tecnica del Fura-2-video imaging che, attraverso un tracciante fluorescente (Fura-2), consente di misurare le variazioni in tempo reale dei livelli di Ca2+ intracellulare. I risultati ottenuti, esponendo le SHSY5Y a dosi sub-tossiche di 3-metilmetcatinone (3-MMC), suggeriscono una riduzione della capacità delle cellule di incrementare i livelli intracellulari di Ca2+ in risposta ad uno stimolo depolarizzante (alto K+) confermando un alterato controllo dell'omeostasi del Ca2+. Ulteriori studi, condotti utilizzando la tecnica elettrofisiologica, hanno rilevato una stimolazione delle correnti del Na+ ed una riduzione della modalità "reverse mode" dello scambiatore Na-Ca2+. Collettivamente, questi risultati suggeriscono che il 3-MMC possa indurre un aumento dell'eccitabilità neuronale.
Considerato che l'eccitabilità neuronale è regolata anche dalla la corrente M sottesa dai canali del K+ KCNQ2 e KCNQ3 risulta interessante valutare gli effetti di queste sostanze su questa corrente. Esperimenti preliminari indicano che le NPS esercitano effetti diversi su questi canali ionici; l'isotonitazene determina aumento delle correnti del K+ mentre il mefedrone ne determina una riduzione.
In conclusione, sebbene siano necessari ulteriori studi sembra che le NPS siano in grado di determinare tossicità neuronale con meccanismi diversi che includono sia l'alterazione dell'omeostasi ionica che l'alterazione dell'eccitabilità neuronale.

SS10 - CO03

Novel Psychoactive Substances (NPS) Footprint by Cytokine Release and Volatilome Profile: Advances in Clinical Toxicology

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The rising widespread availability of NPS has heightened interest in clinical toxicology. NPS are substances that mimic the effects of traditional drugs but whose pharmacological and side effects are poorly known, giving birth to NPS monitoring centres (Early Warning

System) aimed to rapidly detect, assess, and respond to public social-health threats. NPS exhibit mostly neurotoxic effects on monoamine and glutamatergic systems. Studies show they affect cytokine and chemokine (CKs) expression and significantly altering cell metabolism. Our aim is to investigate the possible effects of selected NPS on in vitro CKs release, as marker of inflammation, and on volatilome profile, as specific metabolite signature.
Whole blood from 8 healthy volunteers (1:1 F/M) were cultured for 48h in presence and absence of selected NPS (35μM): PCA, α-PHP, 3-CMC, Butyrylfentanyl, 5F-AKB-48. CKs levels were detected in the medium via Luminex technology. Volatile metabolites were characterized using an HS-SPME-GC×GC mass spectrometry. Coupled t-test shows PCA, an amphetamine-like stimulant, decreases IP10 levels (P=0.011), suggesting a downregulation of the inflammatory response IFNγ-mediated. Conversely, αPHP, a synthetic cathinone, significantly increases IL8 (P=0.001), IP10 (P=0.008) and MCP1 (P=0.031) levels, potentially triggering excessive inflammation and tissue damage. Accordingly, the cathinone 3CMC increases IL8 levels (P=0.048). Butyrylfentanyl, unlike other opioids, increases IL8 levels (P=0.02). As previously reported, the cannabinoid 5FAKB48 downregulates the anti-inflammatory cytokine IL10 (P=0.041). Finally, to trace a possible bloodvolatile NPS-footprint, the high-separation and identification capabilities of the GC×GC-TOF MS system allowed us to detect a profile of more than 700 specific metabolites changing after treatment.
Our results suggest NPS impact CKs release and volatilome profile, raising awareness in NPS toxicology. In particular, volatilome assessment approach represents a promising tool for studying the in vivo NPS effects on cell biology and improving toxicological screening. It also enables personalized multi-OMIC analyses to assess individual dose-dependent and time-dependent response, also considering the different genomic and epigenomic backgrounds.

SS11- Diagnostica Molecolare e Biopsia Liquida

SS11- 01
Liquid biopsy in blood malignancies

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Liquid biopsy contains disease□related biomarkers present in body fluids. Among them, diseased cells, circulatingcell□free deoxyribonucleic acid (cfDNA), microRNA (miRNA), and extracellular vesicles (EVs) are the key markers for various hematological diseases. Irregular concentrations of these components in liquid biopsies indicate abnormal dynamics of the target biomarkers, which may provide clinicians with important information about the pathological condition.
Recently, liquid biopsy has been used for early diagnosis, treatment guidance, prognostic decision□making, and tumor monitoring. In the context of hematological malignancies, liquid biopsy is a minimally invasive and real-time procedure that can potentially overcome the intrinsic limitations of tissue biopsies, which expose patients to procedural risks and cannot account for spatial intratumor heterogeneity. The use of liquid biopsy has rapidly expanded in the setting of lymphoproliferative disorders, in particular in diffuse large B-cell lymphoma (DLBCL) and Hodgkin lymphoma (HL), where ctDNA analysis on the liquid biopsy recapitulates the mutational profile of the tissue biopsy and can identify mutations otherwise absent on the tissue biopsy.
This noninvasive method also enables monitoring of minimal residual disease (MRD), which may facilitate personalized treatment for patients with hematological malignancies.
Qualitative and quantitative detection of markers from liquid biopsies can provide an alternative when routine sampling involves painful and invasive procedures.
Once an abnormality is diagnosed, biomarkers can be used to track and evaluate the disease status and identify high-risk patients at risk of recurrence, which can effectively prevent disease progression and promote recovery.
In addition, real-time monitoring by liquid biopsies allows treatment plans to be made based on the patient's clinical outcomes.
Selecting the right technology to detect and manage biomarkers serves as a benchmark for individualized prevention and treatment.

SS11- 02
Janu-seq: a pan-cancer tumor agnostic platform to evaluate the prognostic role of plasma tumor fraction

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Recent advancements in sequencing technologies have provided substantial insights into the genomic architecture of human tumors. However, translating this knowledge into clinical practice remains a challenge due to the inherent genomic instability driving spatial and temporal heterogeneity within tumor cells. Conventional single-biopsy analyses often fail to capture this complexity effectively. Circulating-free tumor DNA (ctDNA) analysis emerges as a promising alternative, reflecting intra-tumor and inter-metastasis heterogeneity through non-invasive means. ctDNA, found in body fluids like blood, mirrors tumor genetic and epigenetic changes and offers advantages such as minimal invasiveness and longitudinal sampling. Despite extensive studies, integrating ctDNA analysis into clinical practice remains limited, posing a challenge for effective disease monitoring and recurrence anticipation in oncology.
We have recently developed a novel platform for ctDNA analysis, termed Janus-Seq, aimed at longitudinal post-treatment monitoring in various solid tumors, particularly in ovarian cancer, mesothelioma, and head and neck cancer. Leveraging next-generation sequencing (NGS), Janus-Seq offers a two-step tumor-agnostic workflow. The first step employs shallow whole-genome sequencing (sWGS) to quantify somatic copy number alterations (SCNA) in plasma, yielding the tumor fraction (TF), an indirect measure of tumor burden. The second step employs targeted re-sequencing to identify

pathogenic single nucleotide variants (SNVs) associated with therapy response or resistance. This comprehensive approach enables both quantitative and qualitative evaluation of ctDNA, providing real-time insights into tumor evolution and potential treatment strategies.
Data obtained so far confirmed the analytic validity of plasma TF as an accurate biomarker of minimal residual disease (MRD); demonstrated the clinical validity of plasma TF as an agnostic biomarker of MRD in different types of cancers and its clinical utility for individual patient surveillance and treatment is currently under investigation.
Overall, Janus-seq is a pan-cancer tumor agnostic platform that would expect to transform clinical practice by enhancing early relapse detection, treatment monitoring, and personalized therapy selection. These findings are expected to impact cancer patient management offering valuable insights into disease dynamics and optimize treatment strategies.

SS12- Allergologia e autoimmunità

SS12- 01

Diagnostica molecolare in vitro per una medicina personalizzata in Allergologia

Diego Faggian

Le malattie allergiche sono tra le principali malattie croniche in Europa e nei paesi in via di sviluppo, con un possibile aumento della prevalenza vicino al 50% nell'ultima generazione. Intercettare, diagnosticare e trattare le allergie, fermandone la progressione verso gravi complicazioni, è il ruolo dello specialista clinico e della Medicina di Laboratorio.
Chiarire la fisiopatologia della sindrome facilita una gestione appropriata ma richiede test in vitro scientificamente convalidati dalla nuova normativa IVD-R. Oggigiorno, il Laboratorio di Diagnostica Allergologica sta assumendo un ruolo importante nell'aiutare a fornire un nuovo approccio basato sulla rilevazione preliminare della sensibilizzazione mediata da IgE per una precisa diagnosi differenziale, offrendo strumenti efficaci alle cure primarie del medico generico. Allo stesso tempo, i nuovi biomarcatori disponibili e la diagnostica molecolare garantiscono un profilo personalizzato, una gestione mirata e accurata per lo specialista in allergologia.
Nel campo delle allergie respiratorie, accanto a test come ECP, FeNO e triptasi, l'Allergologia Molecolare offre un'importante gamma di marcatori IgE monomolecolari in grado di distinguere le sensibilizzazioni primarie da quelle cross-reattive. Sebbene il Sottocomitato per la Nomenclatura degli Allergeni dell'Unione Internazionale delle Società Immunologiche (IUIS) abbia classificato ben oltre 1800 molecole allergeniche, studi biologici e immunologici hanno dimostrato che molti allergeni si comportano in modo simile alle loro controparti naturali e un numero limitato e ben selezionato di componenti allergeniche è sufficiente per diagnosticare la maggior parte dei casi di allergie respiratorie.
Secondo gli attuali protocolli diagnostici avanzati abbiamo descritto gli algoritmi più importanti per le allergie respiratorie armonizzando il nuovo approccio molecolare con quello tradizionale basato su fonti allergeniche estrattive. Sono stati riportati algoritmi completi per sospetti sintomi di inalazione perenne causati da acari, animali e muffe, a partire da fonti allergeniche estrattive. Algoritmi per sospetti sintomi da inalanti stagionali causati da polline di graminacee, erbe e alberi completano il quadro respiratorio secondo i Clinical Consensus delle più importanti Società Scientifiche: EAACI, WAO, SIAIP, AAIITO e SIAAIC.
Pertanto, illustrando l'intera gamma di nuove risorse che la Medicina di Laboratorio può fornire per il percorso diagnostico iniziale per la gestione delle allergie, il primo passo critico per il medico è determinare se il paziente ha un vero disturbo allergico. Per indirizzare i pazienti selezionati verso il percorso appropriato, il secondo passo è riconoscere e gestire i semplici problemi di allergia in modo sicuro ed efficace con le cure primarie o identificare quei pazienti che hanno realmente bisogno di una valutazione specialistica accurata dall'allergologo.
Nel prossimo futuro l'aumento delle informazioni acquisite quotidianamente popolerà i Big Data e rappresenterà un settore in cui sarà vantaggioso applicare l'uso dell'Intelligenza Artificiale, con auspicabili benefici nella corretta interpretazione e spiegazione dei molteplici e complessi profili di sensibilizzazione del paziente atopico.

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SS12 - CO04

Related PR-10 protein: not only Oral Allergy Syndrome

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Background: Despite the majority of scientific knowledge present in literature, heat and pepsin sensitive food allergens could also be the trigger for systemic symptomatology in addition to the well-known local effects (OAS = oral allergy syndrome) (Asero et al.2021). Cases of systemic reaction (SR) in patients with a history of PR-10 sensibilization have already been reported, especially when assuming soy-based drinks (kleine-Tebbe J. et al. 2002).
Objective: To highlight the risk factors such as alcohol for SR induced by labile food allergens. Methods: Analysis were performed on patients with SR to labile food allergens, with a history of OAS induced by the same foods. Specific IgE of harmful food were quantified both in singleplex (ImmunoCAP 1000) and in multiplex (ISAC). Results: First case: 52-year-old woman experienced an event of anaphylactic shock after drinking “sangria” containing peach; before that event, she only reported OAS when consuming this fruit. Both in the ISAC test and with Immunocap1000, the main allergenic molecules usually involved in severe adverse reactions from peach (Pru p 3 LTP and Pru p 7 Giberellin-regulated protein), for which we would have expected anaphylactic shock, were

negative. In both tests, positivity for Pru p 1 (PR-10 peach) is observed (1.88 ISU-E in ISAC, 3.69 kUA/l in ImmunoCAP). Second case: 43-year-old woman presents a history of already known sensitivities to peach, cherry and hazelnut.
The patient had undergone hyposensitizing therapy for birch and hazelnut. Among all symptoms she claimed to have had anaphylaxis after drinking a home-made liqueur made from raw cherries. The cherry tree belongs to the Rosaceae family. Both ISAC and ImmunoCAP1000 confirmed negativity for Pru p 3 and Pru p 7, while they showed positivity for Pru p 1 (4.7 ISU-E in ISAC, 3.02 kUA/ l in ImmunoCAP).
Conclusions: In subjects who present OAS it is not necessary to provide them with self-injectable adrenaline. However, it is important that they are informed about the role of cofactors. It is likely that fruit in infusion (the liquid form enhances the assimilation) and the presence of alcohol have boosted the adverse response. Laboratory medicine provides excellent support in the diagnostic process for food allergies.

SS13- Aging e medicina di laboratorio

SS13- 01
Fraily, long-COVID and laboratory medicine

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Frailty is commonly defined as a state of increased vulnerability to stressors due to decline in physiological reserve and function across multiple organ systems. Coronavirus disease 2019 (COVID-19) and frailty have a complex relationship, as the virus tends to disproportionately affect older adults and individuals with underlying health derangements, both of which are common characteristics of frailty. On the other hand, the COVID-19 pandemic has had a significant impact on frailty, both directly and indirectly, contributing to increase the number of frailty people and also to deteriorate further the psychological and mental decline of already frail individuals. In particular, frail subjects who develop long-COVID may face unique challenges and complications due to the intersection of frailty-related vulnerabilities and the lingering effects of COVID-19. In this detrimental scenario, laboratory medicine may play a pivotal role in the comprehensive care of frail individuals with long-COVID, by facilitating diagnosis, assessing disease severity, monitoring organ function, evaluating coexisting conditions, assessing nutritional status, detecting biochemical abnormalities, monitoring treatment response, and supporting long-term follow-up and surveillance. A multidisciplinary approach that integrates laboratory testing with clinical assessment and other diagnostic modalities is essential for optimizing outcomes and enhancing the quality of care for these individuals. To this end, the identification of biomarkers of frailty in people with long-COVID is an area of ongoing research, and while specific biomarkers for this population may not yet be fully established, some of these are associated with frailty and COVID-19, and may thus provide useful insights into the intersection of these conditions. These specifically include biomarkers of viral persistence, hematological and hemostasis parameters, inflammatory biomarkers, cardiac and muscular biomarkers, biomarkers of oxidative stress, hormonal biomarkers, biomarkers of endothelial and immune dysfunction, along with biomarkers of neurological and cognitive impairment. Integrating biomarker assessments with clinical evaluation and functional assessments may help identify individuals at increased risk of frailty- and COVID-19-related complications, thus guiding targeted interventions to improve outcomes in this fragile and highly vulnerable population.

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