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ID 005

TITLE: **THE UTILIZATION OF PATIENT PORTALS IN A PEDIATRIC CLINIC: A PILOT SCREENING REVIEW**

C. Pillai; H. Lantigua; S. Lugo; K. Velez; A. Shah; M. Rivera; N. Rubio; M. Yafi; R. Yetman

UTHealth The University of Texas Health Science Center at Houston, The department of Pediatrics - Houston, TX USA

The availability of electronic system such as patient portals have allowed patients and parents to retrieve updated health information electronically anywhere, anytime via computer, laptop, mobile device, or smart phone.

Some systems allow patients and parents to submit appointment requests, receive reminders of upcoming appointments, request prescription refills and communicate securely with physicians. Patients can also track online their vital signs, weight and height and can update personal demographic information and track their health progress.

Aim:

To screen parents about their knowledge of an existing patient portal system.

Methods:

Parents were asked to complete a survey during a regular pediatric endocrinology clinic visit which included three questions regarding awareness of the portal system, whether they are currently utilizing the portal and their willingness to utilize it in the future.

Results:

Of the 151 questionnaires completed, 34% of our population studied where aware of the Patient Portal System and 33% of them were enrolled. The majority of people, 70%, wanted to know more about the Patient Portal System.

Discussion:

About 1 in 5 Americans currently have online access to at least some part of their medical records, a number anticipated to grow as healthcare providers establish electronic medical records. In chronic pediatric conditions, portals can help in coordination of care and integration of services within the clinical setting and the transition and continuity from one location of care to another. Furthermore, it can be used as an external measure of quality as well as a basis of trust in the health care system.

Patients are increasingly taking a more active role in their care. Patient feedback has become integrated into ongoing measures of quality, and family members, friends and patients play a strong role in creating solutions.

Patient access to clinical information may help in addressing health concerns from home. The use of the online portal was mostly to examine findings, review notes, and send messages of clinical importance.

Multiple studies have showed that, many patients who register to use Internet portals do not become active users. The use of e-mail notifications helped patients become more active in the Internet portal and increased the use of patient reading prior and after appointments

We recognize that providing information to all patients' parents regardless of their knowledge of the Patient Portal System can encourage them to become users. Regular feedback from the portal via surveys or repeat in-office questionnaires can help tackle any further interventions needed to optimize the portal system to place patients at the center of care.

ID 006

TITLE: **DEVELOPING A COGNITIVE HOSPITAL**

D. Gates, I. Hennessey, W. Calvert, J. Ouyang

Innovation Team, Alder Hey Children's Hospital, Liverpool, UK

A formal presentation will be developed to deliver at the conference. The PDF attached provides an overview of our vision.

We aim to develop the world's first 'cognitive' hospital by harnessing big data and the power of IBM's Watson technology in partnership with the Hartree Centre's Science & Technology Facilities Council based in the UK. We envisage a hospital that can, in essence, 'think, sense and feel' what is happening within it. Patients and their families will be able to access a digital application before, during and after their visit, providing them with information about their stay, their illness and its treatment. Watson will be carefully trained to respond to, and even anticipate, common health-related questions such as what to expect from an anaesthetic. This will help relieve patient / parental anxiety and save precious time with clinical staff. It will also extend the care before and after their visit, prompting with reminders such as the timing of appointments or appropriate care of dressings post-operatively. Watson will be able to 'sense and feel' the tone and sentiment of interactions, providing valuable insight to clinicians about how a child is feeling to make their stay less daunting, provide a more personalised service and expedite recovery and discharge. In the future we hope integrated information from sensors will expand the possibilities of a 'cognitive' hospital such as automatically adjusting lighting, sound and temperature for individual patients.

Initially our focus is on patient and family experience. A digital app is currently in development which will provide an interface for accessing the AI as well as other functionality including patient distraction and reward. Watson will be able to identify or anticipate problems along a specific patient journey and address these issues in real time. As the project is progressing our focus is expanding to more clinical applications including pre-admission and post-procedural care. Watson will be able to address both the patient and family with timely prompts or responses to questions.

This application of cognitive computing will provide patients and their families with more accessible information about their care, improving their overall experience. It will streamline appointments and may also help avoid unnecessary visits to the emergency department following a procedure, generating savings for the hospital and the NHS as a whole. This innovation will be groundbreaking within the UK. Watson continuously learns, gaining in value and knowledge over time from previous interactions. By training Watson in a leading Paediatric hospital in the UK, our experience and expertise will be accessible on a global scale. Cognitive computing is already expanding across many industries internationally and this is set to continue. Our innovation will be key in shaping this development in healthcare, which we hope will have far reaching effects on improving global health.

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ID 008

TITLE: **PATIENT EXPERT IN THE CLINICAL CENTRE**

P. Kruger

MS Centre, S. Camillo Hospital, Rome, Italy

The concept stems from direct experience as a chronic disease patient coupled with a 5-year collaboration in the Clinical Centre (CC) of a large, busy hospital in Rome. The fundamental question: what is missing in a CC that would really improve patients' lives and how could the disease experience and its routine be turned into an empowering project with patients having a truly proactive role? Hence the concept of the Patient Expert in the CC.

3 Steps:

1 - Setting up a Helpline

2 - Having trained Expert Patients available in the CC for 2 hours twice a week

3 - Fundraising activity in the CC

1 The Helpline allows patients to call the CC during the day to solve their small problems connected with the daily management of the disease. Questions that doctors and nurses don't have the time to answer over the phone but that make a real difference to patients' lives. Nurses will answer the phone after being trained by a HCP, a specialist nurse and a Patient Expert.

2 Patient Associations already active in the CC can select a couple of young members to be trained and start working in the CC as Expert Patients to provide information and peer-to-peer support to patients. The service is particularly useful for newly diagnosed who have the chance to speak to other patients that have first-hand experience of the disease, avoiding the search for support online where the information is often not reliable. The Expert Patients undergo a specific training with a psychologist, a senior Patient Expert and a communication specialist and are paid for their service to give them a sense of purpose, sense of responsibility and support their professional growth (they could train other Expert Patients in the future). A double advantage: to do something valuable for other patients and acquire a more relevant role within the Association.

3 The fundraising activity has two important objectives: to provide sustainability for the project, but most of all to create a sense of "disease Community" within the CC. And an online CC's own Community could be launched subsequently. Two major assumptions behind this activity:

-Patients often donate without knowing where the money goes to, this time they donate to their own CC for services they will benefit from. Patients become active contributors and help shape their own care opportunities, which is the real meaning of patient empowerment.

-The CC is part of every chronic patient's life, however there is no sense of Community there. Rarely patients know other patients and in the CC the patients' ability to help each other is not channeled.

All the different stakeholders in the management of a chronic disease: HCPs, nurses, patients work together as a team to reach a common objective. Patients' small queries are solved on the phone and once in the CC they find support from fellow patients.

Patients' active involvement in the CC can benefit the whole disease Community.

ID 011

TITLE: **DYNAMIC MONITORING OF MONOCYTE HLA-DR EXPRESSION AS PREDICTOR OF OUTCOME IN CHILDREN WITH ACUTE BACTERIAL MENINGITIS AND MENINGOCOCCEMIA**

C. Aydın Kaya; F. Genel; C. B. Erdur; E Ozbek; I. Devrim

Department of Pediatrics, Dr. Behcet Uz Children's Hospital, Izmir, Turkey

Acute bacterial meningitis and meningococcemia are one of the serious causes of mortality and morbidity in childhood. We need faster tests for early diagnosis and for preliminary prognosis and complications. The aim of this study is to get serial measurements of monocyte HLA DR expression rate to help the diagnosis, to predict the clinical course and to correlate with the prognosis.

Eighteen patients between 1-180 months who were diagnosed as acute bacterial meningitis and meningococcemia and 36 patients as control group were included in our study. Monocyte expression of HLA-DR was determined by flow cytometry at diagnosis and on the third day of follow up.

The percentage of monocytes expressing HLA-DR was lower on admission (30.1±23.4%) than on the third day of therapy (49.9±24%)($p<0.05$). Both levels were also significantly lower than control group (93±5.1%)($p<0.05$). During clinical follow-up, neurological complications occurred in five patients. On the third day the percentage of monocytes expressing HLA-DR was significantly lower in patients with neurological complications (25.7±20.1%) compared with that in patients without neurological complications (59.3±29.9%). Six patients were applied antibiotics before hospital referral. On admission, in patients without antibiotic application before hospital referral the percentage of monocytes expressing HLA-DR was significantly lower as 19.1±12.8% than in patients referred with prior antibiotic treatment as 52.3±25.1% ($p<0.05$).

Monocyte HLA-DR expression is down regulated in patients with acute bacterial meningitis and meningococcemia. Higher percentages of monocytes expressing HLA-DR in patients referred with prior antibiotic treatment supports the importance of early treatment of acute bacterial meningitis and meningococcemia The percentage of monocyte HLA-DR expression on the third day also seems to be valuable predictive marker for evaluating complications during follow up.

ID 013

TITLE: **COST-EFFECTIVENESS OF WHOLE EXOME SEQUENCING TO SOLVE THE UNSOLVED: AN ITALIAN PILOT STUDY**

F.C. Radio; M. Tartaglia; B. Dallapiccola

Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy

While rare, ultrarare and orphan diseases affect few than 1/2000 persons, several millions of people, principally children, suffer of these conditions worldwide. To date, more than 8,000 nosologic entities have been reported due to a monogenic/oligogenic etiology, and around 1/3 of affected patients does not reach a diagnosis, sometimes never during the life.

The needs of these patients and their families represent a medical, economical and societal challenge.

Second generation sequencing technologies (SGS) revolution has guaranteed a rapid increase of knowledge attended by a rapid reduction of costs. In particular, the use of whole exome sequencing (WES) in daily care has been improved diagnostic tools with advantage in terms of diagnostic rate, diagnostic time and costs.

Approximately 200 patients affected by rare, ultrarare and orphan diseases were enrolled in the present study at the Bambino Gesù Children's Hospital between 2014 and 2016. Each patient was suspected to have a monogenic disorder, which had been remained unrecognized despite extensive multidisciplinary clinical, genetic and instrumental evaluation. WES and data analysis were performed using an in-house workflow. The cost-effectiveness analysis was ruled out on a sub-cohort of 69 patients, aged between 2 and 25 years, with a conclusive diagnosis identified by WES.

The total costs and costs per year of diagnostic delay were compared with the WES cost (around 3.000 €/trio). The minimum, maximum and average costs were calculated for each indicator.

Total cost for each undiagnosed patient (all diagnostic investigations, procedures and inpatient/outpatient assessments) was calculated to be 14.188 €, on average. The range was comprised between 75.110 € and 660 €, and showed a direct correlation with the complexity/severity of phenotype, considering the age of patient. Each year of diagnostic delay costed 2.366 €, ranging between 75 € and 10.495 €. A schematic representation is showed in figure 1.

Rare and genetic diseases represents the first cause of hospital access for children. While a subset of patients generally receives a diagnosis at the first evaluation based exclusively on the clinical appearance and phenotype, a significantly large cohort of patients shows non-pathognomonic signs, incomplete disorder presentation, a complex phenotype that apparently does not fit with any recognized condition. During the last decade, the development of new cytogenetic and molecular approaches makes available efficient and cost-effective tools for the diagnostic use. SGS, in general, and WES, in particular, guarantees a high-throughput approach for genetic heterogeneous disorders and undiagnosed patients. The present study provides evidence of the cost-effectiveness of application of WES as a first line diagnostic tool in patients affected by a monogenic/oligogenic disorders in absence of a specific clinical suspicion.

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ID 014

TITLE: **OPBG UNDIAGNOSED CLINIC: REPORT OF THE FIRST SIX MONTHS OF ACTIVITIES**

A. Bartuli; F.C. Radio; M. Macchiaiolo; B. Dallapiccola

Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy

Rare diseases affect <1/2000 individual in general population. These conditions are heterogeneous both clinically and molecularly. Nevertheless, diagnostic, care and social issues are shared. A significant proportion of patients affected by these disorders (around 1/3-1/2) remains undiagnosed, even if a multidisciplinary approach is performed. The Genetics and Rare Disease Unit of Bambino Gesù Children's Hospital is daily involved in diagnosis, management and care of rare, ultra-rare and orphan patients on a case-to-case approach based on a multidisciplinary team. This activity and the strong cooperation with patient organizations have driven the need to create a dedicated "undiagnosed clinic". This outpatient clinic is the first service for undiagnosed children in Italy. The clinic is helping patients and families, both with a web-based (telehealth) and a frontal approach, to solve the unsolved. Based on the clinical presentation and needs, a case manager is designated to coordinate the multidisciplinary team with the goal of reaching the diagnosis and improving the management. Genetic testing is performed based on the clinical presentation in a multi-step plan, ranging from specific tests driven by clinical suspicion to whole/clinical exome sequencing. Here we report on the first six months of activity.

Approximately 170 patients affected by a rare, ultrarare or orphan disease were consecutively evaluated at the OPBG undiagnosed clinic in a web-based fashion. Based on the family/patient needs, a subset of patient was evaluated at the outpatient clinic. Clinical and molecular tools were used in a case-to-case specific approach to solve these unsolved cases.

More than 95% of patients chose the TeleHealt approach as a first assessment. More than 30% of families contacted the clinic to obtain more accurate information on their diagnosed condition (18% of cases) or asked for logistic and/or social support (14%). The patients affected by an undiagnosed disease were assessed at the dedicated outpatient clinic, and molecular analyses (targeted resequencing, high resolution CGH/SNP array and/or whole/clinical exome sequencing) were performed on the basis of the clinical suspicion. A schematic representation of the first six months of activity is showed in figure 1.

The collected data shows that the undiagnosed patients' needs are not lone to reach a diagnosis. Frequently the families ask for a multidisciplinary care, in a recognized referred center that guarantee the availability of the latest technologies/therapies. A psychosocial support is often the principal request, also in the telehealth approach. The presence of the case manager guarantee a peer support also in the absence of a conclusive diagnosis.

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ID 015

TITLE: **KEY LEARNINGS FROM A PATIENT ADVISORY BOARD MEETING AND NEW WAYS TO BRING PATIENT CENTRICITY IN THE DEVELOPMENT AND LIFECYCLE OF MEDICINES**

V. dos Reis Ferreira

Patient Advocacy Department, Santhera Pharmaceuticals

Patients are the experts on their unique experiences living with their condition, they represent an important stakeholder to engage, not only for the companies that develop new therapies, but also for the authorities that assess, regulate and decide which drugs are effective, well tolerated and cost-effective for patients and the community. Patient engagement is an expanding area, elevating patients from solely research subjects to active partners along development and lifecycle of medicines. A variety of methods that are used to engage patients have been described , the most common of which are focus groups, interviews, surveys and the most active form of engagement which is serving on a study board or advisory council and attending regular meetings with researchers (as in active participatory research studies and community based participatory research) . Accordingly, Santhera Pharmaceuticals have developed activities to empower and to engage Patient Advocacy Groups (PAGs) for Leber's hereditary optic neuropathy (LHON), a rare disease causing progressive, central vision loss in both eyes.

A mixed method approach was used to identify LHON organisational leaders and patient representative's needs, priorities and experiences. An independent party built and conducted a questionnaire that has been completed by ten LHON participants from seven European countries. Quantitative and qualitative data were analysed using basic descriptive statistics and content analysis, respectively.

The questionnaire involved five main themes. Its results have been used to select key issues and questions for the advisory board. The advisory board provided unique information about the experiences of LHON community concerning diagnosis, treatment and care. During this presentation, we will describe participants' valuable contributions about information sources, tools and needs, while also providing insights into the difficulties for small organisations trying to promote awareness and research activities. The study is relevant internationally because of what it tells us about LHON at European level; however, we draw attention to specific opportunities at country level for the current LHON activities led by these patient organisations and their representatives.

LHON patient organisations and their representatives are few. With the goal to improve patient preferences and values in research and lifecycle of medicine development their information should be used wisely and efficiently. The mixed method approach applied proved to have a unique potential to be used to extensively explore in a robust manner the needs, priorities and experiences of the community at European level. Future initiatives should include the development of additional trainings and educational resources to empower LHON patient community and facilitate patient engagement in research and lifecycle of medicine development.

ID 016

TITLE: **THE «UNDIAGNOSED PATIENTS PROGRAM» @ OPBG**

M. Tartaglia, S. Barresi*, A. Bruselles*, A. Ciolfi*, M.L. Dentici*, M. Niceta*, F. Pantaleoni*, S. Pizzi*, F.C. Radio*, M. Macchiaiolo, A. Masotti, M. Trivisano, A. Capuano, R. Carrozzo, L. Travaglini, G. Zanni, A. D'Amico, A. Baban, R. Cutrera, G. Zambruno, G. Torre, C. Dionisi-Vici, N. Specchio, A. Novelli, A. Bartuli, M.C. Digilio, E. Bertini, B. Dallapiccola.

*equal contribution, alphabetical order

Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy

In Europe, a disease is considered rare when it affects less than 1 person per 2,000 or ultrarare when it affects 1 in every 100,000 people or fewer. Many conditions have been described as possible nosologic entities in single reports. To date, more than 8,000 diseases have been recognized clinically. Although individually rare, these diseases are collectively frequent (8% of the global population). Proper patient management requires prompt diagnosis. However, the poor characterization of the clinical variability and natural history of the majority of rare diseases results in a substantial diagnostic delay. Such a delay might also be caused by the co-occurrence of unrelated diseases or because the absence of diagnostic "handles". Importantly, a significant but still undetermined number of disorders has not been recognized yet. A delayed or uncertain diagnosis is reported in > 30-40% of patients. The development of high-throughput and relatively unexpensive sequencing technologies, current knowledge on the extent of genomic variation in human populations, and the implementation of bioinformatics tools able to manage and analyze "big data" make it possible the use of genomics to improving the diagnostic rate of rare, ultrarare and orphan patients, reducing times and costs. Here we report on the results of a recently concluded pilot project directed to use whole exome sequencing (WES) for the diagnosis of 200 undiagnosed patients.

All patients were suspected to have a monogenic disorder, and had consecutively been enrolled at the Bambino Gesù Children's Hospital, between 2014 and 2016. WES analysis was performed by using an in-house implemented workflow. Each patient was evaluated by a multidisciplinary team of experts. To standardize phenotyping, compare individual phenotypes with those reported in international databases and prioritize the genomic variants, the Human Phenotype Ontology (HPO) was applied. Clinical and molecular data were merged in an all-inclusive database to facilitate matching with other databanks. WES was performed to attain 100x reads depth and >98% coverage at 10x. Following WES data analysis, clinical and molecular data were discussed by the multidisciplinary team.

The overall diagnostic yield of the present study was 40%. Among patients with conclusive diagnosis, 33% of patients were found to carry mutations in an already established diseases gene. In a significant proportion of these cases, an atypical presentation of the disorder was recorded; similarly, a high percentage of cases was observed to carry mutations in recently identified disease genes. Remarkably, novel disease genes were discovered to account for around 10% of patients. In 13% of cases, WES allowed to identify novel candidate genes. Clinical and/or functional validation is ongoing.

This study provides evidence that WES has a high diagnostic yield in undiagnosed patients, and can be considered as a first diagnostic approach in clinically well-characterized undiagnosed patients.

ID 017

TITLE: **MORE THAN A GAME: HOW SERIOUS GAMES CAN FIGHT PEDIATRIC CANCER**

H. Oliveira 1,2; N. Patraquim 2; H. Lima 3

1 Faculty of Medicine of University of Porto and Faculty of Engineering from University of Porto; 2 Faculty of Engineering from University of Porto; 3 Faculty of Arts and Humanities from University of Porto

During the past few years, several studies presented an association between increased physical activity levels in childhood cancer patients and an improvement in the quality of life during hospitalization. In particular, physical functioning is increased, anxiety is reduced, and social integration is encouraged. Considering the fact that physical activity plays a vital role in the physiological and psychosocial development of children, therapeutic exercise in pediatric oncology is particularly important to create a better body response to treatments. However, there is still a lack of comprehensive and evidence-based data in the field of exercise interventions in pediatric oncology.

This work intends to present the conception and the evaluation results of a 2D video game for tablets, the Hope Project, which was developed to solve major issues related to treatments adherence and the sedentary lifestyle of children between 6 and 10 years old, that are diagnosed with cancer. The serious game component allows building a tool that goes beyond entertainment and has the goal to teach cancer subjects, increasing adherence to treatments. On the other hand, the exergaming technology seeks to encourage the practice of physical exercise, using the front camera of mobile devices.

A characterization study was conducted, with the release of a survey for 78 children, to understand their tastes and routines in relation to video games. A prototype of the video game was then developed by a multidisciplinary team of informatic engineers, designers, and oncologists according to the children attitudes and beliefs towards cancer. This prototype was evaluated in controlled sessions with 13 children with cancer, measuring the intrinsic motivation of the participants, as well as the exergaming and the usability components.

The results of the characterization study prove that video game for tablets is the indicated tool to try to address the problems identified. 94.5% of children who have played videogames on tablets really enjoy playing on these devices.

The implementation of the first Hope Project prototype reached high levels of intrinsic motivation on children with cancer, with a mean of 77% of the participants being highly motivated in all the evaluation criteria. The video game entertains the children and the extreme motion technology offers a robust solution for the implementation of exergaming challenges, using the front camera of mobile devices in different scenarios.The main menu and buttons present in the different challenges are logical, minimalist and consistent.

The prototype use increased the knowledge about cancer in 80% of the participants.

Video Games can be an important tool to disseminate knowledge about cancer in hospitalized children, improving at the same time their physical condition. The combination of a serious game component with the exergaming technology can facilitate a change of attitudes in children, promoting therapeutic adherence and decreasing sedentary lifestyle.

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ID 018

TITLE: **TRANSPLANTCHILD, AN EUROPEAN STRATEGY TO ATTEND "THE SECONDARY RARE DISEASE" INDUCED BY PAEDIATRIC TRANSPLANTATION**

E. Frauca 1; E. López-Granados 2; A. Pérez-Martinez 3; F. Hernandez 4; J. M. Torres 5; M. Tejedor 5; A. Coloma 5; J. Cobas 5; P. Jara 1; on behalf of TRANSPLANT-CHILD

1. Hepatology Department; 2. Clinical Immunology Department; 3. Paediatric Haemato-Oncology Department; 4. Paediatric Surgery Department; 5. La Paz Institute for Health Research - IdiPAZ. University Hospital La Paz, Madrid, Spain

Paediatric transplantation (PT), both solid organ (SOT) and hematopoietic stem cell transplantation (HCST) has greatly improved survival in children with several rare end-stage diseases. PT approach requires a multidisciplinary team that supports this complex procedure in common processes as immunosuppression, immune reconstitution, rejection, tolerance, risk of infection and psychosocial wellbeing, present in all types of transplants; therefore a holistic a cross-cutting approach will improve further the expectancy and long-term quality of life of children and their families. The aim is to describe the strategic approach of TRANSplantCHILD to the improvement of life expectancy and quality of life for EU paediatric patients.

TRANSplantCHILD is an European reference network (ERN) focused on a highly specialized medical procedure that gereates a low prevalent and complex chronic clinical condition in children, the post -ransplant period. TRANSplantCHILD aims are: (1) Ensuring their access through the network to the best possible care practices and support procedures related to a transversal and multidisciplinary approach to children´s transplant. (2) Developing and gathering efforts within the network for integrative, innovative and better procedures, information, training, knowledge and expertise. (3) Integrating stakeholders in the transplantation process and making available the knowledge and information. As established in the Strategic approach of TRANSplantCHILD, the strategic areas have been approved in order to ensure the achievement of the mission and vision of the Network: (1) To improve patient healthcare; (2) To harmonise clinical best practices; (3) To harmonise research and innovation; (4) Spread knowledge; (5) Education and training; (6) Network organization, quality and safety.

TRANSplantCHILD integrates 18 Healthcare providers from 11 Members states (figure 1) which have proven experience in PT and related complications in order to gather the knowledge and experience available throughout Europe. The holistic model will favor efforts for the development, validation and routine implementation of promising biomarkers for a better patient-oriented precision care based on an pediatric oriented pipeline of development. based in all stages. The crosscutting approach of TRANSplantCHILD allow the identification of common topics to all transplants such as clinical, personal and socio-economic issues, and the improvement of the transplanted patient handling, their life expectancy and long-term quality of life of children and their family by: (1) preventive practices to anticipate and minimise patients' risks; (2) Treatment standardisation; (3) Harmonisation of clinical best practices; (4) Improving chronicity approach and the treatment of secondary diseases related to PT; (5) The provision of psycho-social support in different phases of patients' life; (6) The provision of grounds for patients' empowerment.

PT care constitutes yet a medical challenge due to the lack of robust data In comparison with the adult transplantation. TRANSplantCHILD focuses the PT as process approach instead of a disease/organ approach, developing an integrative model for share within the network the knowledge or expertise from highly specialised support and advice at national healthcare providers for the transplanted children.

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ID 019

TITLE: **INFANT MOTOR DEVELOPMENT BETWEEN 0-4 MONTHS: A NEW LOOK AT THE EFFECT OF THE 'BACK TO SLEEP' PROGRAM**

E. Wiliams 1; B. Eldridge 2; M. Galea 3

1. Department of Medicine (Royal Mebourne Hospital), The University of Melbourne, Melbourne Australia. 2. Royal Children's Hospital, Melbourne, Australia

An unexpected consequence of the Sudden Infant Death Syndrome (SIDS) prevention campaign, or 'Back to Sleep' program, is an increased incidence of deformational plagiocephaly, with a prevalence of 46% in 7 – 12 week old infants. Plagiocephaly has been shown to be associated with delayed cognitive, adaptive behaviour and language development. While 'tummy time' is recommended as a preventative strategy, parents do not appear to be heeding this advice. This research sought to address gaps in knowledge of infant head control and its development by investigating head control in typically developing infants and those with deformational plagiocephaly at a specialized tertiary hospital clinic.

Study 1. A longitudinal study of the development of head control in typically developing infants aged 0-4 months, with assessments at 1, 2 and 3 months.

Study 2. An audit of referrals to the Deformational Plagiocephaly Clinic at the Royal Children's Hospital, Melbourne and investigation of head control in infants attending the clinic.

Study 3. Development of a fact sheet on development of head control in the infant and a review by experts as a first step in developing an online education resource.

Study 1. The longitudinal study has revealed that the biomechanics of head control development in infants is complex and points to one factor in the aetiology of the development and persistence of deformational plagiocephaly in some infants, namely the action of the sternocleidomastoid muscles.

Study 2. The audit showed that 4000 reviews (of 1990 individual infants), with plagiocephaly were conducted in three Deformational Plagiocephaly clinics at the Royal Childrens' Hospital over a three-year period. Random samples of infants from each of the three years show the referral patterns were consistent, indicating no change in referral rate; 99% were referred by General Practitioners; average age was 7 (SD=2) months; there was a 2 month waiting period; 65% were male infants; 60% had right-sided plagiocephaly; 72% were classified as mild or mild-moderate and 50% had only one review. An investigation of head control in 25 infants, average age 7 (SD=2) months showed that they had poor head control and often extended the legs when pulled to sit.

Study 3. A fact sheet on the development of head control, aimed at health professionals and carers of infants has been developed from a synthesis of information from Studies 1 and 2.

There is a gap in knowledge about the aetiology of deformational plagiocephaly and the development of head control in the infant is poorly defined and described. Our results form the basis for better education programs about the development of head control in the infant which may lead to a reduction in the incidence of deformational plagiocephaly over time.

ID 020

TITLE: **ADDRESSING PATIENTS NEEDS IN INTESTINAL INSUFFICIENCY – BENEFITS OF NETWORKING**

J. Amil-Dias 1; G. Prieto-Bozano 2; E. Ramos 2; P. Guerra 1; E. Trindade 1; C. Espinheira1

1 Centro Hospitalar S. João, Porto, Portugal; 2 Hospital Infantil Universitario La Paz, Madrid Spain

Intestinal failure is a rare but very severe situation in Paediatric patients. Most cases occur following severe intestinal disease in the early months of life, often after surgical procedures that require extensive resection. Proper early management of this situation is of great importance for the overall prognosis of the patient as adequate nutrition, growth and development in critical phases of growth will determine health and quality of life for the entire life. Measures to promote intestinal rehabilitation and expert use of parenteral nutrition techniques are vital in order to prevent, if at all possible, or to delay, if unavoidable, intestinal transplantation. For the small group of patients that eventually require transplantation it is also to have good preparation and the best conditions. The number of paediatric transplants required across Europe is limited and a small number of Units are advisable in order to keep high standards and experience. Therefore the cooperation between these few Units and many more centres that handle patients with intestinal failure should be encouraged.

Portugal and Spain have initiated a cooperation program that hopefully will allow to improve care of children with intestinal insufficiency, promoting rehabilitation by sharing experiences and managing patients with common protocols, but we also hope this may enable early and smooth referral for those cases that will ultimately need small bowel transplantation.

Expected results will consist in improvement in outcome measures for patients (reduction of hospital admissions, improved intestinal rehabilitation), improved team cooperation and protocols and timely referral in case of worsening of clinical condition and absolute need for transplant. It is also expected that hospital stay before and after transplant may be reduced by earlier and smoother hand-over process and joint follow-up.

Improving network cooperation and early referrals using this method may allow better management of critical patients in areas where expertise in limited centres must be preserved, while still providing easy access to more remote location of patients. The required number of intestinal transplants is not expected to raise sharply but correct management of increased number of patients may still be optimal by joint cooperation.

ID 021

TITLE: **RAPID SEQUENCING IMPROVES THE DIAGNOSIS AND TREATMENT OF INFANTS IN THE NICU**

L. Brunelli 1; S. Malone Jenkins 1; J. Flores 1; B. Ostrander 1; S. Patel 1; R. Mao 2; S. Dames 2; C. Miller 2; T. Tvrdik 2; S. Andrews 3; S. Bleyl 3; J. Gudgeon 3

1. University of Utah School of Medicine; 2. ARUP Laboratories; 3. Intermountain Healthcare, Salt Lake City, Utah, UNITED STATES

Conventional genetic testing often fails to identify a diagnosis in acutely ill infants in neonatal intensive care units (NICUs). Although next generation sequencing (NGS) can increase diagnostic yields, its standard turn-around time of weeks to months makes it difficult to improve the care of these infants. Clinicians and families are left making difficult decisions with incomplete information, possibly missing the opportunity to implement specific treatments. We recently deployed rapid sequencing (turn-around time ~1 week) of a targeted gene panel (TGP) in our level IV NICU (Brunelli L et al., Am J Med Genet A, 2017 In Press).

After developing a 4,503 known disease-associated genes panel at a cost per infant-mother-father trio of $6,000, we defined NICU-specific enrollment criteria. We sequenced 12 infants and their parents. The overall enrollment rate was >90%. Preliminary and final results had no discrepancy, and the mean time to report was 9 and 16 days.

We identified a diagnosis in 67% of infants, and six of the eight diagnoses (75%) resulted from de novo mutations. In none of the eight positive cases was the diagnosis strongly suspected prior to rapid TGP. A change in medical management occurred in ~90% of positive cases. One patient had an actionable diagnosis that led to a specific treatment and earlier discharge. Taking into consideration this early discharge and the cost for testing twelve trios, the overall savings were at least $500,000. In a different case, we identified the diagnosis in the infant, and discovered that the mother and other relatives carried an incorrect genetic diagnosis.

Overall, rapid TGP can be implemented at about half the cost of whole genome sequencing. Our strategy might accelerate the adoption of rapid NGS in NICUs across the world, providing prognostic data and therapeutic options to the surprisingly high number of acutely ill infants with Mendelian disorders.

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ID 022

TITLE: **HYPOGLYCEMIA DUE TO GROWTH HORMONE DEFICIENCY IN A CHILD WITH ACHONDROPLASIA**

C. Pillai; A. Shah; N. Rubio; D. Rodriguez-Buritica; M. Yafi

The Department of Pediatrics - UT Health The University of Texas Health Science Center at Houston

Achondroplasia is the most common form of skeletal dysplasia with disproportionate short stature. Patients have rhisomelia, macrocephaly, frontal bossing and midface retrusion. The average final height is 131 cm (4.3 ft.) for men and 124 cm(4 ft.) for women. No studies exist to show a substantial difference on adult height in achondroplasia patients with growth hormone treatment. As such, the use of growth hormone (GH) for the treatment of achondroplasia is uncommon and not standard of care as it can worsen spinal stenosis, obstructive sleep apnea and body proportion

We present a case of an achondroplasia patient with documented hypoglycemia and GH deficiency.

A seven –year-old girl with achondroplasia had documented hypoglycemia. She had a history of obstructive sleep apnea and also required a cervical medullary decompression at 20 months of age. Mother reported documented hypoglycemic episode at home of 33 mg/dl when the patient was sweating and fatigued. Fasting test in hospital induced and confirmed hypoglycemia. A critical sample showed low growth hormone level while IGF-1, insulin, cortisol levels were normal for age.

After documenting GH deficiency, growth hormone therapy is being considered as she is also evaluated for possible disorder of gluconeogenesis or carnitine deficiency. If evaluation is normal she will start growth hormone for treatment of hypoglycemia. She also will need evaluation for sleep apnea.

GH is not a standard of care therapy for achondroplasia since it has not been shown to improve height significantly. Concerns for worsening leg length discrepancies and worsening body disproportion were reported in treated cases. GH therapy is considered for this case to treat hypoglycemia after sleep apnea is treated . She is also being followed by neurosurgery due to concern for spinal stenosis. Careful monitoring and follow up will be established.

ID 023

TITLE: **A FEMALE WITH KALLMAN SYNDROME**

S. Lugo; A. Shah; D. Rodriguez-Buritica; M. Rivera -Davila; M. Yafi

The Department of Pediatrics - UTHealth, The University of Texas at Houston Health Science Center

Idiopathic hypogonadotropic hypogonadism (IHH), previously known as Kallman syndrome is very rare in females.

We present the case of a 15-year-old with chief complaint of primary amenorrhea and short stature. Mid-parental height was estimated at 5'7" +/- 2 inches or 170 cm, 50th-75th percentile for age. Initial height was 4'11" (151 cm), 4th percentile for age. Family history was positive for father growing late into his teens. Patient's weight was within 25th-50th percentile.

Father mentioned that daughter was unable to sense different smells. No history of congenital disorders, chronic illnesses, trauma or dietary problems reported.

Physical examination was unremarkable, with Sexual Maturity Rating (Tanner Staging) 3 for breasts and pubic hair.

Genetic and endocrine conditions associated with female short stature were considered. Karyotype revealed a 46, XX genotype. Further genetic testing, including Kallmann Syndrome gene panel, was negative.

After imaging and testing was performed, with essentially no growth (0.5 cm) in the 9 month follow-up, the patient was started on ¼ of the 0.025mg/24h transdermal estrogen patch of daily. Improvement was noted with growth velocity of 4 cm in 4 months

Laboratory studies showed low LH, FSH and Estradiol and normal IGF1 for bone age age.

Bone Age X-ray = Read by method of Greulich and Pyle was 13 years old, with chronological age of 15 years.

Pelvic Ultrasound = Uterus size of 2.1 centimeters in length, no clear definition of ovaries.

Pelvic Magnetic Resonance Imaging (MRI) = anteflexed, small uterus measured 3.5 x 0.8 x 2 cm with stripe thickness of 0.2 cm and bilateral ovaries of 2 cm each.

Brain MRI = negative for any structure abnormalities. No pubertal enlargement of neurohypophysis and adenohypophysis.

Idiopathic hypogonadotropic hypogonadism (IHH), previously known as Kallman syndrome in cases of anosmia or inability to smell, is considered to be a rare condition with various genetic inheritance patterns.

Incidence is 4 times greater in males than females and diagnosis is made around 14 to 16 years of age due to delayed puberty. Misdiagnosis can occur with constitutional growth delay prior to age 18.

Clinical presentation is variable. Midline defects like cleft lip, cleft palate, imperfect facial fusion, sensorineural hearing loss, short metacarpal bones, and pes cavus can be seen.

Anosmia or inability to smell, is due to migration failure of the olfactory placode towards the medial basal hypothalamus around week 5-6 of fetal life. Although anosmia is a distinguishing factor in patients with Kallmann syndrome, MRI is helpful in diagnosis as 90% of cases will have abnormal imaging of the olfactory sulci-bulbs.

Multiple genes have been identified with Kallmann syndrome 1 and 2 gene (KAL 1 and 2) being the most widely known, located in chromosome Xp22.3 locus. To date, there are over 7 types of Kallmann Syndrome. We consider our patient to have a variant that has not yet been determined.

ID 025

TITLE: **THE DAPHNE PROJECT**

G. Cinelli 1; T. Lobstein 2; T. Silva 3; C. Gibbons 4; G. Bailador 5; R. Ram 6; A. Palomares Pérez 7; H. Schwietert 8; O. Kudrautsevae 9; M. Manco 1 for the DAPHNE Project Consortium

1 Bambino Gesù Children Hospital, Rome, Italy; 2 World Obesity Federation, London, UK; 3 Treelogic SL, Madrid, Spain; 4 University of Leeds, Leeds, UK; 5 Technical University of Madrid, Madrid, Spain; 6 IBM Research, Haifa, Israel; 7 ATOS SE, Madrid, Spain; 8 Evalan BV, Amsterdam, The Netherlands; 9 SilverCloud Health, Dublin 8, Ireland

DAPHNE Data-as-a-Service platform for Healthy Lifestyle and preventive medicine is a research project funded by the European Commission under the ICT Theme of the Seventh Framework Programme. The objective of the DAPHNE project was to develop a state-of-the-art breakthrough ICT plat-form for reducing sedentariness and unhealthy habits, based on data-as-a-service and person-alized services, providing the necessary organisational, security and business models for the exploitation of project results.

The DAPHNE system has been thought of to provide personalised services for the prevention and the care of overweight and obesity. Wearable sensor and personalised services (mobile application and web portal) have been developed to reduce sedentariness by initiating behav-ioural change and to support physician in their clinical treatment. A pilot study has been carried out in the Bambino Gesù Children Hospital in order to evaluate the feasibility of the use of DAPHNE system in the clinical treatment of obese adolescents and patients' compliance to the system.

ID 026

TITLE: **CAVATICA: SHARING AND ANALYZING PEDIATRIC DATA ON THE CLOUD**

M. Mattioni

Seven Bridges UK, London, United Kingdom

The availability of vast amounts of genomic data offers unprecedented opportunities to improve treatments for rare pediatric diseases, including childhood cancer.

However, the rapid growth of pediatric genomics data presents a complex set of technological challenges.

Under current infrastructures, many research hospitals struggle to effectively manage existing data, let alone scale to support future growth and analytics.

Data sharing and usability have not kept pace with the explosive growth of genomics data. Data siloing is especially problematic for rare diseases with limited samples that require non-local domain expertise.

Reproducibility is also a problem, as data is often generated by multi-institutional consortia operating on different computation environments.

To address these challenges, we've built CAVATICA, a data analysis and sharing platform designed to accelerate discovery in the field of pediatric medicine.

CAVATICA is a scalable, cloud-based compute environment where data, results, and workflows are shared among the world's research community. CAVATICA is enabling researchers to collaboratively deposit, access, integrate, share, and analyze data on pediatric cancers, congenital disorders, epilepsy, and autism.

CAVATICA's innovative structure ensures that users maintain full control of their data and how it is used, while also facilitating collaborative analysis. Researchers can view information about available datasets and request access directly from the data owners, letting researchers broaden their focus across multiple diseases.

CAVATICA is designed to appeal to users from a variety of clinical and research backgrounds. Users can work within an intuitive website interface or operate programmatically via API.

Importantly, the Common Workflow Language makes analyses in CAVATICA fully reproducible.

CAVATICA enables genetic studies of rare pediatric conditions at a greatly expanded statistical power and shifts current research paradigms toward collaboration and reproducibility.

The extensive data collections of The Children's Brain Tumor Tissue Consortium (CBTTC) and the Pacific Pediatric Neuro-Oncology Consortium (PNOC), collectively representing more than 20 pediatric hospitals, are now available in the cloud for the first time.

CAVATICA also interoperates with the Genomic Data Commons and other NIH data repositories.

CAVATICA supports researchers and patients worldwide. CAVATICA and its partners continuously seek to collaborate with other data platforms in order to empower data across diseases, ages, and geography. Seven Bridges and its partners in the CAVATICA commons call on scientists, patients and their families around the globe to join the work of accelerating the discovery of treatments for children.

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ID 030

TITLE: **STORYTIME: IN-HOME AUTOMATIC ASSESSMENT FOR SPEECH AND LANGUAGE DEVELOPMENT IN YOUNG CHILDREN**

Y. Du 1; H. Abbas 2; S. Taraman 3; S. Seger 4

1, 2, 3, 4 Cognoa, LLC; 1,3 University of California, Irvine; 3 Children's Hospital of Orange County

Speech and language delay affects 5-12% of US children between 2-5 years.1 Atypical speech, language, and social communication are also the core characteristics of children with autism spectrum disorders. Although common, identification in primary care settings can be inefficient and is often addressed by referral to speech therapy. The process can result in delays in treatment due to long waitlists. Early identification and intervention allows for better future communication and literacy skills for school readiness and is protective against behavioral and mental health problems as well as academic failure.2

Presently, the vast number of children are digital natives with frequent use of mobile devices. Despite this, there are no autonomous assessments of communication impairments in children utilizing mobile technology. Furthermore, shared storybook reading is common for many families as well as an evidence-based intervention technique for improving language and literacy skills.3 The goal of this study is to present a mobile storybook for autonomous speech and language assessment in the home setting.

A digital storybook, "Cognoa Storytime" was developed with input from a speech therapist, developmental psychologist, and pediatric neurologist. Children age 4-6 years old with and without communication impairments who are digital natives were evaluated using the storybook. During the study, the parent-child pair sit side-by-side and interact with "Cognoa Storytime". The story comprehension section is a video story read by a built-in voiceover and prompts the child to answer questions about the story. The story narration section asks the child to create an oral story based on a picture. During the sessions, the child's behavior is documented using an adapted observational protocol. The child's voice and interaction are recorded for signal processing and featurization algorithms for speaking rate, duration, pauses, pitch control, vocabulary use, and sentence structure patterns. Machine learning and statistical modeling will be applied on these features to automatically assess speech and language abilities to distinguish children with and without speech and language impairments.

Our initial pilot test demonstrated that the mobile storybook is a flexible tool to capture speech data and interaction patterns in six children with and without impairment across various settings.

We hypothesize features from speech and language signals extracted during this interactive storytime can offer valuable clinical information to classify pediatric communication disorders. This study will combine automatic speech recognition and machine learning analysis of acoustic and linguistic features for an automated assessment at home. It has the potential to alleviate burden of care for primary care providers, support parents with reliable information about their children's development, and provide access to early intervention during critical neurodevelopmental periods.

ID 031

TITLE: **UNRAVELLING THE ROLE OF AMBRA1 IN PEDIATRIC BRAIN TUMORS**

F. Nazio 1; A. Po 2; E. Miele 3; F. Diomedi Camassei 4; L. Abballe 2; A. Mastronuzzi 3; E. Ferretti 2; F. Locatelli 1, 3, 5; F. Cecconi 1, 6, 7

1. Department of Pediatric Hematology and Oncology, IRCCS Bambino Gesù Children's Hospital; 2. Department of Experimental Medicine Sapienza University of Rome; 3. Department of Hematology/Oncology and Stem Cell Transplantat

Ambra1 is a pro-autophagy gene, whose role as a tumour suppressor has recently been recognized in a number of studies. Moreover, AMBRA1 is important in controlling cell proliferation through its direct interaction with the protein phosphatase PP2A, by which it tightly regulates the stability of the oncoprotein and pro-mitotic factor c-Myc. In the context of the nervous system, AMBRA1 has first been implicated in impaired embryogenesis and found to be involved in mouse congenital malformations and human neurological disorders. Depletion of Ambra1 during embryogenesis interferes with autophagy, cell proliferation, and apoptosis, this suggesting that these processes interplay in order to prevent uncontrolled cell death and cell growth. Moreover, Ambra1 is an essential co-factor for different E3 ligases, during both autophagy and mitophagy.

There are very few studies that evaluated the expression of Ambra1 in human brain neoplasms at a tumour tissue level. Medulloblastoma (MB) is the most common malignant solid brain childhood tumor, in which the Myc family (c-Myc and n-Myc) is crucial in the regulation of cell proliferation, stemness and differentiation. We found differences in Ambra1 expression and its subcellular localization between non-neoplastic and neoplastic tissues, among different tumour medulloblastoma subtypes. Moreover, modulation of Ambra1 levels in medulloblastoma cell lines has an impact on proliferation, cell death and staminal properties. Interestingly, by analysing brain extracts from Ambra1-deficient embryos, we found an increase in n-Myc levels. Since N-myc expression in the developing nervous system is essential for the correct timing of cell-cycle exit and differentiation, and since its deregulation is finely related to medulloblastoma initiation, our studies suggest that AMBRA1 could act as a key modulator of proliferation and/or autophagy in MB.

Our results may thus pave the way for novel page-turning approaches aimed at modulating, in a coordinated way, autophagy and Myc-mediated proliferation in proneural cancer cells.

ID 033

TITLE: **EARLIEST FUNCTIONAL SIGNATURES OF HUMAN GUT MICROBIOMES REFLECT BIRTH MODE**

L. Wampach 1; A. Heintz-Buschart 1; J. V. Fritz 1; M. Herold 1; S. Narayanasamy 1; A. Kaysen 1; A. Hogan 2; L. Bindl 3; J. Bottu 3; C. O. Sjöqvist 4; J. Ramiro-Garcia 1; P. May 1; A. F. Andersson 4; C. de Beaufort 1, 3; P. Wilmes 1

1. Luxembourg Centre for Systems Biomedicine, University of Luxembourg, Esch-sur-Alzette, Luxembourg; 2. Integrated BioBank of Luxembourg, Luxembourg, Luxembourg; 3. Centre Hospitalier de Luxembourg, Luxembourg, Luxembourg; 4. KTH Royal Institute of Techno

Studies have reported differences in the gut microbiota of infants born by caesarean section (CS) when compared to their vaginally (VD)born counterparts.There is paucity of data reflecting the transfer of microbiota from mother to neonate,including the potential functions conferred to human physiology by specific strains. We compare and contrast neonates born vaginally or by caesarean section and relate the respective neonatal gut microbiome to the microbiota of their respective mothers. We investigate whether essential gene complements are encoded by microbial strains vertically transferred from mothers to neonates.

In 12 mother-neonate pairs (4 VD, 4 CS and 4 CS and born small for gestational age) we analyzed snap-frozen samples of maternal vaginal flora (day 0) and stool and of infant stool (day 1,3,5, and at 1,6 and 12month). DNA was extracted using an optimized low-yield extraction protocol, random shotgun sequenced, and the resulting metagenomic data was processed using an integrated,reference-independent analysis pipeline; an in silico strategy was devised for the identification and removal of artefacts. Tracking of vetical transmission was based on taxonomic annotations, phylogenetic marker genes and single nucleotide variants (SNVs). The genes of the curated metagenomes were annotated with functional categories (KEGG orthologous groups; KOs) and we quantified their abundance. To determine whether the strains vertically transmitted also carry the genes that were depleted in CSD neonates, we tested all reconstructed genomes for enrichment in differentially abundant functions. we collected plasma samples around day 3 after birth from a total of 31 neonates to measure specific cytokine levels linked to LPS stimulation.

We detected taxonomic differences analogous to previous studies.

Genes involved in LPS biosynthesis were found to be enriched in VD neonates (FDR-adjusted P = 8.0 x 10-6) and present in increased relative abundances (FDR-adjusted P = 2.3 x 10-2).The enriched degradation of glycosaminoglycans (FDR-adjustedP = 4.3x 10-2) and other glycans (FDR-adjusted P = 2.1 x 10-4) demonstrated higher aggregated relative abundance in VD neonates compared to CSD (± SGA) neonates (FDR-adjusted P = 3.5 x 10-3 and 2.1 x 10-3 respectively). The genomes, which could be linked to maternal metagenomes, were more likely to be enriched infunctions that were depleted in CSD neonates (odds ratio 3.7, Fisher's test P = 9.7 x *10-6). We observed a significantly higher abundance of TNFa in VD neonates (FDR-adjusted P = 3.0 x 10-2).

Delivery by CS not only alters the composition of the earliest neonatal gut microbiome, but also prevents vertical transfer of important microbial functions encoded by specific strains from mother to neonate. This could potentially result in a delayed immune stimulation as well as in an impaired gut metabolic activity, thereby resulting inchanges to the inter-relationships between the gut microbiome, microbial metabolism and neonatal immunological responses.

ID 034

TITLE: **QUALITY OF LIFE IN PATIENTS WITH CYSTIC FIBROSIS**

N. Kolarova-Yaneva 1; P. Kolarov 2; N. Yanev 3; V. Nedkova 1

1.Paediatric Dept, University Hospital of Pleven, Bulgaria; 2.Psychiatric Dept, Univerity Hospital of Pleven, Bulgaria; 3.MHATPD "St. Sofia", Medical University Sofia, Bulgaria; 4.Paediatric Dept, University Hospital of Pleven, Bulgaria

Cystic fibrosis (CF) patients experience difficulties in adapting to their condition which often leads to lowering the level of their quality of life (QoL). The aim of this study was to determine the QoL in CF patients and study the relationship between QoL and the clinical course of their disease.

We evaluated the following clinical parameters regarding anthropometric data, pulmonary exacerbations and bacterial colonization of 25 patients with CF aged 1 -32 years. To assess the QoL, overall physical activity, nutrition and radiographic changes we applied the Schwachman-Kulszyki scale.

53.4% of the investigated patients had severe clinical manifestation of CF, and only 22.4% had a good QoL score. In 60% of the CF patients the body mass index (BMI) was below 20 which resulted in frequent pulmonary exacerbations.Ps. Aeruginosa was most commonly observed amongst the isolated bacterial agents, followed by Staph. aureus, or a combination of both.

The observed frequent pulmonary exacerbations had a negative impact on the physical and the psychosocial determinants of the QoL in patients with CF.

ID 035

TITLE: **GENETIC SUSCEPTIBILITY TO HASHIMOTO'S THYROIDITIS. A CLINICAL REPORT ON TWIN GIRLS WITH PRIMARY MICROCEPHALY AND ACQUIRED HASHIMOTO THYROIDITIS**

P. Pavone 1; R. Falsaperla 1; A.D. Praticò 2; M. Piccione 3

1University-Hospital "Policlinico-Vittorio Emanuele", University of Catania, Italy; 2 Department of Clinical and Experimental Medicine, Section of Pediatrics and Child; 3 Azienda Ospedali Riuniti Villa Sofia Cervello, Università degli Studi di Palermo, Pale

Twin girls affected by Primary Microcephaly with occipital-frontal- circumference (OFC) of -2SDs / -3SDs and a mild-moderate cognitive delay are reported. At the age of 10 years due to growth retardation and behavioral disturbances, laboratory investigations on thyroid' s function disclosed a high level of Ab TPO and a diagnosis of Hashimoto's thyroiditis was made. To our knowledge, the association primary microcephaly and acquired Hashimoto's thyroiditis in twins has not been previously described. This report may give further support to a genetic susceptibility is on the basis of HT disorder.

These 11 years-old- twins, who were born from Italian 's origin parents, soon after their birth were adopted by a well-of Sicilian family. Their small heads were noticed since the first days of life. The developmental stages were reached with a slight delay, but the twins attended the nursery and primary school with support . At the age of 10 years persisting growth retardation and the recent appearance of behavioral disturbances required an endocrinological assessment with thyroid laboratory investigations that disclosed a diagnosis of Hashimoto's thyroiditis .

Twin 1. At the physical examination she presents in good condition. Her weight is 25 Kg. (3 pc), height 136 (25 pc) and OFC 48 (-2 DSs). She shows a distinctive receding forehead, protruding and large ears. Syndactyly between second and third toes are present. Heart, thorax, abdomen and genital organs are normal. She attends elementary school with mild insufficiency. Her I.Q. is 60 (WISC).

Twin 2. Clinical examination and laboratory investigations are common to that of her sister with exception of Ab TPO less increased 447 (n.v. mx 60). The weight is 24 Kg. (> 3 pc), height 134 (10 pc), OFC 47,5 (-2/-3 SDs) and I.Q. is 58 (WISC).

Routine laboratory investigations including hemogram, electrolytes, plasma and urinary amino acids, thyroid testing (TSH, FT3, FFT4) are normal. Thyroid Peroxidase Antibodies (TPO) displays high value: 1.041 UI/ml (n.v. mx 60) in twin 1 and 447 UI/ml in twin 2. Brain MRI, EEG, ECG and Echocardiogram are normal. Ultrasound investigation , the thyroid presents with normal dimension and scattered area of hypoechogenecity in the twins.

In the twins WES investigation is in progress.

The twins present with primary microcephaly and acquired Hashimoto's Thyroiditis. They show an -2SDs/ -3 SDs OFC measurement and a quite sufficient cognitive development. Both attend the elementary school with scholastic performance just below the normal standard. At the age of 10 years the consultant endocrinologist for their short stature and for recent appearance of behavioral disturbances required to carry out laboratory investigations including thyroid tests that disclosed high levels of Ab TPO with normal T3, T4, TSH levels. Diagnosis of HT was made with no goiter.

Primary microcephaly (also called "vera") refers to congenital abnormal cerebral growth more frequently transmitted as an autosomal recessive inheritance, not associated with abnormalities of other organs and with a not progressive course (1-2). The measurement of the OFC usually range between -2SDs and -3SDs and a cognitive delay is more commonly variable from mild to moderate. The Brain MRI shows no abnormalities with the exception of the small cortex (3).

Hashimoto's Thyroiditis is a not uncommon autoimmune disorder presenting with a spectrum of thyroid function anomalies with or without goiter. Pathogenesis of this disorder is still not completely known , but immune defect in association to environmental factors in genetic susceptible individuals seems the most accredited pathogenesis (4-5).

The congenital origin of microcephaly presented by the twins and the diagnosis of HT with the positivity of Ab TPO registered at the same age in both the girls seem to confirm a genetic susceptibility in association with acquired trigger factors in the development of the HT disorder.

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ID 036

TITLE: **MATCHING CLINICAL TRIALS WITH PATIENTS: GLOBAL EHR BASED PATIENT RECRUITMENT**

L. Magalhaes; B. Erdoğan; D. Aronsky

Clinerion Ltd

Patient recruitment for clinical trials is a well-known problem that has been extensively documented. Challenges in patient recruitment are the most prominent reason for clinical trial delays. Such delays have a knock-on effect on the entire drug development process, costing pharma companies lost sales revenues. Beyond financial considerations, delays also result in avoidable suffering of patients. These challenges can be overcome by introducing a technology-assisted process for finding patients who could benefit from inclusion in a clinical trial.

We propose a system which performs real-time, Big Data analytics on electronic medical records from connected hospitals to identify patients for clinical trial recruitment. The system can perform data-assisted protocol optimization to speed up the protocol development process, site feasibility evaluation to improve site strategy (fewer sites with more patients), and patient search to find eligible patients for recruitment with 24/7 notification of new candidates.

We present three example cases which demonstrate the results of use of the system:

1. during recruitment for an ongoing dyslipidemia trial, where recruitment was behind schedule

2. for recruitment for an atherosclerosis trial where recruitment could be completed ahead of schedule

3. in a series of trials wherein the identified number of patients consistently exceeded the Investigators' expectations.

This electronic patient recruitment system addresses the critical barrier of slow patient recruitment. It enables search and identification of suitable clinical trial candidates using the electronic records of multiple hospitals in real time. The system has been shown to find 10-30x more patients than traditional methods and maintains patient privacy.

ID 037

TITLE: **THE IMPORTANCE OF ECHOCARDIOGRAPHIC AND BIOCHEMICAL PARAMETERS FOR OUTCOME OF PERINATAL ASPHYXIA**

M. Vasiljević; V. Vukomanović; S. Prijić; Z. Rakonjac; J. Martić; K. Pejić; G. Marković

1Institute for healthcare of mother and child of Serbia "Dr Vukan Čupić", Belgrade, Serbia

Heart disorder among newborns with asphyxia can contribute to damage of various organs and increase of mortality. Effects of heart disorders are usually contemporary, but they can also lead to cardiogenic shock and death. Aim of work: Gold is to establish the importance of echocardiographic monitoring and analysis of certain enzymes and biochemical markers of cardiocirculator insufficiency for surviving and duration of hospitalizatiom among newborns with perinatal asphyxia.

There were 34 examined newborns; 17 with perinatal asphyxia: (i) APGAR 5 < 6/10 (ii), lactate > 2,5mmol/l and base excess (BE) > 10mEq/l in first 6 hours (iv) disorder of one or several organic systems (group I) and 17 asymptomatic newborns.

We established that bad prognostic parameters for surviving (in group I and unified group) are: a) decrease of pH in first day, decreased BE in first and third day and increase of lactate in third day b) increase of troponin I in third day c) decrease of LVEDD in first day and decreased LVFS in third day d) more days on mechanic ventilation and inotropic stimulation e) increased NT-ProBNP and eccentricity index in first and third day and its positive trend (for unified group). Duration of hospitalization (in unified group) depends on: 1) lactate level in first day and NT-proBNP in third day 2) LVEDD and LV EF in first day.

Echocardiography, especially eccentricity index and its trend, analysis of NT-proBNP, lactate and BE in first and third day are important to estimate the result of the disease among newborns with perinatal asphyxia.

ID 038

TITLE: **BUILDING A PREDICTIVE SCORE OF VACCINATION RESPONSE FROM A TRANSCRIPTOMIC APPROACH: FORGING THE PATH TOWARDS PERSONALIZED IMMUNIZATION**

N. Cotugno 1,2; I. Pepponi 1,2; E. Manno 1; P. Zangari 1; D. Amodio 1; S. Rocca 2; E. Morrocchi 2; L. Sessa 1; S. Bernardi 1; P. Rossi 1; P. Palma 1

1. Academic Department of Pediatrics (DPUO), Bambino Gesù Children's Hospital-University of Rome Tor Vergata, Rome, Italy; 2. Department of Public Health, University of Rome "Tor Vergata", Rome, Italy

The number of children affected by chronic diseases with special vaccination needs due to a suboptimal response to vaccinations is continuously burgeoning. Tailoring immunization practices in such populations represents one of the major challenges in pediatric public health system. In this scenario, predictive markers of immunogenicity, as well as signatures of immune responses are still missing and would improve the selection of personalized immunization practices especially in immune compromised patients. We here dissected in one of the pediatric population with special vaccination needs, such as HIV infected children, whether transcriptional analysis of sorted B cell from samples collected before Influenza Trivalent Inactivated Vaccination (TIV) could be used to build a predictive model of vaccination response.

PBMCs, collected before TIV from 23 vertically HIV infected children under ART and virally controlled were stimulted with H1N1 peptides (stim) or left in medium (med) for 16 hours. Fixed numbers of Resting memory B cells (RM; CD19+IgD-CD27+CD21+), activated memory (AM; CD19+IgD-CD27+CD21-) and Double negative (DN; CD19+IgD-CD27-) B cells were sorted (FACS Aria II-BD) and analyzed by multiplexed-qPCR for 96 genes (Fluidigm, Biomark). The ability to respond to TIV was assessed through hemagglutination Inhibition Assay (HIV) and ELIspot and patients were classified as Responders (R) and Non Responders (NR).

Twelve NR and 11 R were analyzed for gene expression differences in 3 different subsets (AM, DN, RM) and 3 conditions (med, stim or Δ (stim-med)). Differently expressed genes between R and NR were selected and tested with the Adaptive Boosting Model (ADA) to build the prediction score (fig. 1). The score obtained from RM in med revealed the best prediction compared to AM and DN, assuming a predicted probability greater than 0.50 is classified as a response, only one misclassified patient in the NR resulting in 94% (17/18 for RM unstimulated data) model accuracy. In particular 2 genes, CD69 and IL2RA were used at least 40% of the time in ADA Boost's internal iteractive classification. When using the Δ in RM, ADA Boost model misclassified 3 patients (1 non-responders and 2 responder) and gave 82% (14/17 for REM stimulated - unstimulated data) model accuracy. To build this model, only three genes (CD69, CCR2, BATF) were used in the ADA Boost model. Interestingly, though the model accuracy is lower than RM med data (82% vs. 94%), these analysis revealed an higher confidence in the predictions scores.

These data show how a predictive biostatistical model applied to transcriptional analysis deriving from in-vitro stimulated B cells may provide novel and predictive vaccination efficacy scores in immune compromised patients such as HIV. Future studies on larger cohorts are needed to validate such OMICS approaches in the context of vaccination trials.

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ID 039

TITLE: **THE "LACTARIUM" IN THE ENTERAL FEEDING OF PRETERM NEWBORN: THE EXPERIENCE OF NEONATOLOGY UNIT OF ST.JOHN HOSPITAL IN ROME**

G. Maragliano; A. Di Paolo; P. Caterini; A. Gallo; M. R. Lucignani

Neonatology and NICU Unit, St.John Hospital, Rome, Italy

Human own mother's milk is the gold standard for the feeding of preterm infants, because of its relevant effects on growth, neurologic development, gut and immunologic maturation. For these reasons, it's important to provide human milk from the first hours after birth.

Soon after birth, preterm newborns are separated from their mothers because of intensive care clinical needs, with consequent significant problems regarding the enteral feeding of these patients.

In the last 10-15 years, Human Milk Banks have been organized in several Neonatal Intensive Care Units, to use human donor milk as the best alternative, when own mother's milk is unavailable or in short supply, as recommended by the World Health Organization and American Academy of Pediatrics.

The Lactarium of Neonatology and NICU of St.John Hospital in Rome is a human milk bank dedicated to specific enteral feeding needs of preterm newborns recovered in our hospital. The Lactarium began its activity in 2003, with the primary goal to collect human milk from the early hours after preterm birth, in order to establish a good human milk production, for every preterm mother, in the following weeks.

The organization of Lactarium is defined by a specific Hospital Procedure, according to the Guidelines of Italian Society of Neonatology and to the Italian law dispositions (State-Regions Conference, agreement 12.05.2013 - GU n.32, 02.08.2014; Ministry of Health, Recommendation 05.12.2016)

The Lactarium is able to provide enteral feeding with own's mother and human donor milk for all preterm newborns recovered in the Neonatologu and NICU of St.John Hospital, for the whole lenght of hospital stay. The management of Lactarium is committed to n.2 pediatric nurses, specifically trained on human milk feeding. Their activity is dedicated to:

1. support preterm mothers during beginning and establishment of breast milk production and feeding;

2. selection of donor mothers (from 24-25 weeks of gestational age), through anamnesis and sero-infectivological screening;

3. Collection, treatment, control and storage of human donated milk.

A room for welcoming mothers is present in the Unit, in which they can express the milk by using an electric vacuum milk extractor, with an individual sterile kit for each mother. Free access to the room is warranted, and mothers can personally modulate the rythm and frequence of milk extraction. Human donated milk is pasteurized according Holder method, and frozen. Before and after pasteurization microbiologic controls are performed. Preterm newborns recovered in the Unit are fed with human milk donated by mothers of same gestational age, to respect and satisfy the specific nutritional needs of each preterm newborn. Minimal enteral feeding is performed from the first hours after birth, with progressive increase on the base of newborn's tolerance. Fortification of human milk is started at the achievement of 100 ml/Kg/day.

Our experience, in agreement with the available literature data, confirm that the presence of a human milk bank is able to reduce significantly the use of preterm formulated milks, without influencing the rate of breastfed infants at discharge.

Our clinical experience is also in agreement with more recent studies, confirming the clear benefits of human milk in preterm feeding, specifically related to prevention of NEC, BPD, ROP and to neurologic development.

ID 041

TITLE: **IN SILICO CLINICAL TRIALS FOR PEDIATRIC ORPHAN DISEASES: A CONGENITAL PSEUDARTHROSIS CASE STUDY**

L. Geris 1-3; A. Carlier 3,4

1. GIGA In Silico Medicine, University of Liège, Liège, Belgium; 2. Prometheus, R&D division of Skeletal Tissue Engineering, KU Leuven, Leuven, Belgium; 3. Biomechanics Section, KU Leuven, Leuven, Belgium; 4. MERLN Institute for Technology-Inspired Regenerative

Today over 350 million patients worldwide are affected with orphan diseases. To tackle the associated challenges, in silico models and virtual clinical trials are increasingly explored. In this study we combined mechanistic modeling with data-driven modeling in an investigative in silico clinical trial to assess the (beneficial) effect of bone morphogenetic protein (BMP) treatment on fracture healing in patients with congenital pseudarthrosis of the tibia (CPT). Although the exact etiology of CPT is still highly debated, it is hypothesized that a mutation in the Neurofibromatosis type 1 (NF1) gene results in an altered phenotype of the skeletal cells and impaired bone healing.

This study builds on work previously published by Carlier et al (Sci Rep 2016) in which a multiscale model of bone fracture healing was succesfully applied to capture the phenotypical variation in healing respone typically found in the NF1-CPT population. This was done throught the alteration of the parameter values of eight key factors which describe the aberrant cellular behaviour of cells affected by NF1 mutation. In the current study, we used the NF1-CPT model to generate a set of 200 virtual patients. Each virtual patient was simulated to receive no treatment and a BMP treatment. Results from these 400 healing simulations were processed using machine learning techniques to look at patient stratification and biomarker identification.

The results show that the degree of severity of CPT is significantly reduced with BMP treatment, although the effect is highly patient-specific. Moreover, four distinct patient groups could be identified: asymptomatic (healing with and without treatment), responders (not healing without treatment but healing with treatment), non-responders (not healing with or without treatment) and adverse responders (healing without but not with treatment). The parameter representing the cartilage formation rate can be used as a biomarker to distinguish between the first 3 categories. Additional analyses are required to fully understand the adverse response mechanism.

This study demonstrates how mechanistic and data-driven modeling are potentially useful tools to simulate and mine data from in silico clinical trials, stratify patient populations, and improve current treatment strategies.

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ID 044

TITLE: **LESS X-RAYS, BETTER DIAGNOSTICS**

P. Kruczek; P. Szymański; A. Sobczak; P. Kwinta

University Childrens Hospital, Jagiellonian University Medical College, Kraków, POLAND

Neonatal Intensive Care Unit of University Children's Hospital in Kraków, Poland was funded in 1998 and nowadays serves as a referral tertiary center. In the last 10 years we managed to almost completely reduce the number of X-rays performed in the Unit and substitute them with ultrasound diagnostics.

The unit owns 2 stationary ultrasound machines and 1 portable within the ambulance. Each patient has an 'ultrasound total body scan' before and during transportation, on admission & discharge, during hospitalization as a routine check up and in case of clinical problems.

/Presented as images - via pdf file, the poster will be send via email/

LUNG DIAGNOSTICS:

- RDS

- PNEUMOTHORAX

- ATELECTASIS, PLEURAL EFFUSION, PNEUMONIA

- PULMONARY EMBOLISM

GASTROINTESTINAL TRACT:

- ESOPHAGEAL ATRESIA

- TRACHEOESOPHAGEAL FISTULA

- SIGMOID STENOSIS

- VOLVULUS

INDWELLING DEVICES:

- ENDOTRACHEAL TUBE PLACEMENT

- VENTRICLE PUNCTURE

- CENTRAL LINES

clotting recognition, position, controlled insertion

Ultrasound is a safe, quick and repeatable diagnostic tool helpful in making clinical decisions.

ID 045

TITLE: **EARLY ADVERSITY, TOXIC STRESS AND SOCIO-EMOTIONAL DEVELOPMENT DURING CHILDHOOD: HOW EPIGENETIC PROCESSES CONTRIBUTE TO SHAPING PRETERM INFANTS DEVELOPMENT**

L. Provenzi; R. Montirosso

Center for the at-Risk Infant, Scientific Institute IRCCS Eugenio Medea

Very preterm (VPT) birth is a leading cause of disease and mortality during infancy and childhood worldwide. Even in absence of critical medical conditions, VPT infants need long-lasting hospitalization in the Neonatal Intensive Care Unit (NICU) during which they are exposed to frequent invasive and painful skin-breaking procedures (i.e., pain-related stress). These early exposure to adversity is a source of toxic stress which might contribute to long-lasting programming of brain, behavioral, and socio-emotional development. Epigenetic processes (e.g., DNA methylation of the stress-related serotonin transporter gene SLC6A4 and increased telomere length erosion) might contribute to the long-lasting programming of childhood development. In the present oral contribution we present findings from a longitudinal study on the epigenetic vestiges of early pain-related stress exposure in a sample of VPT infants compared to full-term (FT) controls.

82 infants were enrolled (51 VPT and 31 FT). Cord blood was collected at birth for both groups and peripheral blood was obtained at NICU discharge for the VPT group. The number of skin-breaking procedures was obtained from medical records. At 3 months (corrected for prematurity), all infants participated to a laboratory procedure designed to elicit age-appropriate stress through the manipulation of maternal behavior (i.e., the Still-Face paradigm) and temperament was assessed through maternal reports. Behavioral (i.e., negative emotionality) and physiologic stress regulation (i.e., salivary cortisol) during the Still-Face paradigm was measured.

No differences emerged in SLC6A4 methylation at birth between the groups. In the VPT group, greater pain-related stress was significantly associated with SLC6A4 methylation increase from birth to discharge and with increased telomere erosion. Increased SLC6A4 methylation at discharge was predictive of heightened behavioral response to the Still-Face paradigm and of lower scores at the Orienting and Approach temperament scales in VPT infants. Finally, the increased telomere length erosion from birth-to-discharge predicted dampened salivary cortisol reactivity in VPT infants, but not in FT infants.

The application of the new omics (i.e., epigenomics) to the study of early development in at-risk infants holds promising of revealing the biochemical pathways through which early adversities are embedded in the lost-lasting developmental trajectories of infants and children. As epigenetics processes (e.g., DNA methylation and telomere length erosion) contribute to behavioral and socio-emotional development even in absence of severe medical conditions, pediatricians are warranted to deal with at-risk conditions assuming a broader care perspective. This innovative and scientific sound perspective implies methodological and clinical challenges for pediatricians.

ID 047

TITLE: **FC-FEV1: NEW APP PATIENT ORiENTED. THE CYSTIC FIBROSIS CASE STUDY**

I. Tagliente 1; S. Bella 2; V. Lucidi 2

1. DIET, Faculty of Engineering University of Rome 'La Sapienza', Italy; 2. Specialist Medicine Department, Complex operational units of Cystic Fibrosis, Children's Hospital Bambino Gesù, Rome -Italy

Cystic Fibrosis is a chronic disease that affects 1 in every 3,000 people. One of the most sensitive organs in the progress of the disease is the lung and thus the airways. A periodic screening of lung function with spirometry is recommended by guide line address to promptly start a specific treatment in case of exacerbation. The Bambino Gesù Children's Hospital (Rome-Italy) is currently ranked as the Regional Support Center for patients with Cystic Fibrosis (CF). Since 2001 is active a service telemonitoring of patients in Telemedicine. The Aim of the project proposed here, is to develop an App for patients with Cystic Fibrosis to improve new Telemonitoring service, to improve the application of the international guidelines and increase the self management and patient autonomy.

During a year of developing process, was possible to develop an innovative App. The developing process was followed by doctors, engineer and patients. Thanks to the synergy between the stakeholders was possible to introduce in to the App, not only the spirometry test transmission but also individual information as genetic mutation, symptomatology and life style information. During the alfa test was also possible to understand the user-friendly feedback. The project was sponsored by the ONLUS Cystic Fibrosis Association.

During a year of developing process, we wanted to develop an App dedicated to CF patients, able to acquire also spirometry data by a special turbine. This App is able to share spirometry test with additional clinical information of the patient. The crypted information sent by patients, can be accessed by doctors of the Telemedicine service for Cystic Fibrosis by Web interface provided with decryption key. The App, developed in Italian, will enable CF patients to have access to spirometers by extending the screening activities and facilitating the local doctors. The development of the App, for CF patients, is well connected to the construction of an integrated platform for the DH in progress at our Hospital. The app could be an important element of integration in order to increase the information available both to clinicians, supporting a better knowledge and management of disease e.g., improving the analysis of comorbidity and patients, increasing compliance, treatment adherence and self-empowerment.

The App is able to connect the Spirometry SmartOne MIR by Bluetooth low energy, download and share FEV1 value. The personalisation for cystic fibrosis patients give the opportunity to share additional information as healthy perception, drugs, days of hospitalisation and related information.

The data acquired give a positive feedback (figure 1) also related to the compliance of patient to the self management activity and the additional information related to the life style of the patient. The elaboration of data can be helpful to adjust the therapy or pronely hospitalization but also to new comorbidity study.

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ID 048

TITLE: **MINI-INVASIVE APPROACH IN PEDIATRIC EPATOBILIARY AND PANCREATIC SURGERY: NEW THECNOLOGY APPLICATION FOR CHALLANGING SURGERY**

R. Angelico 1; C. Grimaldi 1; M. C. Saffioti 1; R. Pariante 2; C. Dionisivici 3; L. Dello Strologo 4; G. Torre 5; A. Inserra 6; M. Spada 1

1. Epatobiliopancreatic Surgery and Abdominal Transplantation Department, Bambino Gesù Pediatric Hospital IRCC, Rome; 2. Anesthesia Department, Bambino Gesù Pediatric Hospital IRCC, Rome; 3. Metabolic disease Department, Bambino Gesù Pediatric Hospital IRCC, Rome; 4. Nephrology Department, Bambino Gesù Pediatric Hospital IRCC, Rome; 5. Epatogastroenterology Department, Bambino Gesù Pediatric Hospital IRCC, Rome; 6. General and Thoracic surgery Department, Bambino Gesù Pediatric Hospital IRCC, Rome

Mini-invasive approach in liver and pancreas surgery has been wildly used in adult patients, showing the advantage of less post-operative pain and complications, small surgical incision, early patient mobilization and shorted hospital admission. Moreover, in the last years the benefits of laparoscopic approach have been reported in the living-donor liver and kidney transplantation, giving indirect benefit to the paediatric recipient in terms of graft outcomes. However, in the children mini-invasive liver and pancreas surgery is still limited due to the complexity of the surgical procedures, the lack of adequate laparoscopic instruments for small child and the long learning curve in laparoscopic and hepatobiliopancreatic surgery.

We prospective collected all data of children who underwent mini-invasive liver and pancreas surgery at the Hepato-bilio-pancreatic Surgical Unit of the Bambino Gesù Pediatric Hospital IRCCS between July 2016 and July 2017. Clinical and surgical characteristics were collected in a prospective database.

Out of 40 children who underwent major hepatobiliopancreatic surgery at a single institution in one year, 7 (18%) patients were treated by mini-invasive surgery of the liver and pancreas. Surgical procedures included: 2 laparoscopic distal pancreasectomy for insulinoma (1) and pancreatic cystic lesion (1); 1 laparoscopic non anatomical hepatectomy for hepatic emangiohendotelioma; 2 mini-invasive epatico-enteroanastomosis for choledochal cyst; 2 mini-invasive Kasai procedure for biliary atresia. Two-dimensional (2D) high-quality vision was used in 4 cases, while 3 procedures were performed with three-dimensional (3D) high-quality vision with imaging magnification. The mean age at surgery was 26 (3-78) months, and the mean weight was 18 (4-35) Kg. None required post-operative intensive-care stay and the mean hospital admission was 7 (4-12) days. All patients had early mobilization by day 2 and the post-operative abdominal pain was easily managed. All children had a good recovery and none experienced complications. In the same period, full laparoscopic approach was used in 14 adult living-donors, who donated in favour of their children: 7 laparoscopic left hepatectomies for living-donor liver transplantation and 7 laparoscopic nephrectomies for living-donor kidney transplantation were performed, with uneventful post-operative course.

Our experience shows that the mini-invasive approach in liver and pancreatic surgery is safe and feasible in children. Complex hepatobiliopancreatic laparoscopic procedures are possible also in very small patients and the use of 3D technology might improve the surgical performance. An adequate learning curve in laparoscopic and hepatobiliopancreatic surgery is essential for the good outcomes of the mini-invasive approach in paediatrics and in living-related organ transplantation.

Figure legend:

Example of mini-invasive approach for hepatectomy: a) Computer tomography showing the liver tumour; 2) Mini-invasive approach for non-anatomical liver resection; c) Intraoperative imaging of non-anatomical hemiepatectomy; d) Post-operative surgical incision after 20 days from liver resection.

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ID 049

TITLE: **EHEALTH & MHEALTH APPLICATION FOR COMORBIDITY STUDY**

I. Tagliente 1, S. Bella 3,R. Schiaffini 4, M.Chinari 3 V. Lucidi 2

1. Department of Information Engineering, Electronics and Telecommunications (DIET), Faculty of Engineering, University of Rome 'La Sapienza', Italy; 2. Specialist Medicine Department, Complex operational units of Cystic Fibrosis, Children's Hospital Bambino Gesù, Rome – Italy; 3. Medical-Surgical Department of Pediatric Cardiology, Bambino Gesù Pediatric Hospital, Rome, Italy; 4. Endocrinology and Diabetes Palidoro Unit, University Department of Pediatric Medicine, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy

This pilot project is one of the first applications of Telemedicine solution (Telemonitoring) for comorbidity and translational study. A total of 20 patients with Diabetes and/or Cystic Fibrosis were enrolled to a telemedical intervention and assigned to different Groups.

The patients, enrolled as voluntarily, were selected as follows: 5 with consecutive Type1 Diabetes Mellitus and assigned to Group 1; 5 with Cystic Fibrosis already under Telemonitoring protocol and assigned to Group 2; 5 with consecutive Type1 Diabetes Mellitus and Cystic Fibrosis already followed at Bambino Gesù Children's Hospital, Unit of Endocrinology and Diabetes and by Telemedicine group of Cystic Fibrosis Unit and assigned to Group 3; and 5 voluntary without disease assigned to Group 4 (Control group).

The Aim of this study was to analyze possible variation of Heart Rate Variability, depending on the glycaemia value or Forced Expiratory Volume in 1 second in adolescent and adult patients with diabetes and/or Cystic Fibrosis by telemedicine protocol and analyze the correlation between compliance and patient's technology background. In the first four months of Telemonitoring we received 855 glycaemia transmissions and 378 spirometry test transmissions. We show a good compliance trend especially in the patients with technology background. For the patient or family patients or patient's family members without technology background, we offered telephonic assistance to verify the home procedures, and to store and download the data. Preliminary analysis of data showed no overall significant differences in Heart Rate Variability parameters among the three groups and a important decrease of RMSSD in patient with decrease of FEV1 (Figure 1).

More months of observation are needed to show possible correlation between Forced Expiratory Volume in 1 second, glycaemia value and Health Rate Variability. More study are needed to analyse if RMSSD could be an additional indicator of decrease of disease. Various Telemonitoring solutions could be import tools for new international comorbidity research. Easy methodology and standard communication protocol to share the data from home to Hospital has taken into consideration planning a Telemedicine protocol assistance.

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ID 051

TITLE: **INTEGRATED GENETIC ANALYSIS: HARNESSING THE POWER OF NGS**

A. Obregon-Tito; C. Lee; J. Li; M. Teguh; Y. Shen

Fulgent Genetics, Temple City, California

The advent of next-generation sequencing (NGS) has revolutionized clinical genetic testing. Empowered by NGS technologies, clinical genetics has transitioned from single gene analysis to multigene panels, exome sequencing and emerging genome sequencing. Still, chromosomal analysis remains the first line of genetic testing for multiple conditions.

Chromosomal analysis is well-established in the clinic, with multiple applications including prenatal, postnatal and somatic testing. While karyotyping is still the gold standard for genome-wide analysis of large rearrangements, with or without net gain or loss of genetic material, the study of copy number variants is often equated to microarray platforms. While it is clear that microarray analysis is an appropriate tool to detect genetic imbalances, it presents some challenges that might be overcome by NGS technologies. Here we propose an NGS based approach to chromosomal analysis that exhibits increased sensitivity with an unbiased representation of the whole genome. Taking advantage NGS, we present pair-ended, low coverage whole genome sequencing as an alternative to microarray testing. We tested 31 samples from cell lines and 19 deidentified controls, using a standard microarray platform (4X180K copy number variant and SNP custom array with a resolution of 1kb in selected disease genes, up to 50kb in OMIM genes and 150kb in the rest of the genome) and low coverage whole genome sequencing. All copy number variants identified by the microarray platform were detected by the NGS-based approach, while additional 46 and 6 copy number variants, in the cell lines and control individuals respectively, were identified by the NGS-based approach only. All the identified variants were verified by orthologous methods. Compared to microarray analysis, the NGS-based test exhibits increased sensitivity, with a detection limit of up to 200bp when average sequencing coverage is 1X and identifying exact break points when higher coverage is used. In addition, NGS-based chromosomal analysis allows the identification of structural abnormalities that microarray is unable to detect.

While up to now, karyotyping has been the only tool available to identify balanced translocations, NGS-based chromosomal analysis allows the positional reconstruction of the genome, revealing possible gene fusions and other balanced chromosomal aberrations. Moreover, primer design for segmental duplication, a critical mechanism of evolution, is extremely difficult for areas of high homology, increasing the probability of missing variants in this region when using a primer-based technology such as microarray, MLPA or qPCR. In contrast, a combination of NGS-based chromosomal analysis and stringent bioinformatic protocols, allow correct mapping of reads with up to 1 base difference in 300 bp DNA block (~99.7% identity) correctly computing CNVs in areas of segmental duplication. More than half of CNVs discovered in this study were located in duplicated regions.

Considering the pace and the direction in which clinical genetic testing is moving, integrated testing options might be an appropriate target for the new generation of genetic tests. While microarray analysis is an independent platform, NGS-based approaches can be integrated in a step-wise testing algorithm that could result in a cost and time effective alternative to current strategies. Thus, NGS constitutes a suitable technique to chromosomal analysis in the post-genomic era.