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Rapid Whole-Genome Sequencing: Faster Diagnosis for Rare and Confounding Conditions

A collaborative effort between the UPMC Newborn Medicine Program, the Division of Medical Genetics at UPMC Children's Hospital of Pittsburgh, and the Institute for Precision Medicine (IPM) — a collaborative effort between the University of Pittsburgh and UPMC — is providing rapid genomic testing for NICU patients who present with rare and difficult to diagnose conditions for which there may be an underlying genetic cause.

The UPMC Genome Center within the IPM, directed by Annerose Berndt, PhD, is providing rapid, low-cost, whole-genome sequencing to support clinical diagnostics and research initiatives, not only for NICU patients, but more broadly for cancer and immunotherapy research throughout UPMC and the University of Pittsburgh.

One of the first efforts of the UPMC Genome Center is examining the efficacy of whole-genome sequencing in critically ill infants admitted to the NICU at UPMC Children's. Rapid, whole-genome sequencing may, in some cases, identify possible genetic-based diseases in an expedient manner.



Thomas Diacovo, MD, chief of the UPMC Newborn Medicine Program, is leading the NICU efforts at UPMC Children's together with Jerry Vockley, MD, PhD, director of Medical Genetics at UPMC Children's, and counterparts at the IPM, including Adrian Lee, PhD, on the NICU sequencing project.

"In addition to making a rapid diagnosis that can have profound implications on clinical care, "A crucially important aspect of any genetic profiling and sequencing program is helping families to understand the genetic information, its implications for the individual and family at-large, and how to interpret the information to make informed decisions for care and follow-up. This information has to be given in the appropriate context and with the necessary assistance to understand what it may mean for the patient and family," says Dr. Diacovo.

UPMC Children's Participates in New National Precision Medicine Clinical Trial

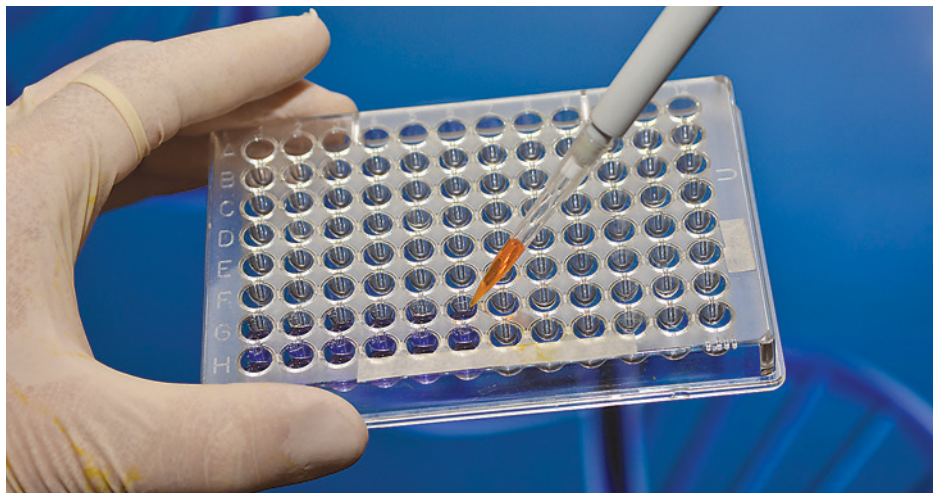
A new multicenter clinical trial sponsored by the National Center for Advancing Translational Sciences (NCATS) at the NIH is studying the use of rapid, targeted, next-generation sequencing technology to diagnose underlying genetic causes for disease in high-risk neonates.

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Over a five-year period, the trial, led by researchers at Floating Hospital for Children at Tufts Medical Center, will enroll neonates who may have a variety of genetic disorders, but whose diagnoses were unable to be determined through the use of standard testing. The new study entails the conduction of whole-genome sequencing of the neonates, as well as a targeted examination of 1,722 genetic disorders known to afflict newborns. The study will then compare the results between the targeted screening and the whole-genome sequencing to determine the viability of the targeted panel approach.

UPMC Children's is participating in the trial with Tufts Medical Center and four other institutions: Rady Children's Institute for Genomic Medicine, Mt. Sinai Hospital, University of North Carolina at Chapel Hill, and Cincinnati Children's Hospital.



"This study holds the promise of profound changes in how newborns are screened for life-threatening disorders, which is currently limited to a dozen conditions. For critically ill patients, time is of the essence and a diagnostic odyssey is out of the question.

Many of these disorders will have treatments that may prevent or slow the progression of disease, but only if we know the cause and can find it quickly. That's the promise of this trial," says Dr. Diacovo.

Liza Konnikova, MD, PhD, Joins Division of Neonatology



The Division of Neonatology at UPMC Children's Hospital of Pittsburgh is pleased to welcome **Yelizaveta (Liza) Konnikova, MD, PhD.**

Previously with Boston Children's Hospital where she completed her pediatric residency, neonatology fellowship, and postdoctoral training, Dr. Konnikova is a physician-scientist

specializing in the area of mucosal immunity and its relation to the development of necrotizing enterocolitis (NEC) and very early-onset inflammatory bowel disease (VEO-IBD).

Past work by Dr. Konnikova has utilized mass cytometry (CyTOF) with mucosal tissues that allows for the identification of populations of immune cells important in VEO-IBD. This technique allows for the detection, at the single cell level, of up to 40 or 50 different cell types simultaneously. "This is beneficial for research because it lets you obtain a very good idea of what immune cells are present and their functions, which in the setting of a rare condition, or with the very small amounts of tissue that we get from humans, especially infants, becomes incredibly important. With a limited amount of tissues to analyze, dividing them up to study multiple

individual cell types is not always possible. This technique circumvents that challenge and provides us with a global view from very limited tissue samples," says Dr. Konnikova. Dr. Konnikova also has developed cryopreservation techniques for storing mucosal tissues so that they can remain fully functional and viable during subsequent analyses.

Dr. Konnikova's current research involves the use of CyTOF to perform functional studies and immunophenotyping to understand the development of mucosal immunity from fetuses to adults, as well as to identify the immune abnormalities in NEC and other GI disorders. With the support of a current Crohn's & Colitis Foundation of America Career Development Award, Dr. Konnikova is working to understand how the mucosal immunity differs in cases of VEO-IBD.

Dr. Konnikova's future plans include working on expanding a translational research program in the neonatal intensive care unit, and the establishment of a neonate tissue bio-bank that can be leveraged in the future for further studies.

Bubble CPAP and Preterm Neonates: A Noninvasive Ventilation Approach to Quality Improvement

As the literature shows, preterm neonates, and particularly extremely preterm neonates who are less than 28 weeks gestational age, are at a high risk for developing bronchopulmonary dysplasia (BPD), which carries with it significant rates of morbidity and mortality.



The use of mechanical ventilation for respiratory support, coupled with the use of pulmonary surfactants, increases these risks. "In those neonates with a gestational age less than

28 weeks, the literature shows a nearly 40 percent rate of BPD. This has both short- and long-term complications for the patients and their families. With the implementation and use of Bubble CPAP, a noninvasive, safe, and effective method of respiratory support for spontaneously breathing babies, we believe rates of BPD will be dramatically reduced, along with overall use of mechanical ventilation and other support measures that have been part of our existing standard of care," says **James Kiger, MD, MS**, medical director for Newborn Respiratory Care and Bubble CPAP implementation lead.

Implementing the Protocol

Bubble CPAP protocol development began in February 2018, at which time the implementation of a multidisciplinary committee was formed, consultations and training with experts in the field from Columbia University in New York occurred, and an extensive literature review of the established evidence of Bubble CPAP use in preterm neonates was undertaken. The protocol moved into active use in the NICUs at UPMC Children's and UPMC Magee-Womens Hospital in September 2018 after all the necessary equipment, training, education, and protocol outcomes and practices were established and executed.

"Longer-term, it is absolutely part of our plan to implement the Bubble CPAP protocol at all of the NICUs in our system once testing and initial outcomes are determined. One of the benefits of using Bubble CPAP is that it is not

an invasive mechanical ventilatory support, so it could easily be implemented in level II NICUs for late- or mid-term infants," says Dr. Kiger.

Protocol Complexities and Implementation Challenges

Implementation of the Bubble CPAP protocol is not without its risks and challenges. Because the protocol entails its use in neonates up to 32 weeks gestational age (more or less time on the device is possible depending on the specific needs of the patient), there is the potential it may be required to support infants for up to nine weeks. "The changes needed to administer this protocol are fairly intensive and require a strict adherence to the use and safety measures that we have put in place. Vigilant monitoring of the positioning of the breathing apparatus and airway pressure are required to ensure the proper levels of positive pressure ventilation are delivered at all times," says Dr. Kiger.

For premature infants with respiratory effort, the goal is for application of Bubble CPAP immediately after delivery and maintenance on it for as long as necessary. In fact, implementation at the time of delivery is key to prevent the development of BPD. "We see so many infants in the NICU for a variety of reasons. There will be cases when intubation and the use of surfactant simply cannot be avoided. However, by placing the majority of spontaneously breathing premature babies on Bubble CPAP, we will minimize the need for potentially injurious endotracheal intubation and invasive ventilation," says Dr. Kiger.

Outcomes and Benefits of the Protocol

The Bubble CPAP initiative in the UPMC Newborn Medicine Program is designed to provide a number of clinical benefits for preterm neonates. "We hope to achieve marked reductions in oxygen exposure, mechanical ventilation, morbidities associated with BPD, length of hospitalization, and the use of agents needed to treat the condition," says Dr. Kiger.

The administrative and cost benefit potentials from the adoption of Bubble CPAP extend to reductions in the number of ventilator days and corresponding fleet size, secondary care costs associated with BPD (short- and long-term), and other financial benefits.

"Within just the first two weeks of starting our Bubble CPAP program, the Division has been able to reduce the use of mechanical ventilation and surfactant administration by 50 percent measured against baseline occurrence. I suspect that we'll see the incidence and severity of BPD drop as well, and we'll of course be monitoring this as part of our outcomes measurements," says Thomas Diacovo, MD, chief, UPMC Newborn Medicine Program and director of Neonatal Cardiovascular Research.

Bubble CPAP Implementation Team

James Kiger, MD, MS —
Implementation Lead

Kalyani Vats, MD

Abeer Azzuqa, MD

Jennifer Kloesz, MD

Laura Jackson, MD

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Karen Ewing, NNP

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Kristen Brenneman, RN

Amy Farren, RN

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Quality Improvement Initiatives in Neonatology

The Newborn Medicine Program at UPMC Children's Hospital of Pittsburgh is renowned for its state-of-the-art care of critically ill newborns, and its decades of ground-breaking clinical advancements and research.

Striving to continually improve the quality of care and outcomes for these most complex and medically fragile cases is on display in the ongoing quality improvement (QI) initiatives of the Newborn Medicine Program and their collaborators within UPMC Children's.



Leading and collaborating in many of these QI programs is **Beverly Brozanski, MD**, IHI Improvement Advisor, professor of Pediatrics, and medical director

of the Neonatal Intensive Care Unit at UPMC Children's. In addition to her roles at UPMC Children's, Dr. Brozanski sits on the executive committee of the Children's Hospital Neonatal Consortium (CHNC), a 34-member group of level IV NICU Children's Hospitals devoted to improving care for high risk infants (www.thechnc.org). Dr. Brozanski is a co-leader of the CHNC's Continuous Improvement Quality Initiatives (CIQI) committee that spearheads national quality improvement collaborative efforts within the consortium's network. The first multi-center project implemented by this group resulted in a 19 percent decrease in central line-associated blood stream infections (CLABSI) across the collaborative, an improvement which was sustained over the subsequent 18 months.

Improving Postoperative Hypothermia and Perioperative Care Failures

Recent initiatives implemented at UPMC Children's in concert with the CHNC aimed to improve perioperative hand-off communication and rates of postoperative hypothermia. These efforts have led to sustained low rates of postoperative hypothermia and a decrease in communication care failures at UPMC Children's, as well as across the collaborative.

Increasing Breast Milk Feeding Rates and Reducing the Incidence of Wrong Breast Milk

At UPMC Children's, concerted efforts and initiatives beginning in November 2013 to increase the percentages of new mothers breastfeeding their infants met with great success, increasing the rate of babies discharged on the mother's breast milk by 45 percent to nearly 82 percent by February 2015 and sustained through spring 2018.

The success of the "Breastmilk = Medicine" project is in its multidisciplinary approach. Transport teams initially deliver the "Breastmilk = Medicine" message to recuperating postpartum mothers at the birth hospital.

Soon after admission to the NICU in Pittsburgh, a neonatologist or advance practice provider contacts the new mother at the birth hospital to update her on her baby's condition and review the benefits of breast milk. UPMC Children's staff nurses assist mothers to continue pumping, when they arrive, with a pump in each patient room, and provide meal tickets to assure adequate maternal hydration and nutrition. Two International Board Certified Lactation Consultants (IBCLCs) with NICU nursing experience and 15 CBC counselors (CBC) offer consistent support and encouragement while also trouble shooting with latching and pumping concerns.

Leveraging Technology to Eliminate Breast Milk Errors

With the increase in numbers of mothers providing breast milk, there was an increased potential for the administration of incorrect breast milk. The existing system for labeling, identification, and administration of breast milk was targeted for a quality improvement initiative to eliminate the potential for the administration of the wrong breast milk to infants during their stay and at the time of discharge.



According to Dr. Brozanski, under the leadership of NICU Unit Directors, Diane Ankney, MSN, RN, NEA-BC, and Carrie Rubino MSN, RN, CCRN, the solution implemented was a protocol similar to positive patient identification used when administering medications and the labeling of lab samples. Orders are placed in the EMR indicating breastfeeding for the mother and her baby. Barcoded labels are generated for milk bottles and tied to each patient through the EHR. Labeled bottles are scanned prior to giving them to the family. They are rescanned to verify the codes match when the mother

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gives milk to the staff for storage. During feedings, the milk is brought to the bedside and scanned prior to feeding to ensure a match with the patient. Bottles going home at the time of discharge also are scanned prior to distribution to ensure they are going to the correct family.

Decreasing Length of Stay in Cases of Gastroschisis

In 2013, UPMC Children's began an initiative to reduce the length of stay for these patients. "We benchmarked our length of stay (LOS) for our patients with gastroschisis against the mean LOS seen in the CHNC partners, and we realized that we had room for improvement at our own institution," says Dr. Brozanski.

A multidisciplinary group included neonatology, neonatal APPs, pediatric surgery, maternal fetal medicine, nursing and respiratory therapy reviewed best practices, developed and

implemented consensus management to decrease the LOS by nearly 50 percent, from 58 days to 31 days. "We've been able to sustain these improvements year after year with fewer ventilator days and less exposure to pain medications," says Dr. Brozanski.

Ongoing Postoperative Pain Reduction QI Initiative

Currently in progress at UPMC Children's is the development of a postoperative pain reduction protocol for NICU patients. This project is designed to identify the type of postoperative pain control and medication necessary for babies before the surgery. "Our goal is to decrease consecutive high pain scores, eliminate excessive sedation, use non-pharmacologic pain therapy whenever possible, and involve families in identification of postoperative pain," says Dr. Brozanski. This initiative is ongoing and quality metrics are underway for analysis of program efficacy.

The Newborn Medicine Program is proud to be a division that targets Quality Improvement to provide evidenced-based care to the most fragile patient population.

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- ² Pallotto E, Piazza P, Smith J, Grover T, Chuo J, Provost L, Mingrone T, Holston M, Moran S, Morelli L, Zaniletti I, **Brozanski B**. Sustaining SLUG Bug CLABSI Reduction: Does Sterile Tubing Change Technique Really Work? *Pediatrics*. 2017 Oct;140(4). pii: e20163178. doi: 10.1542/peds.2016-3178. PMID: 28951441.

About the UPMC Newborn Medicine Program

The Newborn Medicine Program has dedicated plans for consensus management of many neonatal conditions, including gastroschisis, congenital diaphragmatic hernia, Pierre Robin sequence, myelomeningocele, NAS, and others. These plans include:

- NICUs at four hospitals
- Children's Hospital is western Pennsylvania's only AAP-designated Level IV NICU
- Immediate access to every pediatric medical and surgical specialty
- 24/7 neonatal transport via ground or air
- Extracorporeal membrane oxygenation (ECMO) patient transports
- Extracorporeal Life Support Organization (ELSO) Center of Excellence
- Quality Improvement Leader in the Children's Hospitals Neonatal Consortium
- One of the nation's fastest-growing pediatric research programs with projects that include:
 - > Developing and testing of novel therapies to prevent and treat blood clots in neonates
 - > Protective strategies for necrotizing enterocolitis
 - > Mechanisms of bilirubin-induced neurotoxicity
 - > Identifying premature infants at risk for necrotizing enterocolitis

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Video Rounds

Congenital Diaphragmatic Hernia

Kalyani Vats, MD, assistant professor of pediatrics, neonatology, and developmental biology, discusses management protocols for congenital diaphragmatic hernia developed at UPMC Children's, including the use of gentle ventilation.

A Model for Neonatal Neuro-Intensive Care

Toby Yanowitz, MD, co-director of the neonatal neuro-intensive care unit, explains the UPMC Children's approach to managing infants with neurological conditions such as neonatal seizures, birth asphyxia, and hypoxic ischemic encephalopathy.

Transport Program Advances: Improving Call Times and Response Rates for Neonatal Patients

When a critically ill neonate in our community is in need of the specialty care at UPMC Children's Hospital of Pittsburgh, the Transport Program is called with hopes of a speedy response and arrival of the team. UPMC Children's Transport Program performs approximately 1,400 transports a year, with 50 to 60 percent being neonatal patients. The referral base for neonates is about a 150-mile radius for ground and helicopter transports, although the team is also capable of international transports via fixed wing aircraft.



Melissa Riley, MD, is a neonatologist and the medical director of neonatal transport since 2011. "The American Academy of Pediatrics set the standard for neonatal/pediatric transport team response time at less than 20 minutes. Analysis of our response rates revealed room for improvement; the team was meeting the 20-minute AAP only goal 59 percent of the time. We started to examine where the issues may be, and where and how we could improve upon them. Getting the team to a patient quickly not only provides them with the world class care they require but also relieves the community hospital of the stress of caring for a critically ill neonate," says Dr. Riley.

The transport units consist of specially trained RNs, RTs, and intensive care physicians, with two to three teams available 24 hours a day, seven days a week. Originally, the teams

were located at UPMC Children's while the vehicles — ambulance and helicopters — were stationed strategically in the surrounding areas. The process was examined to see where crucial time could be gained and whether there were inefficiencies to be eliminated: time spent on a call, time for a vehicle to travel to the destination, time involved with loading equipment and necessary supplies.

The first improvement involved education for the MedCall dispatchers in knowing that intubated neonates or those coming from a birthing center with the need to be in an incubator would automatically require a neonatal transport team. "The dispatchers can now efficiently arrange for a vehicle to be en route before the call is even finished."

While small, incremental gains were wrought from this change in procedure, Dr. Riley explains that the bigger hurdle was how to reduce the transit time for the vehicle to get to the UPMC Children's team given their

separate locations. Logistical challenges and cost barriers were scrutinized while evaluating the option of stationing a helicopter at UPMC Children's but the better solution turned out to be moving one of the teams to the helicopter.

"A helicopter and flight crew is stationed at the Allegheny County Airport which happened to have space for one of the UPMC Children's teams. Minor renovations and IT infrastructure were proposed, approved, and made to the base site in October 2014 to accommodate the UPMC Children's team and the specialty neonatal/pediatric equipment. We observed a positive increase in our compliance rates with this major change," says Dr. Riley.

Striving for perfection, two dedicated ambulance units were incorporated into the program in July 2017: one housed at UPMC Children's and the second at the Allegheny County base, placing both ambulances in proximity to the teams. This led to a further upward trend in response time compliance.

Community satisfaction is another metric to measure program success and the improved response times has led to a decrease in lost transports (transports by other institutions) and allowed an ability to focus on the needs of our community facilities. "Our transport teams bring the ICU to our referral centers and they can offer outreach and educational initiatives such as procedural skill training and case reviews that are tailored to the needs of each center," says Dr. Riley. "We are continuously working to test and implement new procedures and operational transport protocols to improve the response times for our transport team."



Telemedicine and Neonatology: Expanding Services for Newborns in Need

Modern technology is bridging the distance between neonates and neonatology at UPMC Children's Hospital of Pittsburgh and UPMC Magee-Womens Hospital. By utilizing state-of-the-art video conferencing technology that is comprised of two-way, secure, real-time interactive communications, the UPMC Newborn Medicine Program physician can virtually evaluate newborns at remote sites any time of the day or night.

Clinical Services

The telemedicine program at UPMC Children's consists of the following services:

- Consultation
- Pre-transport Care
- Virtual telerounds at
 - Excelsa Westmoreland Hospital level II NICU
 - UPMC Horizon Special Care Nursery
 - Wheeling Hospital (beginning in early 2018)

Telemedicine brings the Neonatal Intensive Care Unit (NICU) to the patient's bedside to help newborns get the care they need in their home communities, and it can be used to facilitate transfer to UPMC Children's for the sickest infants. The program also allows infants in a level II NICU to receive neonatal care at their local hospitals that are closer to their families, thus minimizing the incidence of unnecessary transfers and reducing associated health care costs.

Telemedicine and Education

The telemedicine technology employed by UPMC Children's also has the benefit of being able to be used for educational purposes. The UPMC Neonatal Telemedicine program continues to provide remote continuing educational opportunities for nurses, respiratory therapists, and physicians at community hospitals. "Our goal is to strengthen and formalize our CME offerings through virtual conferences and the like to all members of the



neonatology team — physicians, nurses, respiratory therapists, and other disciplines," says **Abeer Azuqa, MD**, one of the neonatologists at UPMC Children's.

On the Horizon: International Outreach

Dr. Azuqa explains that the next few years are likely to see an expansion of neonatal telemedicine services on the international stage. The focus during the first few years of the program has certainly been on the immediate communities in and around western Pennsylvania. However, as she and her colleagues have worked to perfect the programs and expand the services offered through the telemedicine platform, and as

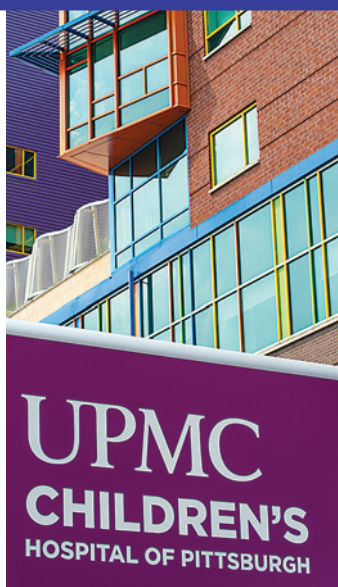
UPMC as a system has invested heavily in telemedicine technologies for a growing contingent of specialties and locations, branching out internationally is a likely next big step to bring the clinical expertise of the neonatology programs at UPMC to the wider world.

"Such advanced technology infrastructure and leading-edge methods mean health care providers can deliver the same high-quality care through remote and virtual means as they do through face-to-face interactions," says Dr. Azuqa. "It's real-time communication between the neonatologist based in Pittsburgh and the medical staff based in Altoona," she says. "State-of-the-art digital technologies allow us to provide complex newborn care through remote and virtual means anytime it's needed."



Dr. Azuqa conducts a telemedicine consult with colleagues at one of UPMC's community hospitals.

UPMC Children's Hospital of Pittsburgh is affiliated with the University of Pittsburgh School of Medicine and nationally ranked in nine clinical specialties by *U.S. News & World Report*.



About UPMC Children's Hospital of Pittsburgh

Regionally, nationally, and globally, UPMC Children's Hospital of Pittsburgh is a leader in the treatment of childhood conditions and diseases, a pioneer in the development of new and improved therapies, and a top educator of the next generation of pediatricians and pediatric subspecialists. With generous community support, UPMC Children's Hospital has fulfilled this mission since its founding in 1890. UPMC Children's is recognized consistently for its clinical, research, educational, and advocacy-related accomplishments, including ranking 13th among children's hospitals and schools of medicine in funding for pediatric research provided by the National Institutes of Health (FY2017).