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Whole genome sequencing helps diagnosis and reduces healthcare costs for newborns in intensive care

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Children who are born severely ill or who develop serious illness in the first few weeks of life are often difficult to diagnose, with considerable implications for their short and longer-term care. Whole genome sequencing carried out quickly has the potential to provide an early diagnosis, and thus improve the clinical care of these infants as well as reducing its cost, the annual conference of the European Society of Human Genetics will hear tomorrow (Sunday).

Dr. Shareef A. Nahas, Senior Director, Rady Children's Institute for Genomic Medicine, San Diego, CA, United States, will report on his team's study of rapid whole genome sequencing (rWGS) of all inpatient children under one year of age who were nominated for genetic investigation at Rady Children's Hospital. Rapid WGS is able to return results in 48 to 96 hours, whereas standard genetic testing takes six to eight weeks to provide a result. They then noted subsequent changes in medical care that occurred while the child was still in hospital. Where there was a significant change in care due to a new diagnosis, the cases were reviewed by an independent expert panel who tried to determine what they believed would have happened had the child not received rWGS.

After 12 months of testing, 363 patients had been enrolled in the study and rWGS interpreted in 340 of them. This yielded a diagnosis in 115 cases (about 34 percent). Diagnosis occurred quickly, on average within

96 hours. Changes in management as a result of diagnosis were identified in 77 patients, or about 67 percent of those diagnosed. Such changes ranged from specific changes, for example surgical interventions, to guidance in palliative care. Among the first 42 infants diagnosed, rWGS provided over $1.3million in net cost saving over the projected standard care.

"To date, our studies have shown a considerable clinical and economic benefit of sequencing children who were identified by clinicians as being suspected of having a genetic disorder. In the course of the study, one child was spared devastating neurological damage,and one had a significantly reduced risk of death. The net cost savings totalled several hundred thousand dollars, even when we included the cost of analysing the genome of the child and both parents," says Dr. Nahas.

Although many studies have shown that WGS improves the diagnosis if genetic disorders in infants and can lead to beneficial changes in their management, the new research has shown that, by implementing rapid sequencing, cost savings will also ensue. " We are now in a situation where we have a technology that leads to improved diagnosis and improved outcomes but is also not a net burden on healthcare resources. This means that for large healthcare payers, there is not a logical cost barrier to implementing rWGS in newborns suspected to have a genetic disorder. There will need to be further data on who else can benefit from early use of this technology but implementation in the current cohort should not be delayed," says Dr. Nahas.

Currently, the use of WGS among sick newborns is very infrequent across the world, and there are few healthcare systems that have the ability to turn round genetic testing quickly enough to be clinically relevant, the researchers say. This is vital if medical management needs to be changed during the childrens' hospitalisation. In the course of Dr. Nahas' study, one child was spared devastating neurological damage and

another had a significantly reduced risk of death.

"The logic for the use of rWGS in these patients, both diagnostic and economic, is totally convincing. We have demonstrated that early sequencing saves money during admission. We were surprised by the proportion of children who received a change in care during that admission—around 25 percent of children sequenced and 80 percent of those diagnosed. This rate is much higher than other published rates for newborns who received WGS. We believe that this difference is due to the fact that the children received results at a much younger age, at a point where medical decisions were yet to be made.

"There is an ethical imperative to act in the best interest of newborns, but implentation will require a concerted effort across all healthcare systems, and this will need to be at government level in Europe. Consistent with many diagnostic tests in the post-natal period, rWGS has the potential to identify conditions associated with lifelong disability or shortened lifespans," Dr. Nahas will conclude.

In a second presentation, Courtney French, Ph.D., a research associate/bioinformatician at the University of Cambridge, Cambridge, UK, will describe how she and colleagues carried out WGS analyses on 145 severely ill babies and children with an unidentifiable disease. As a result, they were able to identify the cause of disease in more than 15 percent of cases.

"We have developed a rapid, affordable turnaround pipeline for this sequencing within the UK National Health Service system. This means that we can feed back clinically relevant information to doctors and parents in a timescale that allows care to be affected. Because it is hard to tell from observation alone who will benefit from genomic diagnosis, we think that it should be carried out on all eligible children, rather than doctors deciding on individual cases based on previous clinical

knowledge. By comparing the entire DNA sequence in children to that of their parents we can identify quickly the likely cause of disease," says Dr. French.

The researchers are using their current data to investigate how rare genetic diseases present at an earlier stage than they are usually diagnosed in newborns. " Greater numbers of patients will expand our ability to do this, and we hope that our work will serve as a model for expanding the programme to other hospitals and regions," Dr. French will say. " The success of this project will depend on people working together across the health research and healthcare system. The translation of this work to routine care will require significant investment of resources in achieving consent from parents, and in giving information at what is a very stressful time for them. "

Many of the conditions characterised through WGS to date can be treated more effectively once identified. In the Cambridge dataset, several epilepsies that respond better to some medications than others were found. And there were cases where the diagnosis was able to prompt better screening for the clinical consequences of a condition and enabled the creation of a properly focused care plan, for example cardiac surveillance, renal follow up, or dietary advice. Even where there is no effective treatment available, having a diagnosis can provide reassurance to families that all that could be done has been done, and it can also provide useful information to parents when they are considering the most appropriate care for their child in the future.

"We were pleasantly surprised at the enthusiastic welcome parents gave to our study, with more than half of those approached wanting to take part. Despite the complications of getting samples from both parents, as well as their child, we managed to achieve this in 85 percent of families. We were also surprised at the huge range of clinical conditions we were able to diagnose, and particularly to find that when a child was already

known to have learnng disability or developmental delay we were more likely to make a genetic diagnosis. This reflects the enormous increase in genetic knowledge over the last decade; ten years ago we would not have been able to do this even if we had sequenced the genome.

"Genome sequencing is currently rare in newborns and paediatric cases, but our research has shown that it can be extremely effective in providing rapid answers in difficult to diagnose cases. It is also be cost-effective, since it can reduce the time spent as an in-patient. Early diagnosis of neonatal and paediatric disease is not only important in pointing the way to the best care and treatment, but also in reducing anxiety for parents," Dr. French will conclude.

Chair of the ESHG conference, Professor Joris Veltman, Director of the Institute of Genetic Medicine at Newcastle University, Newcastle, United Kingdom, said: "Both these studies confirm the value of genome sequencing to detect the cause of unexplained disease. The study of Nahas shows that this can now even be done within four days, which is very impressive. This greatly increases the practical use of genetics in an acute clinical setting where treatment decisions can now be made based upon this powerful test. Personalised genomic medicine is becoming a reality."

More information: Nahas: Abstract no: CO7.5. Rapid Whole Genome Sequencing Improves Clinical Utility and Cost Effectiveness of Acutely Ill Children admitted to Neonatal Intensive Care Units

French: Abstract no: CO7.4 Next Generation Children Project: Whole genome sequencing for rapid diagnosis of severely ill children in intensive care

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