Rapid Whole Genome Sequencing Leads to Improved Diagnoses, Reduced Costs

Spectrum Health Helen DeVos Children's Hospital is playing a key role in developing a project that will make rapid whole genome sequencing (rWGS) available to every critically ill baby born in Michigan in order to improve care for these babies and demonstrate the impact of rWGS on reducing health care costs.

Rapid WGS implies the return of results within a matter of hours instead of the weeks currently required for these test results. When conducted on critically ill neonates, rWGS can in many cases produce more accurate diagnoses and often result in improved care at lower aggregate costs than in cases without rWGS.

Titled “Project Baby Deer” for Michigan’s state animal, the white-tailed deer, the rWGS project is similar to the 2019 Project Baby Bear in California but on a broader scale, says Caleb Bupp, MD, medical geneticist at Helen DeVos Children’s Hospital.

“Project Baby Bear was limited to five sites and only to babies with Medi-Cal,” Dr. Bupp says. “The study in Michigan will be open to all medical facilities that care for children and will go beyond Medicaid by engaging insurance companies in Michigan to show the value. We are acknowledging up front that there is a lot to be learned from the health economics standpoint, and that is one of the study’s explicit goals.”

In June 2019, California set aside $2 million in funding for a pilot program to provide rWGS to acutely ill newborns at five hospitals statewide. Led by Rady Children’s Institute for Genomic Medicine, Project Baby Bear sequenced 154 babies with an average of three days to deliver results. Non-rapid WGS typically returns results in two to four months. Of those babies, 45 had their care changed as a result of rWGS.

A conservative early analysis indicated Project Baby Bear and rWGS resulted in 430 fewer hospital days; 11 fewer major surgeries, including a major reconstructive surgery on the upper airway and a bowel surgery; and 17 fewer invasive diagnostic tests, including open muscle, liver and other biopsies under general anesthesia.

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In addition, in Project Baby Bear, rWGS substantially reduced Medi-Cal spending and hospital costs, largely because it allowed babies to be discharged sooner, and reduced the number of unnecessary procedures. It improved the experience of care for families by providing timely diagnostic and prognostic information, reducing uncertainty and empowering families to make life-altering medical decisions. It improved the clinicians’ experience by bolstering confidence in treatment decisions, their comfort with the implications of those decisions, and their satisfaction by fostering delivery of more effective care in an efficient, collaborative team environment.

Michigan’s Project Baby Deer was sparked by a presentation Dr. Bupp made in 2019 to a meeting of the Michigan Hospital Association’s Council on Children’s Health. “That discussion last summer prompted the leadership of children’s hospitals in Michigan to express interest in conducting an expanded version of Project Baby Bear,” Dr. Bupp says. Helen DeVos Children’s Hospital was the first in the state to conduct rWGS, “and is at the heart of this effort,” he says. “We are more than eager to share our expertise in order to save babies’ lives and reduce costs.”

The disorder is caused by mutations in a gene known as ornithine decarboxylase 1 (ODC1) and is defined by a number of clinical features including large birth weight, enlarged head size, hair loss, reduced muscle strength, skin lesions, hearing loss and developmental delays. The disorder, discovered in patient Marlene “Marley” Berthoud and named Bachmann-Bupp Syndrome, was the subject of a study published in the American Journal of Medical Genetics Part A.

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Rapids Whole Genome Sequencing Leads to Improved Diagnoses, Reduced Costs, Continued

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Caleb Bupp, MD

Dr. Bupp is widely recognized as an authority in WGS. In 2018, he and André Bachmann, PhD, professor and associate chair for pediatric research at Michigan State University, along with researchers from Michigan State University College of Human Medicine and Surender Rajasekaran, MD, director of research for Helen DeVos Children’s Hospital, identified for the first time in a human patient a genetic disorder only previously described in animal models.
The disorder is caused by mutations in a gene known as ornithine decarboxylase 1 (ODC1) and is defined by a number of clinical features including large birth weight, enlarged head size, hair loss, reduced muscle strength, skin lesions, hearing loss and developmental delays. The disorder, discovered in patient Marlene “Marley” Berthoud and named Bachmann-Bupp Syndrome, was the subject of a study published in the American Journal of Medical Genetics Part A.

Genetics are a bigger factor and sequencing is far more accessible than ever before,” he says. “We now understand more about what genes do and because of that are identifying more rare disorders.”

He says genetic tests continue to become simpler, faster and less expensive. He advises primary care physicians “if you are thinking about referring a patient to a geneticist, you probably should.” Helen DeVos Children’s Hospital has six geneticists on staff and is adding another this summer.
Advanced Robotic Surgical System Keeps Pediatric Patients in One Place Care

The addition of a da Vinci XI robotic surgical system—and its smaller, more advanced instrumentation—now enables surgeons to perform a wider array of minimally invasive procedures on pediatric patients at Spectrum Health Helen DeVos Children’s Hospital.

To obtain the advantages of robotic-assisted surgical procedures, pediatric patients previously had to be admitted to Helen DeVos Children’s Hospital, then taken to the adult surgical suites at the adjacent Spectrum Health Butterworth Hospital, then back to recuperate in the pediatric facility following surgery.

“The availability of the da Vinci XI at Helen DeVos Children’s Hospital has made it so our patients never have to leave the children’s hospital,” says Theodore Barber, MD, pediatric urologist at Helen DeVos Children’s Hospital. “Seamless care is a tremendous benefit to the patients and their families. It allows dedicated pediatric services at all steps of the perioperative process, significantly reducing both patient and parental anxiety.”

Having the new robotic system at the pediatric facility also encourages collaboration between specialties, Dr. Barber says. “All care is delivered in one facility, and that makes it easier to coordinate care with other services, and often combine procedures with other specialists so that only a single anesthetic is required,” he says.

The da Vinci XI robotic system offers increased dexterity and precision when performing minimally invasive surgeries. Robotic surgeries and minimally invasive techniques are often able to provide equivalent outcomes compared to “open” surgeries, and they offer benefits to the patient including decreased pain, faster recovery and an improved cosmetic outcome.

One of the minimally invasive procedures the da Vinci system makes possible is hidden incision endoscopic surgery (HiDvES). With HiDvES the incisions (ports) are placed so that the scars that are normally visible after traditional laparoscopic or open surgeries are placed along the pant line in a natural skin crease, making them less visible. “These incisions remain hidden as the child grows, whereas an incision in a traditional open surgery often needs to be significantly larger and placed in a more conspicuous location,

We are very judicious about the robotic procedures we offer,” he says. “But in the right situation, it offers tremendous precision and visualization with equivalent surgical outcomes.”

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Theodore Barber, MD

and will grow in size as the child grows,” Dr. Barber says.

The HlDES procedure is one of several robotic surgical techniques being performed at Helen DeVos Children’s Hospital by Dr. Barber and David Weatherly, MD, both of whom are board-certified urologists and specially trained in Pediatric Urology and robotic-assisted pediatric surgery.

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Dr. Barber joined the pediatric urology department at Helen DeVos Children’s Hospital in 2010 after completing a two-year pediatric urology fellowship at Children’s Medical Center of Dallas, University of Texas Southwestern Medical Center. As a fellow in Dallas, Dr. Barber learned the HlDES technique by working alongside its inventor, Patricio Gargollo, MD.

The da Vinci system consists of the surgeon’s console, the patient cart with the instruments and camera, and the vision cart, which facilitates communication between the components and supports the 3D high-definition vision system.

The system translates the surgeon’s hand movements at the console in real time, bending and rotating the instruments while performing the procedure. The tiny wristed instruments move like a human hand but with a greater range of motion, while the camera delivers highly magnified, 3D high-definition views of the surgical area.

The instrument size makes it possible to operate through one or a few small incisions.

The refined, smaller instruments of the XI version make them easier to use on younger patients, Dr. Barber says.

“Where nine months was the youngest age for these surgeries before this system,” he says, “now we can start at six months, and on occasion even younger.”

In addition to smaller instrumentation, the da Vinci XI allows easy repositioning of the robotic “arms” during surgery, thereby expanding the surgical field without the need for additional incisions.

“Having a larger working field gives us many more options for procedures that can be performed in a minimally invasive fashion,” Dr. Barber says.

He says pelvic surgeries, for example, are traditionally difficult. “To operate in the pelvis, often the surgeon’s vision and access are limited when using traditional open approaches,” he says. “The XI is a great tool for pelvic reconstructive surgery because the new instrumentation allows us to reach deep into the pelvis with excellent visualization and markedly improved access.”

Dr. Barber says the robotic system, while a revolutionary tool for pediatric urology surgery, is not right for every operation. “We are very judicious about the robotic procedures we offer,” he says. “But in the right situation, it offers tremendous precision and visualization with equivalent surgical outcomes.”
Telemedicine Virtually Eliminates Many Obstacles of Long-Distance Care

Expanding the availability of telemedicine “virtual visits” is significantly increasing access to Spectrum Health Helen DeVos Children’s Hospital specialists and comprehensive pediatric specialty care while also easing the burdens of travel, health costs and the anxiety that these can create for patients and families across Michigan.

In the past year, Helen DeVos Children’s Hospital has launched nearly a dozen projects designed to enhance its telemedicine presence, where travel is difficult or restricted, the patients can access specialists from their homes using their computer, tablet or smartphone through the Spectrum Health MyHealth app and portal. In either method, patients and their families speak with a physician confidentially as they would in a face-to-face visit.

“Our larger vision has always focused on optimizing care in three major areas: partnering with inpatient facilities to enhance the great care children are already receiving across Michigan,

In May, Helen DeVos Children’s Hospital forged an agreement to provide specialty consultation services for pediatric ventilator management via telemedicine to inpatients at the Mary Free Bed Rehabilitation Hospital in Grand Rapids. says Ajay Khilanani, MD, Medical Director of Digital Health and pediatric critical care physician at Helen DeVos Children’s Hospital. “Many of these are foundational programs that will allow us to expand and advance care as we move forward,” he says. Telemedicine virtual visits are secure video calls enabling a patient and their parents or guardians—as well as physicians at outreach clinics in Lansing, Ludington and Traverse City; inpatient facilities; and Emergency Departments (ED) across the state—to see, hear and speak with a pediatric specialist at Helen DeVos Children’s Hospital.

For some medically complex cases establishing a model telemedicine practice for each of our outpatient subspecialty programs, and embedding efficient telemedicine practices within our outreach clinics outside of Grand Rapids,” says Dr. Khilanani. The service will also benefit ventilator-dependent patients at hospitals throughout the region, who will gain the opportunity for rehabilitation at Mary Free Bed.

“Traditionally, a pediatric patient who had suffered a debilitating neurological injury such as trauma, stroke, spinal cord injury, or meningitis that resulted in a dependence on a tracheostomy and ventilator would have to be transferred

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for inpatient rehabilitation because of their needs for advanced respiratory support,” Dr. Khilanani says. “Because of this partnership, children can potentially begin rehabilitation even earlier, and we’re hopeful this will play a role in a more meaningful recovery over the long term.”

One of the hospital’s initial telemedicine projects was to provide pediatric critical care consultation to physicians at Spectrum Health emergency departments.

“When an ED doctor determines that a patient needs to be transferred to Helen DeVos Children’s Hospital’s pediatric intensive care unit (PICU), they can access the guidance of our critical care specialists,” Dr. Khilanani says. “Being able to see the patient allows our pediatric caregivers to gain a more comprehensive assessment of their condition compared to the traditional telephone call, and can result in more informed diagnostic and treatment recommendations prior to transfer.”

With telemedicine, parents and their child are able to put a face with the name of the receiving physician at Helen DeVos Children’s Hospital, and when they arrive they are reassured by that familiar face.

This PICU telemedicine initiative additionally led to the implementation of the first pediatric telestroke program in Michigan by Helen DeVos Children’s Hospital. “Pediatric stroke can be even more difficult to diagnose than adult stroke because there are many conditions that mimic it,” Dr. Khilanani says. “By enabling simultaneous assessments of patients at outlying EDs, we believe our recommendations can be even more impactful in the early diagnosis, management and recovery of pediatric stroke patients.”

The hospital also piloted a tele-education project for medical students at Michigan State University College of Human Medicine across many of their clinical locations throughout the state. “Many times, these students are not in a location where they can see high pediatric patient volumes and high acuity,” Dr. Khilanani says. “With this, they can see patients, round, and enhance their medical education online.”

He says that as the Helen DeVos Children’s Hospital Digital Health program evolves, “we remain open to creative ideas and unique partnerships that leverage this technology, improve relationships and ultimately enhance pediatric care.”

COVID-19 Shifted Virtual Visits Into High Gear

The dream of expanding the number of providers and patients taking part in telemedicine “virtual visits” became reality in very rapid fashion in March at Spectrum Health Helen DeVos Children’s Hospital as a response to the coronavirus pandemic.

“Before we started this effort on March 16, we had one or two providers and about 10 virtual visits a week,” says Bridget Menzel, Director of Operations at Helen DeVos Children’s Hospital. “Two weeks later, we had 125 providers trained to respond. By May 6, we completed 300 virtual visits in one day.”

Menzel says the hospital had originally planned to convert from 5 to 10 percent of face-to-face medical appointments to virtual visits over a three- to five-year period. “That day in March, we learned that in two hours we would close down all face-to-face operations,” she says.

Spectrum Health assembled a team led by Rima Shah, MD, to implement virtual visits across the system. As part of the larger organization, Menzel immediately assembled a project team that included representatives of more than 20 specialties, along with managers, physician leaders, technical specialists and others. They began by identifying what patient types could transition from face-to-face visits to virtual visits, and which patients needed to be seen more urgently.

Fortunately, Spectrum Health already had an online platform in place with MyHealth. “We had the functionality, but we needed the resources to be able to help families download the app and train them how to use it,” Menzel says.

Within two weeks, a “base camp” was assembled with laptops and headsets, staffed by employees trained how to offer instructions and answer questions about the MyHealth app and portal.

She says virtual visits will afford them the opportunity to serve their medically complex patients and families by coordinating with several specialists, each of whom joins the call from their office or clinic.

Because of the acceptance and success of virtual visits, the hospital is planning for 25 percent of all hospital visits to be conducted virtually, if and when the coronavirus crisis eases. “Virtual visits can benefit all stakeholders,” she says. “We are in this for the long haul.”
Expanding Movement Disorders Program Features Comprehensive Care, New Clinics Place Care

The ability to offer patients and their families advanced medical and surgical care, as well as the opportunity to access other pediatric specialists all in one location, is the foundation for several comprehensive movement disorder clinics being established at Spectrum Health Helen DeVos Children’s Hospital.

These clinics will feature a highly skilled, multidisciplinary team that includes a fellowship-trained pediatric movement disorders specialist and the only pediatric-trained functional neurosurgeon in the state of Michigan.

We will bring together a multidisciplinary team of child neurologists, child rehabilitation specialists, neurodevelopmental pediatricians, physical therapists, occupational therapists, speech therapists, orthotic specialists, nutritionists and social workers all in one clinic.

Pediatric movement disorders include:

- **Ataxia**, a failure of motor coordination caused by injury or dysfunction of the cerebellum;
- **Chorea**, where children have irregular, flowing movements that are sometimes described as “dance-like” that can be slow and writhing or more forceful;
- **Dystonia**, where faulty brain signals cause groups of muscles to contract abnormally;
- **Myoclonus**, which involves very quick, sudden, involuntary muscle jerks that the child cannot suppress;
- **Parkinsonism**, where children have at least two symptoms of Parkinson’s disease: muscle rigidity, balance problems or frequent falls, slow movement or tremor while at rest;
- **Tics**, sudden, involuntary movements or sounds that come and go over time;
- **Tourette syndrome**, a tic disorder characterized by involuntary, repetitive movements and vocalizations; and
- **Tremor**, a rhythmic shaking or trembling of a limb.

“Many children with abnormal movement disorders have mixed medical phenomena,” says David Moon, MD, who was fellowship trained in pediatric movement disorders at Cincinnati Children’s Hospital and now serves as section chief of the Pediatric Movement Disorders Program at Helen DeVos Children’s Hospital. “The specialized programs we have in place, and the programs we are creating, enable us to effectively diagnose and manage these complex conditions.”

For example, many children are diagnosed with cerebral palsy (CP) without the precise nature of their movement disorder being delineated, Dr. Moon says. “There has been a tendency to label everything as spasticity even though there are other conditions present,” he says. “The reality is almost every CP child I have met has mixed movement phenomena.”

CP is a group of disorders that affect a person’s ability to move and maintain balance and posture. CP is the most common motor disability in childhood and is caused by abnormal
brain development or damage to the developing brain that affects the ability to control muscles.

While the symptoms of CP vary from person to person, all people with CP have problems with movement and posture. Dr. Moon says many also have related conditions such as intellectual disability, seizures/epilepsy, problems with vision, hearing or speech; changes in the spine such as scoliosis; joint problems such as contractures; feeding issues; behavioral issues; and orthopedic needs.

“This class of patient has complex needs but often is receiving disjointed and fractured care, or care that is delayed or redundant,” Dr. Moon says. “They are not being served very well because they require multiple subspecialists. There are very few comprehensive programs to address the needs of these children.”

As a solution, Helen DeVos Children’s Hospital has created a Comprehensive Cerebral Palsy, Spasticity and Tone Management Program to further collaboration and better serve these children.

“We will bring together a multidisciplinary team of child neurologists, child rehabilitation specialists, neurodevelopmental pediatricians, physical therapists, occupational therapists, speech therapists, orthotic specialists, nutritionists and social workers all in one clinic,” Dr. Moon says. Patients will also have quick access to pediatric neurosurgeons, geneticists and orthopedists.

Dr. Moon offers unique expertise as the only fellowship-trained pediatric movement disorders specialist in the state of Michigan. The team also includes Michael Bercu, MD, Michigan’s only fellowship-trained and functionally trained pediatric neurosurgeon.

Dr. Bercu’s extended knowledge and skills in the treatment of spasticity and pain disorders, including implantation of intrathecal delivery systems as well as spinal cord and dorsal root ganglia stimulation systems, enable him and Dr. Moon to deliver advanced therapies that include:

- Selective dorsal rhizotomy.
- Deep brain stimulation.
- Intrathecal baclofen pump.
- Sedated botulinum and phenol injection.
- Complex medication management.
- Complex equipment management.

Dr. Moon says each child will be evaluated to determine the precise cause of his or her overall presentation to ensure it is consistent with their prior medical history. “We believe that understanding the cause of a patient’s chronic motor and cognitive challenges is extremely important,” he says. “That is why we will not simply carry forward diagnoses.”

“Because of our access to a multitude of subspecialists including movement disorder specialists and pediatric and metabolic geneticists, we are capable of complex diagnostics including advanced metabolic testing and whole genome sequencing.”

Dr. Moon often receives referrals for these patients who, because of a lack of resources or a limited ability to travel to obtain comprehensive care outside of Michigan, wound up being managed by a single physician or an adult neurologist who could not fully address their conditions. “This is an underserved patient population whose complex medical needs are not being met,” he says. “We will make it possible for movement disorder patients in Michigan to stay within Michigan for the care they need.”

The Comprehensive Cerebral Palsy, Spasticity and Tone Management clinic first opened in March 2020. “We anticipate the demand to be very high,” he says.

In addition, Helen DeVos Children’s Hospital is creating a Comprehensive Tourette Clinic for management of patients with chronic tic disorders/ Tourette syndrome and significant co-morbid attention deficit hyperactivity disorder (ADHD), anxiety or obsessive-compulsive disorder (OCD). This clinic will include neurologists, psychiatrists, psychologists and social workers.

Drs. Moon and Bercu have also established a Surgical Deep Brain Stimulation Program at Helen DeVos Children’s Hospital. The first implantation of a deep brain stimulation device in a pediatric patient at Helen DeVos Children’s Hospital occurred in January 2020. They are currently identifying additional children older than 7 with dystonia, parkinsonism, tremor or dyskinesias as potential candidates for deep brain stimulation.

Dr. Moon says children with cerebral palsy or complex tone issues should be referred to and seen by a neurologist, a neurodevelopmental pediatrician or a rehabilitation physician before being seen in the multidisciplinary clinics at Helen DeVos Children’s Hospital.

“We want to make certain that if they require multidisciplinary care they are directed to us,” he says. “Our goal is to provide cohesive, comprehensive and timely care that will improve function and quality of life.”
The number of children presenting with tetrahydrocannabinol (THC) in their systems, largely through unintentional consumption of marijuana-infused edible products, has risen sharply since the legalization of recreational marijuana in Michigan, according to research underway at Spectrum Health Helen DeVos Children’s Hospital.

Data suggest that the number of children as young as 2 accidentally ingesting marijuana through consumption of marijuana-laced edible products such as candy, cookies and brownies will likely continue rising as these products become increasingly popular and more widely available, says Allek Scheele, MD, FAAP, a pediatric hospital medicine fellow at Helen DeVos Children’s Hospital.

Dr. Scheele is conducting the marijuana-related research along with Andrea Hadley, MD, FAAP, Chief of Pediatric Hospital Medicine at Helen DeVos Children’s Hospital. Dr. Hadley is also a clinical assistant professor at Michigan State University College of Human Medicine. Amy Herbig, MD, a third-year pediatrics resident, is assisting with data analysis.

Their research is designed to identify trends locally, classify the exposures, and gather data to present to lawmakers in order to expose areas for improvement in the current laws. “We felt like we were admitting an increasing number of pediatric patients to our inpatient service who were suffering from acute effects related to accidental THC ingestion since the legislation changes took effect in Michigan, and we wanted to see if it was actually a trend,” Dr. Hadley says.

Dr. Scheele says the preliminary data gathered through Spectrum Health medical facilities including Helen DeVos Children’s Hospital regarding unintentional marijuana ingestion are similar to the data collected in Colorado between 2009 to 2015, where both the use of “medical” marijuana and “recreational” marijuana have been legal since 2014.

In Colorado:
- Pediatric marijuana-related calls to poison control tripled after legalization.
- 74 percent were ingestion related.
- 88 percent occurred at home.

Of the children evaluated in Colorado emergency departments, the average age was 2. One-third of the children treated had ingested “medical use” marijuana, while 50 percent had consumed marijuana-infused “recreational products” such as cookies, brownies, cake or candies.

Legislative changes since legalization in Colorado have included child-resistant and opaque packaging, dose limitations, limited marketing and banning specific edibles. The impact was mixed. While the average age of children accidentally consuming the marijuana increased to 3, the number of ED visits doubled and calls to poison control increased 17 percent.

Collaborative research such as Drs. Scheele and Hadley’s project is an integral element of the pediatric hospital medicine fellowship at Helen DeVos Children’s Hospital. Through the fellowship, Dr. Scheele is also a clinical instructor at Michigan State University College of Human Medicine.

Availability of Marijuana Edibles a Rising Danger for Children

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and works with residents from a variety of programs and specialties. This fellowship, the only one of its kind in Michigan, trains pediatricians to become academic pediatric hospitalists. Through its Michigan State University affiliation, the fellowship offers academic, educational and research experiences traditionally provided by university-based programs.

The data in Dr. Scheele’s current marijuana-related research go back to 2014. Medical marijuana became legal in Michigan in 2008. Recreational marijuana was legalized in Michigan by voters in 2018, and sales began in 2019. “Since recreational legalization, we have also seen a sharp increase in newborns with THC in their system, as revealed through meconium testing, and we see similar increases in THC positive tests in children and adolescents,” she says.

In January 2020, 24 pediatric acute care cases at Helen DeVos Children’s Hospital involved the consumption of marijuana, she says. “If we maintain that pace, the numbers are on track to surpass the number of cases from 2019,” Dr. Scheele says.

In one such incident, a 2-year-old child presented to the Helen DeVos Children’s Hospital ED with her mother, who reported a one-day history of subjective fever, increased sleepiness and severe irritability. The mother also reported significantly decreased oral intake—essentially nothing to eat or drink in the previous 12 hours—and decreased urine output. The mother said she was worried about dehydration so she brought the child to the ED.

“The exam in the ED revealed an irritable and inconsolable patient,” Dr. Scheele says. “She would not regard the examiner or answer questions. Her strength appeared normal, but the rest of her neurologic exam was very difficult due to agitation.”

Given the girl’s ill appearance and acute presentation, a broad workup was initiated. A non-contrast head CT was negative. Basic labs, including a urine analysis, comprehensive metabolic panel and complete blood count, were unremarkable. A lumbar puncture was performed and her CSF studies were unremarkable.

“The child was admitted for ongoing altered mental status and irritability,” Dr. Scheele says. “Upon admission, a urine drug screen that had been sent in the ED returned positive for THC.”

She says the girl’s mother was confronted with the positive test result. “A family member who had arrived by that time admitted to having marijuana cookies in the house and noted that an unknown number of them were missing,” Dr. Scheele says.

The girl was admitted with a diagnosis of drug-induced delirium due to unintentional THC ingestion of an edible product. She improved over the next 24 hours with supportive care and was able to be discharged.

Dr. Scheele says the incident illustrates how many of these marijuana-infused products are packaged in a manner to be appealing to consumers, and that fact can unintentionally entice very young children. “These products are extremely dangerous to young children as they are visually identical to other food products that children desire, and they taste good,” she says.

Products containing several “doses” of marijuana in one package also pose a danger, as toddlers and other children don’t understand the portioning and may consume the entire package.

“The onset of action can be delayed anywhere from 30 minutes to two hours, so a child will continue to ingest the product without feeling any immediate effect,” she says. “The THC content is completely variable and serving sizes are small, meaning a young child can quickly ingest many servings.”

Additionally, the THC contained in these products is much more potent than marijuana produced in the past. “The central nervous system effects can be severe, requiring hospitalization and even PICU admission, and can last up to 24 hours in these young children,” she says. “We are seeing increasing cases similar to this and predict that with legislation changes there may be a further increase in the future.”

That is why it is critical for pediatricians to counsel families on safe storage of any THC containing products and the dangers of unintentional ingestion, she says.

“The threat to children and adolescents accidentally or intentionally ingesting marijuana edibles is rising in direct correlation to their popularity,” Dr. Scheele says. “Awareness of this danger is one way to keep kids safe.”
Impact: Journal for Physicians

Systematic Inflammation Poses a New Challenge

Physicians and scientists in late May began actively seeking answers to an increasing number of reports of pediatric post-infectious hyperimmune response with a severe systemic inflammatory state that appeared to be associated with the coronavirus (COVID-19).

In many cases, COVID-19 seemed to have a relatively benign acute course in children in comparison with many other respiratory tract viral illnesses that tend to affect younger patients more severely. However, in some pediatric patients, it was not fully clear if the SARS-CoV-2 virus, which causes COVID-19, was provoking a "typical" or "classic" Kawasaki disease, or if this newly associated post-acute hyperimmune response only mimicked Kawasaki disease.

With multisystem inflammatory syndrome in children associated with COVID-19, the most prominent findings were fever and additional systems involvement, including abdominal pain, diarrhea, rash, conjunctivitis and mucosal changes. Some patients presented with signs and symptoms consistent with toxic shock syndrome. Systemic inflammation with serositis and pleural, pericardial and abdominal effusions were also seen.

The most life-threatening finding at the time was myocardial dysfunction with or without evident coronary artery involvement. Centers were treating these patients as if they had Kawasaki disease with intravenous gamma globulin and using infliximab or anakinra to modulate the marked inflammatory process. The results on effectiveness were not immediately known.

Lab findings included evidence of acute system inflammation with elevation of C-reactive protein (often >100), ESR, ferritin and even procalcitonin. The elevation of ferritin and characteristics of autoimmune disease, as well as hemophagocytic lymphohistocytosis and macrophage activation syndrome, led some centers to tocilizumab. Patients with multisystem inflammatory syndrome in children require expert tertiary and quaternary pediatric specialty care, such as that which is available at Spectrum Health Helen DeVos Children's Hospital.

There were also reports of coronary artery involvement, but the COVID-19-associated Kawasaki-disease-like syndrome patients were more acutely ill, often with a shock state presentation rare in typical Kawasaki disease.

Specialists at Helen DeVos Children's Hospital stay aware of these changing conditions and how they affect children. Concerned physicians may contact the infectious disease specialist on call via Helen DeVos Children's Hospital (877.391.2345) for help and advice on these patients with this pediatric inflammatory disease/syndrome.

Additional information on MIS-C in children associated with COVID-19:

- There may be genetic/ethnic predisposition.
- Male gender may be a risk factor.
- It is currently not known if this syndrome is exclusive to children.
- The Center for Disease Control and Prevention requests that suspected cases be reported to help define risk factors, pathogenesis, clinical

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Course and treatment to help further characterize this new condition.

Case definitions extracted from the CDC for Kawasaki disease:
- Fever >5 days or until date of IVIG-if given before five days of illness
- Four of five of the following:
  - Rash
  - Cervical lymphadenopathy of at least 1.5cm
  - Bilateral conjunctival injection
  - Oral mucosal changes
  - Peripheral extremity changes

Patients whose illness does not meet above Kawasaki disease case definition but who have fever and coronary artery abnormalities are classified as having atypical or incomplete Kawasaki disease.

MIS-C diagnosis details:
- An individual age < 21 years presenting with fever, laboratory evidence of inflammation and evidence of clinically severe illness requiring hospitalization, with multisystem (≥ 2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological).
- No alternative plausible diagnosis.
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology or antigen test; or COVID-19 exposure within the four weeks prior to the onset of symptoms.
- Fever ≥ 38.0 °C for ≥ 24 hours, or report of subjective fever lasting ≥ 24 hours including, but not limited to, one or more of the following: an elevated CRP, erythrocyte sedimentation rate, fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase or interleukin 6, elevated neutrophils, reduced lymphocytes and low albumin.

Some children may fulfill complete or partial criteria for Kawasaki disease, but should be reported if they meet case definition for MIS-C. Physicians should also consider MIS-C if any pediatric death occurs with evidence of SARS-CoV-2 infection.

Additionally, patients with the syndrome should have cardiology referral with an EKG and serial echocardiograms including detailed study of the coronary arteries. If there is cardiac involvement, these patients will likely require long-term follow-up.
Aileen Aldrich, MD
Pediatric Infectious Disease

Leisha Cuddihy, PhD
Psychology

Linda Pauliks, MD
Pediatrics Cardiology

Timothy Moss, MD
Genetics

**Aileen Aldrich, MD**, is a board-certified pediatrician specializing in infectious diseases. Dr. Aldrich earned her medical degree from University of North Dakota in Grand Forks. She completed her pediatrics residency at Helen DeVos Children’s Hospital in Grand Rapids and her pediatric infectious diseases fellowship at University of Nebraska Medical Center, Children’s Hospital & Medical Center in Omaha.

Her clinical interests include pediatric HIV, tropical and travel medicine, and global health.

**Leisha Cuddihy, PhD**, is a sleep psychologist, board certified in behavioral sleep medicine. After completing her master’s and doctoral degrees in clinical psychology at the University of Arizona in Tucson, Arizona, she completed her internship at The Warren Alpert Medical School of Brown University in Providence, Rhode Island, and her postdoctoral fellowship in adult psychology and behavioral sleep medicine fellowship at the University of Michigan in Ann Arbor, Michigan. Before joining Spectrum Health, Dr. Cuddihy served as a behavioral medicine psychologist at Pine Rest Christian Mental Health Services in Grand Rapids, Michigan.

Dr. Cuddihy has clinical interests in insomnia, continuous positive airway pressure (CPAP) adjustment, sleep medication issues, and circadian abnormalities.

**Linda Pauliks, MD**, is a board-certified pediatrician specializing in pediatric and congenital cardiology. Dr. Pauliks earned her medical degree from Free University of Berlin in Germany and her master’s degree in public health from Harvard University in Cambridge, Massachusetts. She completed her pediatric residency at University of Maryland Medical System in Baltimore, her pediatric cardiology fellowship at New York Presbyterian Hospital Cornell Medical College in New York City and her congenital heart disease and critical care fellowship at the German Heart Institute in Berlin.

Her clinical interests include all aspects of cardiac imaging, including echocardiography, cardiac magnetic resonance imaging (MRI) and CT.

**Timothy Moss, MD**, is a board-certified geneticist specializing in molecular genetic pathology. Dr. Moss earned his medical degree from University of Iowa in Iowa City. He completed his medical genetics residency at Baylor College of Medicine in Houston, Texas and his molecular genetics pathology fellowship at University of Minnesota in Minneapolis. His clinical interests include epigenetics, overgrowth disorders, vascular anomalies and variant classification in exome sequencing.
Clinical Case:
A 3-year-old healthy fully-immunized girl presented Helen DeVos Childrens Hospital Emergency Department with fever for five days. Her daily fevers ranged from 101 to 103. Her mother also reported a dry cough, a splotchy red rash in various parts of her body, pink eyes, and progressive swelling of her hands and feet. She was more tired than normal, with poor oral intake, abdominal pain, occasional vomiting and no diarrhea. No other household members had been sick. A day prior to the girl becoming ill, the extended family had an outdoor gathering, where there were no known ill contacts.

Diagnostic Evaluation:
In our emergency department, she was ill appearing and moaning. She was hypotensive with tachycardia. Her capillary refill was five seconds. She was treated for shock with normal saline fluid boluses, an epinephrine drip, vancomycin and ceftriaxone. She was admitted to the pediatric intensive care unit, where she was intubated, and central and arterial access was obtained. She received aggressive vasoactive medication support including norepinephrine, dobutamine, vasopressin and hydrocortisone.

Her initial diagnostic studies revealed negative a rapid strep test and pyuria. Her white blood cell count was 24,900 (absolute neutrophil count of 20,320 and absolute lymphocyte count of 1,440), hemoglobin was 10.7 and platelets were clumped. Her blood urea nitrogen was 48 with creatinine of 1.78 and bicarbonate of 17. Her C-reactive protein was markedly elevated at 339, procalcitonin was 32, sedimentation rate was 29, and ferritin was 1,728. Her COVID-19 nasopharyngeal PCR test was negative. Her chest radiograph showed mild pulmonary edema and possible superimposed pneumonia. Her echocardiogram showed normal cardiac structures with moderate depressed global left ventricular systolic function, no regional wall motion abnormalities, normal coronary artery origins and sizes, mitral regurgitation, and small pericardial and bilateral pleural effusions. All microbiological studies were negative.

This critically ill patient was managed in the pediatric intensive care unit for several days, with several consultant services collaborating on her care. She was treated for Kawasaki shock syndrome and toxic shock syndrome with intravenous immunoglobulin followed by infliximab. A bone marrow biopsy was done and showed some hemophagocytosis. She completed seven days of ceftriaxone for culture-negative septic shock. She showed gradual improvement and was eventually extubated. Her cardiac function eventually normalized, but she continued to have mild mitral regurgitation.

The patient was discharged home with close follow-up. Antibody testing for the novel Coronavirus (SARS-CoV-2) was positive, indicating that her illness was likely triggered by this virus.

“The analogy I’ve drawn recently is that finding MIS-C can feel like finding a needle in a haystack right now, because fevers and systemic symptoms are so common in pediatrics. But we do need to keep a high level of alert until the scientific community can provide more specifics about how pediatric patients present and progress with MIS-C.”

Rosey Olivero, MD
Specialized Care Across Michigan

Our hospital and main outpatient clinics are located in:
Grand Rapids

Additional outreach clinics are available in:
Cadillac  Lansing  Owosso  Traverse City
Grand Haven  Marquette  Reed City  Zeeland
Holland  Mt. Pleasant  Rockford
Kalamazoo  Muskegon  St. Joseph

For information on our locations and services, visit helendevoschildrens.org.