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biliary atresia

current understanding and approach to a devastating disease of infants

by Daniel K. Robie, MD

learning objectives

Following the completion of this article, the reader should be able to:

1. Describe the various causes of biliary atresia and the condition of the bile ducts in most cases of biliary atresia.
2. List the steps in establishing the diagnosis of biliary atresia.
3. Summarize the current outcomes with the Kasai procedure and with liver transplantation.

Biliary atresia (BA) is a rare disease of infancy and has widely variable incidence rates between eastern (Taiwan and Japan: 1 in 6,000) and western countries (UK: 1 in 17,000). Four distinct clinical groups of biliary atresia have been characterized: Isolated BA which occurs in 70-80% of cases, cystic BA found in 5-10% of cases, CMV-IgM positive found in approximately 10% of cases, and syndromic BA in approximately 5% of cases.[1] A scarred, obliterated extrahepatic biliary drainage system is identified in the majority of all these cases. Cystic BA is characterized by prenatal detection of a cystic structure at the porta hepatis often confused with a choledochal cyst. However, at surgery the cyst is found in the presence of an otherwise scarred and obliterated extrahepatic biliary system. The fourth clinical group, syndromic BA, is characterized by an absent common bile duct, splenic malformation with possible situs inversus and occasionally a preduodenal portal vein. This type of BA likely represents primary failure of embryogenesis during the first eight weeks of gestation.

etiology

The cause of the progressive obliterative cholangiopathy in the majority of BA cases remains unknown. A common theory is a viral-triggered pro-inflammatory auto-immune response that selectively obliterates the bile ducts.[2] Much interest has focused on CMV. The CMV-IgM positive group of BA patients is distinguished by being older at time of diagnosis and surgical treatment. Whether a CMV infection is causative is yet unknown, as the virus has not yet been identified in liver biopsies from these patients. Other viruses that have been considered as possible triggers are reovirus, rotavirus, Epstein-Barr virus and parvovirus B19.[3] However, no consensus has been reached or direct cause and effect established as to the role of viruses in BA.

Two other possible causes of BA are maternal microchimerism and maternal ingestion of plant toxins.[2] In the former, transplacental passage of circulating maternal cells into the developing fetus and in particular the fetal liver could trigger an immune response or act as immune cells themselves. Plant toxins have been linked to the occurrence of BA in sheep and calves. A plant toxinbilatresone, is being used to study BA in zebrafish and mice.

It is yet unclear the role of genetics in causing biliary atresia. The strong geographic variance in incidence of BA would suggest an association exists. Two single nucleotide polymorphisms (SNPs) in the ADD3 gene have been identified in both Chinese and Caucasian patients with BA.[2]

history and progress

The natural history of BA is progressive jaundice, failure to thrive, poor weight gain, liver failure and death usually by 2 years of age. Dr. Willis Potts in his seminal book *The Surgeon and the Child*, published in 1959, lamented that "it is discouraging to be able to do nothing for infants in whom no remnant of bile ducts can be found... During the past 12 years approximately 60 patients have been operated upon and only three cured." Coincidental to this publication date was the work of Dr. Mario Kasai of the National Tohoku University School of Medicine in Japan. His operation, hepatic portoenterostomy or Kasai procedure, first performed in 1955 and published in 1959, forever changed the outlook for infants with BA.[1] Now with the availability of liver transplant, first performed on a patient with BA in 1967 by Dr. Tom Starzl, and

subsequent refinement in surgical technique and post-transplant immunosuppression, the vast majority of these infants will live full lives.[4]

presentation and diagnosis

Infants with BA initially present to the pediatrician with jaundice, a common finding in healthy newborns. The pathologic causes of jaundice in the newborn are broad and include viral and bacterial infections, metabolic diseases (e.g. Crigler-Najjar, Alpha-1 antitrypsin deficiency), neonatal hepatitis, Alagille syndrome and many others. Characteristic of BA patients is the increased level of conjugated bilirubin (>20% of the total bilirubin level) and in many cases an enlarged liver with often a firm liver edge. Additional studies readily available that can help differentiate BA from other causes of jaundice include GGT levels, right upper quadrant ultrasound with focus on gallbladder (GB) anatomy and presence of a triangular cord sign (TCS), HIDA scanning, and liver biopsy.[5] Often overlooked but critically important is to inspect the infant's stool. Pale or light-colored stool indicates a lack of bile pigment — an acholic stool. The nation of Taiwan designed an Infant Stool Color Card for mass screening to identify earlier infants with BA (figure 1).[6]

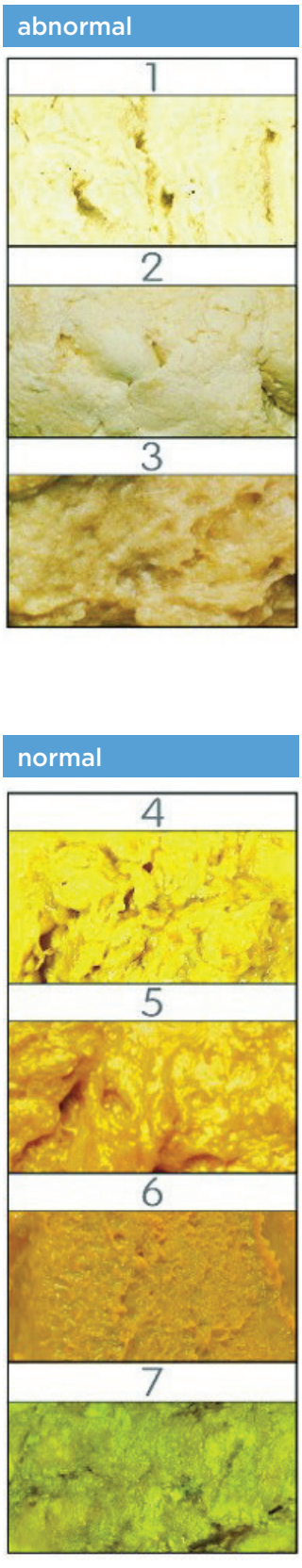

figure 1. infant stool color card

A recommended step-wise diagnostic approach to the jaundiced infant includes several key steps:

1. Thorough history and physical including visual inspection of the stool.
2. Obtain specific lab tests: total bilirubin (TB) and direct bilirubin, GGT, AST and ALT.
3. Right upper quadrant ultrasound with attention to gallbladder and the triangular cord sign.
4. Either percutaneous liver biopsy or definitive exploration with open liver biopsy and cholangiogram.
5. A HIDA scan or MRCP may be considered but should not delay definitive surgical exploration.
6. To rule out other causes of jaundice, tests such as TORCH antibody titers and Alpha-1 antitrypsin levels may be ordered.

the Kasai procedure and postoperative management

The Kasai procedure is the primary surgical approach to the majority of infants with BA regardless of age at presentation. The superiority of the open to a laparoscopic approach is widely recognized.[7] Essential steps are to attempt an intraoperative cholangiogram; removal of the scarred obliterated bile duct remnants and, if present, the gallbladder; transection of the scarred ducts flush with the capsule of the liver to uncover the tiny patent intrahepatic ductules; creation of a Roux-en-Y limb of jejunum; and meticulous sewing of the limb to the newly cut liver surface (Figure 2).[8]

The postoperative management following the Kasai procedure should follow an established protocol designed to optimize results and reduce variability of care. The use of IV steroids to reduce inflammation is institutional dependent and favored by this author. Dose should be 4-5 mg/kg per day of methylprednisolone for 1-2 weeks followed by a 4-week taper.[9] In addition, IV broad spectrum antibiotics are given for 7 days followed by transition to a po antibiotic for prophylaxis against cholangitis (e.g., trimethoprim-sulfamethoxazole). Once the infant is tolerating oral

feeds, ursodiol is added to facilitate bile drainage as well as multivitamins. Routine early postoperative ordering of liver enzyme and bilirubin levels is not necessary. A single total bilirubin level and direct bilirubin level should be checked just prior to discharge.

A successful Kasai is expected in two-thirds of patients and current long-term (10-year) survival with native liver varies from 24-53% in large series.[1] Though liver transplant is necessary in the majority of patients, a successful Kasai procedure defined as TB < 2.0 at 6 months allows the transplant to be delayed until the patient is older. Operative and early postoperative complications of the Kasai procedure are rare. Unfortunately, a number of these patients experience one or more episodes of cholangitis most often within the first two years postoperative. Cholangitis is an independent negative predictor of survival of the native liver.

prognosis

The success of the Kasai procedure is dependent on several factors. These include the cause of the BA, the age at the time of the Kasai operation, and the degree of liver damage (fibrosis/cirrhosis) present at time of the operation.

We previously reviewed the four clinical groups of BA. The most common, isolated BA, has traditionally been labeled as either correctable or uncorrectable. The correctable type of isolated biliary atresia represents the small percentage that has only partial obliteration of the extrahepatic biliary system with preservation of the two main hepatic ducts (types 1 and 2). While the uncorrectable type of isolated biliary atresia, the vast majority of these cases, have obliteration of the entire system (type 3). The cystic BA group is most often diagnosed early and allows for an earlier Kasai operation with resultant less liver damage. Unfortunately, the remaining two groups, CMV-IgM positive BA and syndromic BA, carry a worse prognosis despite the Kasai procedure.

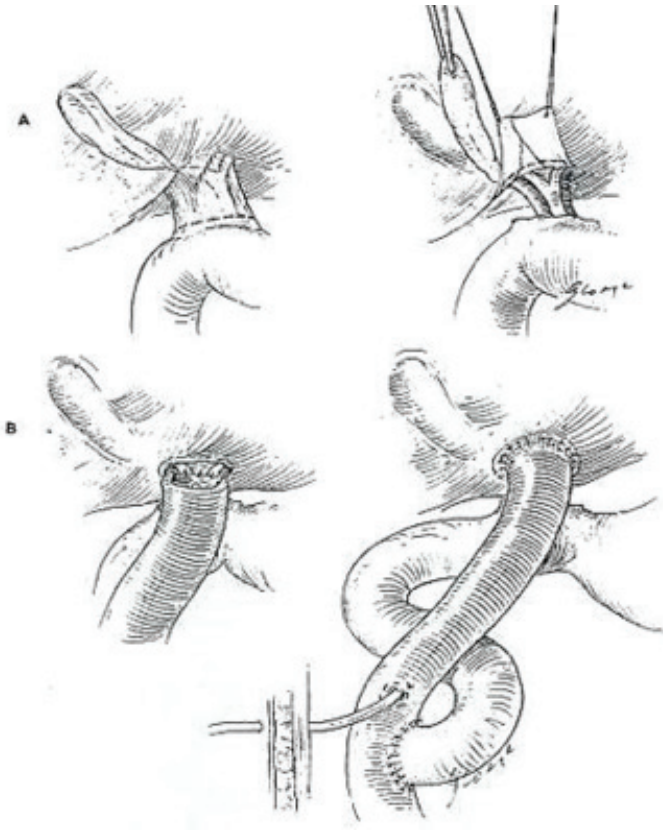

figure 2. Steps in the Kasai procedure

Age in days at the time of the Kasai has long been considered important in predicting outcome. This is due to ongoing progressive liver damage in the presence of continued biliary obstruction prior to surgical intervention. Ideally, the diagnosis is made early enough to allow the Kasai operation to be performed in the first 45 days of life. However, even for infants presenting with BA as late as 6 months of age, the Kasai procedure is still recommended as the initial surgical option in most.[7] The effect of liver fibrosis or damage present at the time of the Kasai on outcome and native liver survival is a focal point of current research.[10] The presence of bridging fibrosis predicts worse outcome.

BA is the most common indication for liver transplant in children. End-stage liver disease requiring transplantation can present as synthetic dysfunction, intractable portal hypertension, refractory ascites, coagulopathy, variceal bleeding, refractory pruritis and failure to thrive.[4] Contemporary outcomes with pediatric liver transplantation are excellent with graft survival at 90 days, 1 year, 3 years and 5 years of 98.4%, 96.6%, 92.2% and 87.7% respectively. In addition, over 50% of graft failures are successfully rescued with re-transplantation.[11]

changing the current paradigm

Though the outlook for infants born with BA is significantly better than in the time of Dr. Potts and prior to the seminal work of Dr. Kasai, the need for liver transplant in the majority of these patients is discouraging. Early diagnosis of BA remains the goal along with performing the Kasai procedure by 45 days of age. Pediatric primary care providers' recognition of BA during routine well-baby checks is key. Population based initiatives such as early parental education about BA as well as use of stool color cards are important adjuncts to consider. Future research should continue to focus on determining the causes of BA, earlier diagnosis, as well as reversing liver fibrosis.

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CME questions

1. **Which of the following clinical groups of BA has the best prognosis?**
   a. **Isolated BA**
   b. **CMV-IgM positive BA**
   c. **Syndromic BA**
   d. **Cystic BA**
2. **Which of the following have not been associated with BA?**
   a. **Viruses**
   b. **Genetics**
   c. **Alpha-1 antitrypsin deficiency**
   d. **Plant toxins**
3. **Postoperative steroids are helpful following the Kasai procedure.**
   a. **True**
   b. **False**
4. **Age at time of the Kasai procedure is not predictive of outcome.**
   a. **True**
   b. **False**

whole genome sequencing (WGS)

first-line diagnostic test to learning population health platform in patients with rare diseases

by Kalliopi Trachana, PhD,
Apostolos Psychogios, MD, FACMGG,
and Lee Hood, MD, PhD

learning objectives

Following the completion of this article, the reader should be able to:

1. Discuss the benefits and limitations of WGS as a first-tier diagnostic test for rare diseases.
2. Recognize the implications of advancing WGS as a population health platform.
3. Describe the principles of a learning health care system.
4. Understand when to refer patients for WGS to the Dayton Children's genome clinic.

Whole genome sequencing (WGS) is being established as the most effective test for rare disease diagnosis. At the same time, it holds a transformative potential for our industry — a paradigm shift from disease-driven care to wellness- and prevention-oriented care. Toward this vision, system-wide changes (infrastructure, policy, workforce development and other capabilities) are necessary. Dayton Children's genetics division emerges as an implementation leader in this new paradigm. We believe that every patient, especially the most vulnerable ones, should have equal access to innovative services that optimize their health outcomes and prolong their lives.

introduction

Whole genome sequencing (WGS) is being established as the most effective test for rare disease diagnosis. At the same time, it holds a transformative potential for our industry — a paradigm shift from disease-driven care to wellness- and prevention-oriented care. Toward this vision, system-wide changes (infrastructure, policy, workforce development and other capabilities) are necessary. Dayton Children's genetics division emerges as an implementation leader in this new paradigm. We believe that every patient, especially the most vulnerable ones, should have equal access to innovative services that optimize their health outcomes and prolong their lives.

Ten million children in the U.S. are affected by a rare disease with a genetic etiology, placing genomics in the essential toolkit for accurate and fast diagnosis. In July 2021, the American College of Medical Genetics (ACMG) released new guidelines that recommend whole exome/genome sequencing (WES/WGS) as first-tier tests for rare disease diagnosis. Below, we discuss how this provides new care and research innovation opportunities for this patient population, and eventually, for all our communities. We introduce a model that transitions WGS from a diagnostic tool to a population health solution for these children and their families, establishing an engagement platform for long-term follow-up to optimize their care experience and, in some cases, provide powerful therapies. Toward this goal, it is essential that care and research operations come together in a single scalable platform with an integrated vision of how to build a learning health care system that meets the standards of other national initiatives and beyond.

whole genome sequencing as the first-tier test for rare diseases

Over the last decade, genomic medicine leaders completed clinical utility and cost-effectiveness studies1 that generated evidence for new guidelines and policies recommending exome/genome sequencing as first-tier tests.[2] WES/WGS as a first test yielded more diagnoses at a lower cost than using exome/genome after the extensive standard testing (e.g., microarrays, large multigene sequencing panels and/or other multiple testing approaches) or using standard testing alone.

A pilot study implemented across California and focused on critically ill Medi-Cal babies (178 participants) showed that rapid WGS (rWGS) improves clinical outcomes, enhances the experience of care for families and clinicians, and reduces net health care expenditures.[3] rWGS results in a healthier neonatal intensive care unit (NICU) population, fewer days in the hospital, fewer invasive procedures, and thus, significantly lower health care costs (Table 1).

Diagnostic rate:	43%
Chance of management:	72%
Reduced length of stay (by 6 days in average):	94%
Avoided major procedures such as invasive biopsies:	6%
Average net benefit of rWGS per patient:	$4,287

table 1. Baby Bear/rWGS Study

WES/WGS as a first-tier diagnostic test for rare diseases is gaining ground as an emerging practice. Payers are still learning the accumulating evidence and drafting new policies[3] to improve market access (overall 64% of insured individuals have access to either an exome or genome test). Payers are expanding testing coverage for outpatients with a diagnostic odyssey. The currently increasing market access and reimbursement information to payers and providers offer an excellent opportunity to accelerate the development of the new genome service at Dayton Children's.

building a genome-enabled population health platform for the rare disease community

Most clinical laboratories performing WES/WGS in the United States report secondary findings based on the ACMG policy, conducting screening for medically actionable risk variants that may inform disease prevention (Table 2). At the same time, academic centers and health care systems with research leadership have begun to offer WES/WGS to healthy individuals leveraging the ACMG recommendations to create genome-enabled population health solutions. This newly emerging field aims to bring the power of precision medicine to primary care settings. Health care systems

Guidance from the ACMG Policy Statement[6] on incidental findings established that clinical laboratories performing WES/WGS should report known pathogenic and likely pathogenic variants in a defined set of genes considered medically actionable even if are unrelated to the primary medical reason for testing (defined as secondary findings — SFs).
Patients need to have the opportunity to informed decision or opt-out if desired. The option to receive SFs should be offered regardless of the patient's age. In case of pediatric patients, child's psychological well-being should be a priority when disclosing genetic risk for adult-onset diseases (i.e., familiar cancers or heart conditions). Pre-test and post-test genetic counseling and qualified provider consulting is essential.
Between ACMG SF v2 and v3, the Board selected 14 new genes underlying several hereditary cancer, heart or other phenotypes; this is a 25% increase in actionable insights for preventive medicine in four years.
There are 74 clinically actionable genes on the list today.

table 2. ACMG SF v3: What labs report after exome/genome testing based on policy

collect genomic, clinical, social and "-omics" (e.g., blood, analytes–proteins, lipids and metabolites, and microbiome) data to understand individual and population risks. This rich dataset combined with the proper care pathways and clinical decision support infrastructure will help them learn and expand their practices to early treatment, prevention and wellness.[4] As every patient's characteristics and experiences will be available for study, best practice knowledge will be immediately available to support clinical and administrative decisions and secure the continuous operational improvement in daily practice routine.[5]

To enable this fundamental genomic-oriented shift in health care today, researchers, implementation experts and providers must collaborate and deliver evidence-based clinical pathways and policy at scale using a learning population health platform. Starting this endeavor in areas that can lead to a return on investment will encourage leaders of health care systems to better engage in these efforts. Therefore, in the Dayton Children's genetics division we plan to bring these two practice concepts together and design a learning population health care platform for rare diseases.

genetics at Dayton Children's

The genetics division at Dayton Children's is working toward developing a new comprehensive genomic medicine program for early diagnosis, tailored management, and familial prevention of heritable and rare disorders of children and adults. We offer a unique comprehensive care experience to our patients including genome sequencing, family and personal history analysis, physical, and morphological examination aiming to:

1. Diagnose their condition, offer detailed genetic counseling and familial genetic testing as applicable, and provide tailored management recommendations to the referring providers and the patients.
2. Deliver actionable risk information that may change the disease development and prevent it in collaboration with their providers.
3. Identify potential research opportunities for new targeted and innovative therapies.
4. Re-analyze and re-interpret their genome annually or on any other interim significant health or life event using advanced artificial intelligence (AI) solutions.

Many studies have demonstrated the added utility of re-analysis of genomic data. This re-analysis can be better facilitated in a health care system with a committed research environment where the analysts and domain-specific experts have access to deep phenotypic information of the patients, and the ability to re-contact them and their clinicians to coordinate management and follow-up. Today, about 10% of patients have multiple pathogenic variants associated with the primary reason for referral, while about 50% have pathogenic or likely pathogenic gene variants that are neither related to the primary presentation nor are included in the 2021 ACMG Secondary Findings (SF v3) per Psychogios' unpublished cohort data raising the question which sets of variants we should report back to the patient and treating provider and whether these can predict the patient's health trajectory (future clinical manifestation).

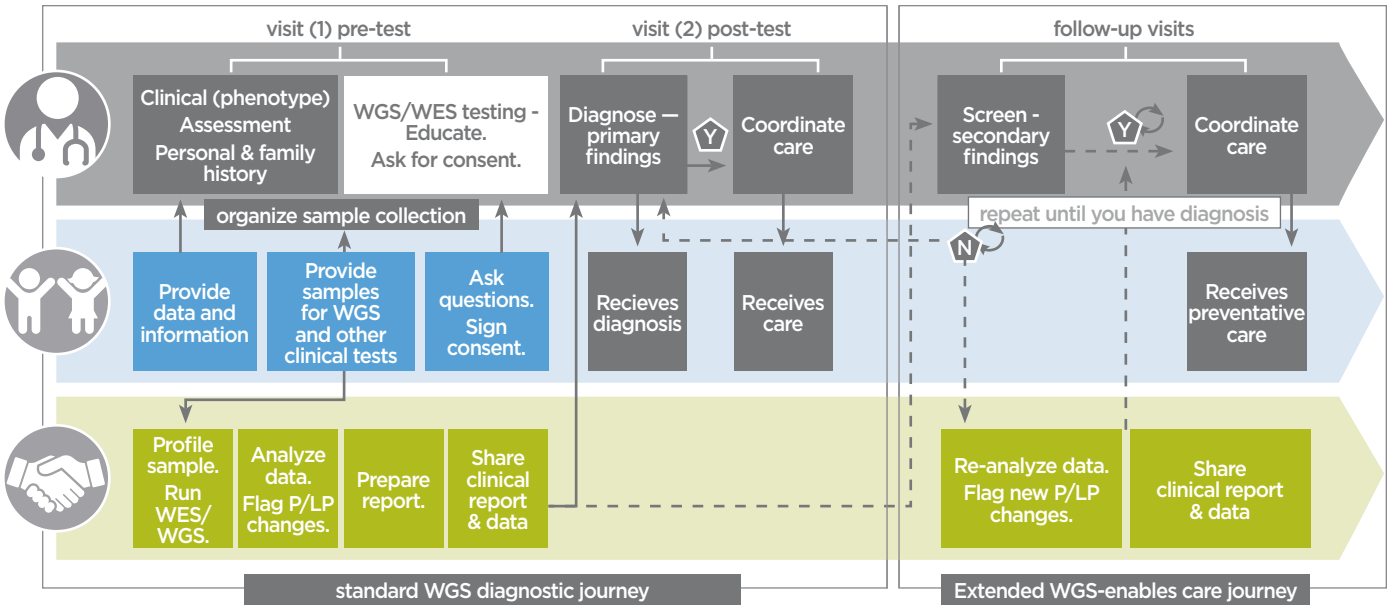

figure 1. Program Overview: On the first visit, the provider informed patients about WGS technology, explained how the results would be used to inform care, and asked patients to consent for genomic data collection, clinical testing and research. Samples were collected and delivered to a commercial clinical lab to perform WGS. The lab returned both clinical reports and the sequencing data to the provider and the patient. The report describes all pathogenic (P) and likely pathogenic (LP) changes that are related or unrelated to the primary phenotype (rare disease manifestation). After synthesizing all available information, the provider recommended a personalized care plan. Genetic counselors and other qualified providers educated patients on the limitations and advantages of testing methodology and clinical interpretation and discussed management change expectations.

Based on the above, we plan to support a clinical team of domain-specific experts including medical geneticists, physician-champions, and other qualified providers and scientists who will re-analyze the patients' genome data in combination with their latest clinical and -omics data. This will secure the continuous generation of new knowledge for medically actionable genes and identify new variants.

identifying barriers and solutions for implementation of a genome-enabled learning platform

Beyond the technical requirements of establishing sequencing and bioinformatic capacity to process samples, a genome-enabled learning population health platform requires adequate and continuing genomic education in the workforce as well as infrastructure that supports complete learning cycles (data collection and interpretation, clinical action and change management, health outcomes, and repetition of the process).

How can we remove the barriers to the promotion and implementation of the genome-enabled learning platform? We propose the following actions regarding
1) data integration and interpretation,
2) workforce capacity and support, and
3) ethical and legislative challenges.

1. Data integration and interpretation

- Develop technical standards and policy guidance, which are high priorities at this crucial inflection point toward more responsible and effective sharing of genomic and clinical data to facilitate evidence-based implementation (clinical pathways).
- Facilitate and accelerate data governance, analysis, and interpretation at scale, which require substantial cloud and personnel resources.
- Validate and apply emerging artificial intelligence tools to efficiently build workflow of data collection and interpretation available to the domain experts and providers.

2. Workforce capacity and support

- Educate the providers and their associates of the WGS value as a diagnostic and preventive tool.
- Develop just-in-time information, guidelines for clinical action, and more information on the clinical utility of genetic testing that would help providers to effectively use the genomic data and integrate it in their practices like the other medical tests.
- Incentivize the primary and specialty care providers to offer WGS as the first test for all patients who visit their clinics and interpret their data for care management throughout their lives.
- Offer continuous training opportunities to physician assistants and other qualified care navigators on genome (and omics)-related workflows in their practice.

3. Ethical and legislative issues

- Inform and be transparent with the patients and families about the benefits and challenges of using WGS in their care. Request and document a written consent for all future activities (re-contact, research opportunities, etc.) with the right to withdraw at any time.
- Educate patients and their families on the broadest value of WGS beyond clinical care and how their participation can change medical knowledge and practice.
- Partner with patients and communities of different ethnic backgrounds often underrepresented in genomic research to achieve higher engagement and promote equity in care access and services.

With our continuous data-driven approach in our daily practice, we aim to create a new population health initiative for the greater Dayton area communities and leverage existing and new philanthropic resources to support it. Clearly as the WGS programs mature, they will identify increasing numbers of clinical conditions and develop the ability to treat them with increasing effectiveness. As this opportunity expands to other institutions, the trajectory of this transformation will accelerate.

Lastly, indications to refer children and adults to our genomic clinic include but are not limited to undiagnosed conditions, medical odyssey, positive family history of a rare condition or a common condition with unusual clinical course and outcome, Autism-spectrum disorders, developmental delay, cognitive disability, mental and behavioral illness, familial cancers, failure to thrive, overgrowth conditions, familial obesity, prematurity, pre-eclampsia, endometriosis, infertility, birth defects, congenital anomalies and syndromes, epilepsy, cardiomyopathy, arrhythmia, sudden death, aorta aneurysms and dissections, coronary artery syndromes, renal disease, arterial and pulmonary hypertension, diabetes, connective tissue disorders, skeletal dysplasias, inborn errors of metabolism, premature aging, and any individual seeking genomic information to prevent disease and support lifelong wellness.

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Lee Hood, MD, PhD

Lee Hood, MD, PhD, is the senior vice president and chief science officer at Providence Health & Services, as well as the chief strategy officer and co-founder for the Institute for Systems Biology. Dr. Hood graduated from the Johns Hopkins University School of Medicine with an MD and from Caltech with a PhD in biochemistry. A pillar in the biotechnology field, Dr. Hood has played a role in founding 15 biotechnology companies including Amgen, Applied Biosystems, Integrated Diagnostics and Arivale. He is a member of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

CME questions

5. **Which statements below are true regarding rWGS, as shown in Baby Bear project?**
   a. **rWGS has a higher diagnostic rate than any other genomic technology.**
   b. **rWGS changes care utilization for most critically ill babies.**
   c. **rWGS can identify targeted therapies**
6. **Which statements below reflect principles of a learning health system?**
   a. **Every patient's care data and experiences are available for study.**
   b. **Best practice knowledge is immediately available to support decisions.**
   c. **Research is the most important part of the learning cycle.**
   d. **Expand the education, training and performance of clinicians.**

health equity

by Destry Fallen, LISW-S,
Shehzad Saeed, MD, and
Jessica Saunders, MPA

learning objectives

Following the completion of this article, the reader should be able to:

1. Define health equity and health disparities.
2. Discuss skills that enable more equitable clinical practices.
3. Identify opportunities for clinicians to engage in the community to promote equity.

Consider two young boys who have been diagnosed with asthma. Thomas lives in a neighborhood with plenty of parks, his home was built within the last five years, and his family has insurance that pays for his medications. Brandon lives in a neighborhood with no parks, no grocery stores and in a home that is very old and riddled with mold. His family has challenges getting medications as family finances typically require Brandon's mom to choose between food and other amenities. Which of these young boys is likely to have poorer health outcomes?

According to the CDC, health equity is achieved when every person has the opportunity to "attain his or her full health potential" and no one is "disadvantaged from achieving this potential because of social position or other socially determined circumstances." Health inequities are reflected in differences in length of life; quality of life; rates of disease, disability and death; severity of disease; and access to treatment. Health disparities define differences between groups. In the scenario above, Thomas and Brandon are in different groups based on where they live. In a community like Dayton, which is very racially segregated, it's likely Thomas and Brandon will experience disparities based on race. Inequity describes the causes of disparities in the context of the social, economic, civil-political, cultural and environmental conditions that are required to generate parity/equality.[1] In the above scenario, disparities exist because of the economic situations and environmental conditions each of the two boys live in.

Health equity is the principle underlying a commitment to reduce—and, ultimately, eliminate—disparities in health and in its determinants, including social determinants. Pursuing health equity means striving for the highest possible standard of health for all people and giving special attention to the needs of those at greatest risk of poor health, based on social conditions.[2]

There are many structural drivers such as poor air quality, unsafe playgrounds, substandard housing and poverty, that expose families to different issues that encourage and/or discourage certain behaviors. The Prevention Institute created the Trajectory of Health Inequity to demonstrate this concept (Figure 1).[3] For example, if a child grows up in a neighborhood located in a food desert, with fewer green spaces and high unemployment (unhealthy community conditions), the child will have fewer available spaces to play outside or access to healthy food. This would substantially increase the likelihood of this child becoming obese (medical conditions). The fore mentioned example compared to a child growing up in a neighborhood where food resources are plentiful, green spaces abundantly available allowing outside play, and low unemployment would yield inequities related to health outcomes.

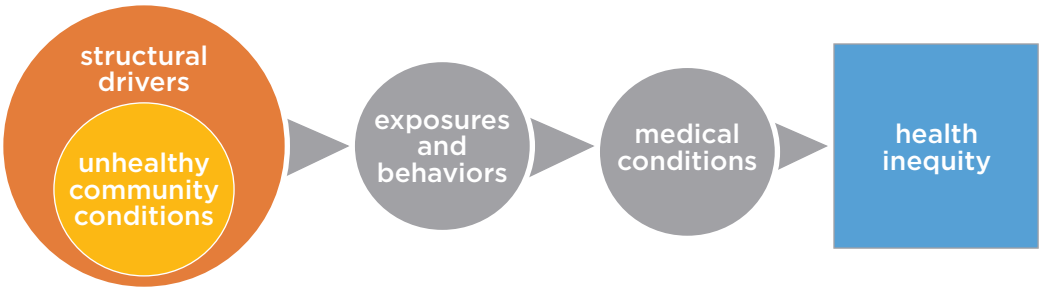

figure 1. Prevention institute's trajectory of health inequity

health equity in our community

In the 2021 Annie E. Casey Kids Count report, Ohio ranks 31st for child well-being.[4] This ranking is based on a variety of indicators related to economic well-being, education, health and community context. Key metrics indicated that in 2019, 8% more child and teen deaths occurred compared to 2010. Nearly 20% of Ohio children did not graduate on time prior to the pandemic, less than the national average, making Ohio 38th out of all 50 states in this indicator. The number of parents who do not have full-time year-round employment is still high, at 26% statewide.

Moving closer to the Dayton region, our children continue to face community conditions increasing the exposure to issues impacting health. In Montgomery County, 23% of children live in poverty. Of the children ages 0-5 living below poverty, 20.3% are White and 61.9% are Black.

The challenges facing our children, especially as we contend with COVID-19 and a mental health crisis, seem overwhelming at times. When we look at children living in poverty with limited access to food, stable housing and broadband connectivity, the need for an equity lens becomes ever more apparent.

the role of pediatric clinicians

Pediatric clinicians are uniquely poised to identify disparities and address elements of health equity not only because of the ubiquity of inequities among children but also because of the relatively high number of touchpoints they have with patients in early life.[5]

There is a great opportunity to address health equity in clinical settings and the authors suggest a relevant framework to implement this work. This framework includes identifying and using good data to drive decision making, honing provider skills in listening to the voice of those with lived experience, and being a community advocate to change the structural drivers that can bring about disparities. This three-layered framework requires intentional work to address inequities within the clinical setting.

The Center for Health Equity isn't just about programs and services. It's about people at Dayton Children's meeting children and families where they are and helping them get where they need to be. Shannon Nicks, PhD, gains valuable feedback from families as one of our outcomes researchers for the Center for Health Equity.

data to drive decision making

Through a recent Institute for Healthcare Improvement (IHI) project, Dayton Children's staff reviewed admission data for asthma disaggregated by race. An initial look at this data revealed that Black children with asthma are significantly overrepresented in the number of emergency department visits compared to White children (53% v. 37.7%), admission rates per 1,000 children per year (7.89 v. 1.48), and readmission rates within 30 days (16.7% v. 9.3%). Black children were also overrepresented in children with two or more hospitalizations.

While there is still a lot of work to understand the "why" behind these numbers, obtaining the right data is a first and crucial step.

Looking at disaggregated data is a first step in understanding where disparities exist and which patients may be most adversely affected.

Hospitals and health systems, including Dayton Children's, are moving toward more universally capturing Race, Ethnicity, and Language (REaL) data consistently to identify if certain groups have different outcomes.

In addition, depending on where clinicians are practicing, the types of disadvantage they will encounter will vary and not always be obvious just by looking at a patient. Screening for social needs to look at the whole child/whole family and taking this information into account when providing clinical recommendations is also becoming a very common practice. Providing resources to address those social needs is also critical.

Capturing REaL data and social needs information can help a clinician build a better context that provides holistic care for a family. Collecting additional information should inform practice. In doing so, clinicians need to recognize and understand their own biases (both implicit and explicit bias), the impact of these biases on clinical care and outcomes, and when necessary, have a plan to address those biases that impact care and relationships.

provider skills in empathy, listening and building trusting relationships with families

When we have spoken to our patient families about their experiences in a clinical setting, a common statement heard is, "I want someone to listen to me." An aspect of equitable care is meeting a patient family where they are. One must intentionally slow down, and sometimes pause, to listen, through the lens of the patient family, and identify where they see themselves in order to truly provide collaborative patient-/family-centered care. There is not a one-size-fits-all solution for families, and understanding the challenges and barriers families face in following medical instructions, obtaining medications or understanding a diagnosis are critical.

One way to build provider skills is to help families become more health literate. Health literacy is defined as the degree to which individuals have the capacity to obtain, process and understand basic health information that they need to make appropriate health decisions.[7] One common method to engage families in improving health literacy is the "teach-back" technique. Through this technique, clinicians can check whether they have adequately explained information in a way that the patient understands. Ways to "teach back" include asking the patient questions like, "I want to make sure I've explained everything to you clearly. Can you explain it back to me to make sure I communicated well?" or "I've given you a lot of information today. In your own words, can you tell me what we talked about?"

community advocacy

There is a broad recognition that the social determinants of health impact health outcomes, yet health care cannot solely provide the solution for this challenge. Improving health equity requires cross-sector work and advocacy to change community conditions enabling health. Physicians have a unique perspective of how social conditions can adversely impact the health of patients. Bringing this knowledge, perspective and experience to legislators, school boards and local governments when policies and investments are being made is critical to improving the community context for families.

Considering these challenges, the role of all clinicians (providers, nurses, dietitians, social workers, etc.) expands from clinical care to include child advocacy at the clinical and community levels to address root causes of childhood illness and morbidities.[8] Clinical experience and research evidence can be used to advocate for social change.[9]

The clinician voice, combined with the voice of those with lived experience, is essential for changing community level systems. For instance, advocating for stronger anti-tobacco and anti-vaping legislation, engaging in efforts to improve air quality, and supporting policy that lowers emissions might all be ways to improve outcomes for children with asthma. There is an important role for clinicians to play in this work.

conclusion

In our new strategic roadmap, Dayton Children's has chosen "health equity" as a focus area and added "equity" as one of our core values. The practices mentioned in this article are the beginning of the work around diversity, equity and inclusion (DEI). Through our diversity and inclusion work, we have held focus groups with employees addressing DEI, provided senior leaders and directors with inclusive leadership training, and started employee resource groups for LGBTQ+ and Black employees as a way to support employees. The hospital has also started a minority nursing program to increase the number of racially/ethnically diverse nurses at Dayton Children's. The hospital is providing training for registration staff on how to obtain REaL data and why it's important. In addition, the hospital is launching the Center for Healthy Equity, which will focus on measuring the outcomes impacted by specific health equity interventions both in the clinical and community settings.

The state of our children's health can be greatly improved, especially for children living in community conditions where the environment makes it difficult to "attain his or her full health potential." Clinicians have a unique opportunity to improve children's disparate health outcomes using data to drive decision making; by honing provider skills when establishing trusting, collaborative relationships; via empathetic listening to lived patient family experiences; by addressing social determinants; and through being a community advocate.

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authors

Destry Fallen, LISW-S

Destry Fallen, LISW-S has worked at Dayton Children's since 1990. He received his undergraduate social work degree from the University of Dayton and master of science in social work degree from the University of Louisville. Destry is an Ohio License Independent Social Worker with Supervision Designation (LISW-S). For 20 years, Destry served as the manager of the department of social work, supervising medical social workers and community health workers, while serving on numerous internal and community committees advocating for children and families. In July 2020, Destry became the director of diversity and inclusion leading the hospital initiatives towards a culture of engagement, inclusion, and belonging.

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Shehzad Saeed,MD, FAAP, AGAF is the associate chief medical officer and a pediatric gastroenterologist at Dayton Children's Hospital. After completing his medical education at Dow Medical College, University of Karachi in Pakistan, he completed his general pediatric training at the University of Chicago Hospital in Chicago, Illinois, and his fellowship in pediatric gastroenterology and nutrition at The Floating Hospital for Children, New England Medical Center, Tufts University in Boston, Massachusetts. In addition to the care he provides for children with chronic digestive diseases, Dr. Saeed is also a professor at the Boonshoft School of Medicine at Wright State University in Dayton, Ohio, and has an interest in leveraging his quality improvement background in improvement opportunities across the health care system.

Jessica Saunders, MPA

Jessica Saunders is the executive director of the Center for Health Equity at Dayton Children's. She has worked at Dayton Children's since 2007 and is responsible for Dayton Children's community outreach and population health programming including the Dayton Asthma Alliance and the Family Resource Connection, a program that screens for social needs of patients. Previously she was the Community Relations Manager at Dayton Children's where she developed and directed a number of programs including the Kohl's A Minute for Kids program, Safe Kids Greater Dayton and the Mead Westvaco Family Resource Center. She is also the project manager for the Dayton Children's Regional Pediatric Health Assessment which is used to set the children's health and safety agenda for the hospital.

CME questions

7. Health equity is achieved when every person has the opportunity to "attain his or her full health potential."
   a. True
   b. False
8. REaL data refers to demographic data about:
   a. Social needs
   b. Race, ethnicity and language
   c. Race and socioeconomic status
9. Community conditions or the social determinants of health account for a significant portion of a child's health.
   a. True
   b. False

COVID-19

recent literature, updates and more

by Sherman Alter, MD

COVID-19 in children and adolescents

Throughout the pandemic, children typically have fared better than have adults with SARS-CoV-2 infections. In the United States, persons under the age of 18 still account for less than 2% of hospitalizations due to COVID-19 (a total of 3,649 children between March 2020 and late August 2021).[1] Over 400 have died. However, the rise of the Delta variant presents unknowns among the pediatric population.

A report from the Centers for Disease Control and Prevention (CDC) noted that weekly COVID-19–associated hospitalization rates among children and adolescents rose nearly five-fold during late June to mid-August 2021, coinciding with increasing circulation of the highly transmissible SARS-CoV-2 Delta variant. Approximately 1 in 4 hospitalized children and adolescents with COVID-19 require intensive care. Hospitalizations were highest among kids aged up to 4 years, and teens 12-17 years. Importantly, the proportion of individuals with severe disease during the latter Delta-predominant period was similar to that seen earlier in the pandemic.

Among adolescents for whom a COVID-19 vaccine is currently approved (persons 12-17 years), hospitalization rates were approximately 10 times higher in unvaccinated compared with fully vaccinated adolescents. Vaccines were found to be highly effective at preventing serious COVID-19 illness in this age group during a

learning objectives

Following the completion of this article, the reader should be able to:

1. Review risk of hospitalization for COVID-19 among vaccinated and unvaccinated adolescents.
2. Discuss estimated occurrence of myocarditis following mRNA COVID-19 vaccination

period when the Delta variant has predominated. Pediatric hospital admissions were nearly four times as high in states with the lowest vaccination rates as in those with the highest rates.2 As of July 31, 2021, 32% of U.S. adolescents had completed a COVID-19 vaccination series. Vaccine uptake is best among younger patients with at least 52% of children aged 12 through 17 years in the U.S. having received at least one dose of a COVID-19 vaccine and about 40% being fully vaccinated. Over 40% of adolescents in Ohio have completed the series (as of early September 2021). Increasing vaccination coverage among adolescents, as well as expanding eligibility for COVID-19 vaccination to younger age groups when approved and recommended should further reduce severe COVID-19–associated outcomes among children and adolescents.

COVID-19 can result in severe disease in children and adolescents and carries additional risk for serious longer-term sequelae (e.g., multisystem inflammatory syndrome in children, or MIS-C). Multilayered preventive measures to reduce transmission and severe outcomes in the pediatric population are critical, including vaccination among eligible age groups, universal masking in schools, and masking by persons aged ≥2 years in other indoor public spaces and child care centers.

safety of mRNA vaccines

More than 342 million doses of COVID-19 vaccines have been administered in the U.S., with the majority being mRNA vaccines from Pfizer-BioNTech or Moderna. In an interim analysis of safety surveillance data from the Vaccine Safety Datalink, over 10 million vaccine-eligible members of eight participating U.S. health plans were monitored with administrative data and medical record review for outcomes of 23 serious adverse events from December 14, 2020, through June 26, 2021.[4] Any serious adverse events typically occur in the immediate period following vaccination. Comparisons were made of outcome incidence during a risk interval of 1 to 21 days after vaccination to that seen in vaccinated comparators 22 to 42 days after their most recent COVID-19 vaccination.

mRNA COVID-19 vaccines were safe for the population overall (i.e., no difference for any of the serious outcomes assessed). In this large surveillance study, mRNA COVID-19 vaccines were not associated with significantly higher rates of different serious adverse events (comparing those seen 1 to 21 days after receiving 1 or 2 doses to those seen after 22 to 42 days). However, while analyses of all ages combined did not detect a significant association between myocarditis/pericarditis and mRNA vaccines, an excess risk of myocarditis/pericarditis was identified for vaccines in those aged 12 to 39 years.

In another study of a nationwide mass vaccination setting of the BNT162b2 vaccine (Pfizer), Israeli investigators assessed adverse events in over 800,000 persons (three study groups: 1) vaccinated, 2) those with COVID-19, and 3) persons who were neither vaccinated nor previously infected) over a 42-day period. Vaccination was not associated with an elevated risk of most of the adverse events examined. Those infections that occurred were generally mild. Again, the vaccine was associated with a minimal excess risk of myocarditis (1 to 5 events per 100,000 persons). The study did note that the risk of this potentially serious adverse event and of many other serious adverse events was substantially increased after SARS-CoV-2 infection.[4] Thus, the benefit of protection from vaccination considerably exceeds the very minimal risk of a serious adverse event related to receipt of the vaccine.

breakthrough infections

A recent study used surveillance data from the county of Los Angeles in evaluating the risk of acquiring SARS-CoV-2 infection among vaccinated and unvaccinated persons as the Delta variant surged from May 1 through July 25, 2021 (10,895 fully vaccinated and 30,801 unvaccinated persons).[5]

By the end of the study period, the infection rate among the unvaccinated individuals was 4.9 times that in fully vaccinated (age-adjusted incidence in unvaccinated persons was 315.1 per 100,000 people over a 7-day period compared to 63.8 per 100,000 incidence rate among fully vaccinated). The hospitalization rate among unvaccinated persons was 29.2 times that seen in fully vaccinated persons (age-adjusted rate was about 1 per 100,000 vaccinated persons versus 29.4 per 100,000 in unvaccinated). Older vaccinated people were most vulnerable to serious illness after a breakthrough infection. The median age of vaccinated persons who were hospitalized for COVID-19 was 64 years. The median age of the unvaccinated who were hospitalized was 49 years.

With any real time PCR assay, a cycle threshold value (Ct) is defined as the number of cycles required for the assay's fluorescent signal to cross the threshold (i.e., exceeds background level). Ct levels are inversely proportional to the amount of target nucleic acid in the sample (i.e., the lower the Ct level the greater the amount of target nucleic acid in the sample). Ct values correlate with the amount of viral nucleic acid present. In July, when the Delta variant was predominant in Los Angeles County, PCR assays documented similar Ct values in unvaccinated, partially vaccinated, and vaccinated persons, suggestive of similar viral loads among the three different populations.

additional viruses of interest (beyond SARS-CoV-2!)

We have had a variation in the typical seasonal occurrence of respiratory syncytial virus (RSV) activity.6 Early in the summer of 2021, increased RSV activity was seen across parts of the southern United States, subsequently spreading across most of the country. RSV infections in temperate climates occur typically during the fall and winter cold and flu season (November through March). With the institution of nonpharmacologic interventions (e.g., masking, social distancing) for the prevention of COVID-19 in March of 2020, however, the number of RSV infections decreased significantly. The characteristic RSV epidemiology might also have been altered through interactions among SARS-CoV-2 and other respiratory viruses.

RSV is the most common cause of bronchiolitis and pneumonia in children under 1 year of age. Severe RSV disease can occur among preterm infants, especially infants born <29 weeks' gestation, those with chronic lung disease of prematurity, infants with certain hemodynamically significant congenital heart disease, infants and young children with certain immunodeficiency states, and infants with pulmonary abnormalities or neurological and neuromuscular conditions that impair ability to clear secretions from the upper airway.

Palivizumab (Synagis®), a humanized monoclonal antibody directed against the fusion protein of RSV, has been used for some time to decrease the risk of hospitalization in infants at significantly increased risk of severe RSV disease during the typical season. Up to five monthly doses are recommended to provide serum levels associated with protection during the typical RSV season.[7] At present, the period for administration of the antibody to eligible infants will be prolonged and should be based on local viral activity. The palivizumab clinic at Dayton Children's began operations early this summer. Since this elevated inter-seasonal RSV activity is a deviation in the typical circulation patterns for the virus, prediction of the likely spread, peak or duration of activity will be difficult.

The AAP recommends annual influenza vaccination for all children ages 6 months and older, without medical contraindications. This is especially important in the midst of the ongoing COVID-19 pandemic. All pediatric and adult seasonal influenza vaccines are quadrivalent, with trivalent vaccines no longer expected to be available. The vaccines include new influenza A(H1N1) and A(H3N2) components. The AAP has no preference of one vaccine over any others and continues to recommend both injectable and nasal spray vaccines. Breakthrough influenza infections among those persons vaccinated do occur. However, illness is generally mild and does not require hospitalization.

Influenza vaccine can be administered simultaneously with or any time before or after administration of the currently available COVID-19 vaccines. Children who have acute moderate or severe COVID-19 should not receive influenza vaccine until they have recovered. Those with mild illness can be vaccinated.[8]

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CME questions

10. Which of the following is true among adolescent vaccinated with a COVID-19 vaccine?

a. Hospitalization rates are approximately 10 times less than for those seen among vaccinated adolescents.

b. Severe illness caused by SARS-CoV-2 infection in vaccinated teenagers is less common than that seen in a comparable group of unvaccinated adolescents with COVID-19.

c. Persons 18 years of age and younger account for approximately 2% of all COVID-19 hospitalizations in the United States.

d. All of the above

11. Which of the following is true pertaining to adverse events following mRNA COVID-19 vaccines

a. The mRNA vaccines have been associated with a small excess risk of myocarditis in persons aged 12 to 39 years.

b. Most adverse events following vaccination occur typically occur after 42 days.

c. Most adverse events that occur following vaccination are generally mild.

d. a and c

e. a, b, and c

Dayton Children's updates

tops in children's hospitals – again!

Dayton Children's Hospital has been recognized as a Best Children's Hospital for 2021-22 by U.S. News & World Report.

The annual Best Children's Hospitals rankings and ratings, now in their 15th year, are designed to assist patients, their families and their doctors in making informed decisions about where to receive care for challenging health conditions.

Dayton Children's was ranked in orthopedics and pulmonology.

"Pulmonology and orthopedics are two of our largest divisions – seeing thousands of children every year," says Deborah Feldman, president and CEO of Dayton Children's Hospital. "While we know it is just one measure that a family should use in choosing the right care for their child, it's another symbol parents can use to show them that Dayton Children's provides expert care."

division of ophthalmology now at Dayton Children's!

Brenda Young, MD

In July, Dayton Children's opened a department of ophthalmology. The new division offers ophthalmology care at the main campus.

Services include:

- Ocular Trauma and other emergencies
- Treatment of medical eye conditions
- Surgical treatment for ocular diseases and conditions
- Optical shop

introducing doctor Brenda Young, MD

Brenda Young is the in-house ophthalmologist. She was born and raised in Middletown, Ohio and graduated AOA from University of Cincinnati College of Medicine in 2002. Dr. Young has extensive experience in both private practice and academic medicine.

referring a patient

Referrals to Dayton Children's department of ophthalmology may be submitted beginning June 28, 2021. All referrals to ophthalmology through the hospital will automatically be sent to Dr. Young.

announcing the center for health equity

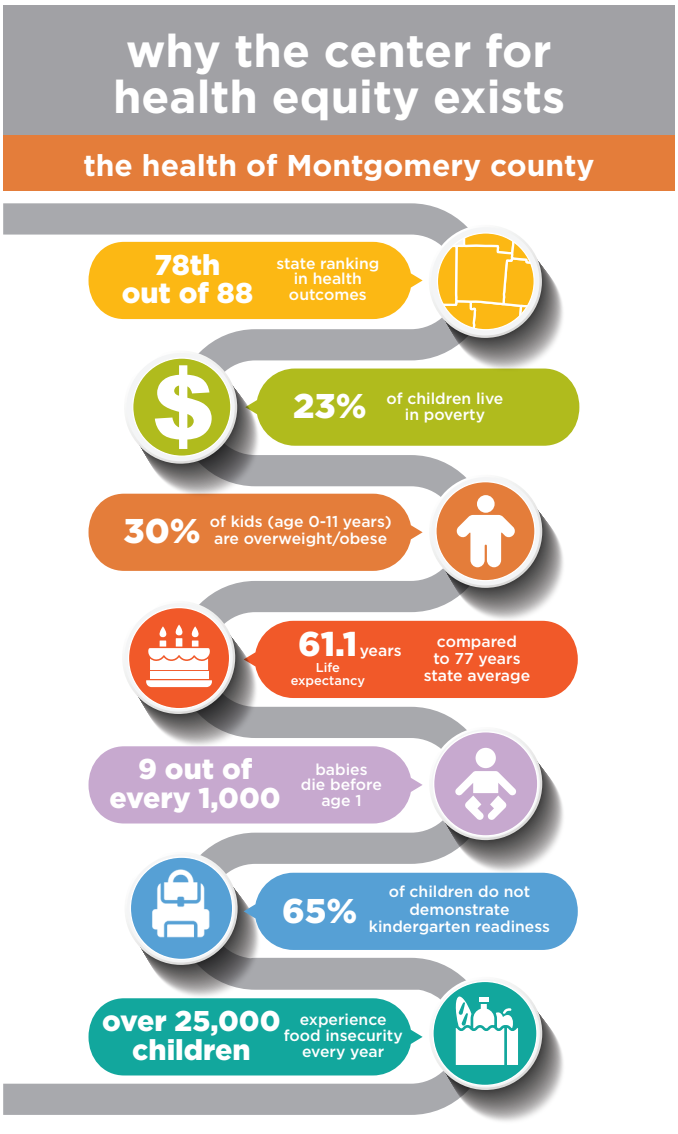
Dayton Children's new center for health equity takes commitment to optimal health for all children to the next level with a deep investment in resources, research, strategy and structure. The goal is to better understand the health disparities that exist amongst our children, identify the reasons behind why a child is not thriving and work with the community to provide the support necessary at a much earlier point.

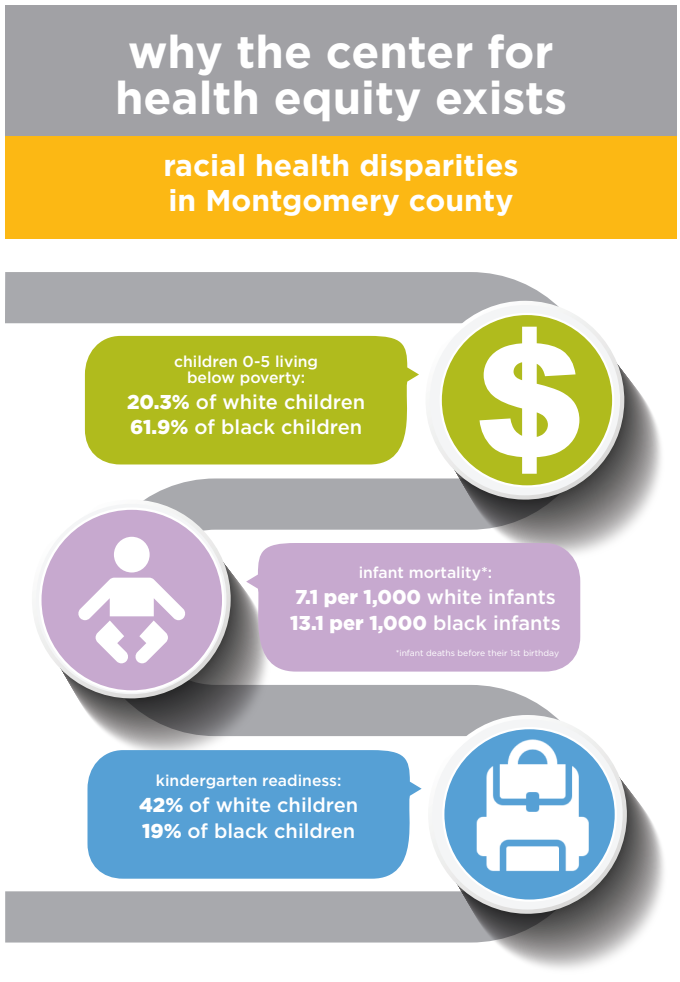
A person's health shouldn't depend on their skin color, zip code, level of education or income. Yet so often these factors, sometimes called "social determinants of health," are what get between many children in the Dayton area and optimal health, putting them at high risk for diseases such as obesity, diabetes and uncontrolled asthma.

This is not a short-term strategy, nor is it a quick fix.

Dayton Children's has been addressing this problem for many years through hospital-based programs and partnerships with other community organizations. The reasons for the problem are complex. No one organization can provide a single solution. But as one of the city's largest employers and the only institution in the Dayton area entirely dedicated to pediatric health care, Dayton Children's has a unique responsibility to help delve into the "why" behind health disparities and work with our partners and parents to find solutions.

"We're really investing in this work," says Saunders. "We've doubled our staff, adding the positions unique to finding the connections between health outcomes and social factors. We've hired researchers to gather the right data, track and measure it, and find opportunities to help that we might have been missing. We hope the connections we find will inform our work with our community partners for a more unified approach."





program evaluation

1. The material presented in this publication met the mission to enhance health care delivery in our region through education based on the essentials and policies of the Accreditation Council for Continuing Medical Education.
   ☐ Strongly agree ☐ Agree ☐ Neutral
   ☐ Disagree ☐ Strongly disagree

2. Did the material presented in this publication meet the educational objectives stated?
   ☐ Yes ☐ No

3. Did the material presented in this publication have a commercial bias?
   ☐ Yes ☐ No

4. Please rate the contents of this issue using the following scale:
   1 = Poor, 2 = Fair, 3 = Good, 4 = Very good, 5 = Excellent *(Circle one response for each.)*

	Poor				Excellent
Timely, up-to-date?	1	2	3	4	5
Practical?	1	2	3	4	5
Relevant to your practice?	1	2	3	4	5

5. Please describe any changes you plan to make in your clinical practice based on the information presented in this program.

   _____

6. Are there any other topics you would like to have addressed in this publication or future educational programs for health care providers?
   ☐ Yes ☐ No If yes, please describe:

   _____

7. Please describe how you will incorporate information obtained from this publication into your practice.

   _____

8. Letter to the editor — Letter to the editor may be emailed to alters@childrensdayton.org or attached to this evaluation and may be published in the next issue.

physician accreditation statement and credit designation

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Wright State University (WSU) and Dayton Children's Hospital.

WSU designates this Journal-based CME Activity for a maximum of 4 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

program test

to obtain CME credit you must:

Read and reflect on each article.

Answer the questions from each article and complete this test — http://cmequiz.childrensdayton.org/PedForumNov2021. 70 percent correct answers are needed to obtain the full 4.0 AMA PRA Category 1 Credits™.

Complete the program evaluation.

Return your completed test and program evaluation by email, mail or fax to: Sue Strader, coordinator
Department of Continuing Medical Education
Dayton Children's Hospital, One Children's Plaza,
Dayton, Ohio 45404-1815
Fax: 937-641-5931

E-mail: straders@childrensdayton.org

Take test online: http://cmequiz.childrensdayton.org/PedForumNov2021

This test must be received by March 31, 2022 for the credit to be awarded

pediatric forum | volume 35, issue 2

your answers to CME questions
(Please circle the BEST answer.)

1.	a	b	c	d	
2.	a	b	c	d	
3.	true	false			
4.	true	false			
5.	a	b	c		
6.	a	b	c	d	
7.	true	false			
8.	a	b	c		
9.	true	false			
10.	a	b	c	d	
11.	a	b	c	d	e

please type or print clearly

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practice name _____

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pediatric forum

fall 2021

One Children's Plaza
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Pediatric Forum is produced for the professional staff and referring physicians of Dayton Children's by the marketing communications department.

The purpose of Pediatric Forum is to provide information and news about pediatric health care issues and to provide information about clinical services and management issues of Dayton Children's.

physician accreditation statement and credit designation

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Wright State University (WSU) and Dayton Children's Hospital.

WSU designates this Journal-based CME Activity for a maximum of 4 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

obtaining CME credit

To obtain CME credit, read, reflect on articles, complete the evaluation and answer at least 70 percent of the quiz correctly. Send the answer sheet and program evaluation to:

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Fax 937-641-5931
Email straders@childrensdayton.org

Take quiz online: childrensdayton.org/providers

The answer sheet and program evaluation must be received by December 31, 2021, for the credit to be awarded.

sponsorship/accreditation information

author information

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target audience

This education activity is designed for pediatricians, family physicians and related child health care providers.

educational objectives

- Identify the four pediatric issues covered in this journal and develop appropriate intervention.
- Appropriately use the resources of Dayton Children's Hospital to improve patient care.

dayton children's

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