June 14, 2024

Rare Disease Advisory Council Annual Report

Table of Contents

Letter from the Rare Disease Advisory Council (RDAC) Chairperson

June 14, 2024

Dear Governor Holcomb and Indiana Legislative Council,

It is with great pride that I present the first annual report on the activities of the Indiana Rare Disease Advisory Council (RDAC) in Indiana as required in HEA 1201, which was enacted in 2023 by the Indiana General Assembly. The RDAC is pleased to be seeking solutions to treat and mitigate the effects of Rare Diseases in Indiana and beyond with the hope of someday eliminating them so all Hoosiers can live long, productive and healthy lives. This committee is proud to be part of the solution and is looking forward to continuing this important work for many more years.

Within this report is a summary of the impressive accomplishments of the council which began meeting monthly on September 26, 2023, and the RDAC's recommendations for consideration and adoption in the coming general assembly. These recommendations are bulleted below:

- Fund a pediatric cancer research and treatment grant program with a priority on innovative research and treatments for pediatric cancer.
- Establish a working group of pediatric oncology specialists whose goal is to meet with and provide recommendations to the state and insurers on issues related to treatments and diagnostic modalities that affect pediatric oncology. This working group should be placed under the RDAC.
- For those cases that are subject to prior authorization and peer review, establish a requirement of the insurance provider to have a pediatric subspecialist in the area of disease expertise as the peer reviewer.
- Provide a state subsidized position for a Learning Specialist/School and Community Liaison at every health system (currently four) serving pediatric oncology and rare disease patients to provide enhanced educational support.
- Require insurance coverage for fertility preservation of pediatric cancer patients, when medically appropriate.
- State appropriation for continued RDAC activities including dedicated staff support.

The expertise of the RDAC is immense with representation from patient/caregivers, industry, research, pharmacy, advocacy organizations, medical providers, minority health groups and state agencies. These members bring their diverse perspective to assessing the landscape of care in Indiana, gathering and sharing resources and developing actionable recommendations for the Indiana General Assembly to enact.

Sincerely,

Wade Clapp, MD

Rare Disease Advisory Council Chairperson; Chair, Department of Pediatrics; Richard L. Schreiner Professor of Pediatrics; Indiana University Distinguished Professor

Introduction

Established by the General Assembly in 2023, the Rare Disease Advisory Council is charged with the following tasks:

Establish a council whose duties include the following:

- Conduct public meetings to survey the needs of patients in Indiana with rare diseases and their caregivers and providers.
- Provide testimony, comments and recommendations concerning legislation and rules that impact the patients in Indiana with rare diseases.
- After consulting with experts on rare diseases, develop policy recommendations to improve patient access to and the quality of: rare disease specialists; affordable and comprehensive health care coverage; relevant diagnostics; timely treatment; and other needed services for patients with rare disease.
- Research and make recommendations to state agencies and insurers that provide services to persons with rare diseases on the impact of prior authorization, cost sharing, tiering or other utilization management procedures on the provision of treatment and care for patients.
- Evaluate and make recommendations to improve Medicaid coverage of drugs for patients with rare diseases to improve coverage of diagnostics and facilitate access to necessary health care providers with expertise in the treatment of rare disease.
- Publish a list of existing, publicly accessible resources on research, diagnosis, treatment and education relating to rare diseases on the state department's website.
- Evaluate the current state and funding of pediatric cancer research taking place in Indiana and how the research interacts with the landscape of pediatric cancer research done nationally.
- Study other issues and provide grants that impact patients with rare diseases.

This report fulfills the requirements of the HEA 1201 (2023) to "submit an annual report to the governor and the legislative council not later than June 15. The report submitted to the legislative council must be in an electronic format under IC 5-14-6." The required report must include the following: "Summary of the council's activities and progress" and "Recommendations of the council to the governor and general assembly on ways to address the needs of people living with rare diseases."

Membership

Chairperson: Dr. Wade Clapp (Physician-in-Chief, Riley Hospital for Children at IU Health, Chairman of Pediatrics, IU School of Medicine)

Term: Ends Sept. 30, 2025

Biopharmaceutical Representative: Dr. Brian O'Neill (Senior Director, Pediatric Development Eli Lilly and Company)

Term: Ends Sept. 30, 2027

Health Carrier Representative: Dr. Joel Feldman (Chief Medical Director of MHS Indiana)

Term: Ends Sept. 30, 2025

Hospital Administration: Dr. Jodi Skiles (Medical Director at Riley)
Term: Ends Sept. 30, 2025

Pharmacist with relevant experience: Dr. Tara Jellison (Ambulatory Services, Parkview Health)

Term: Ends Sept. 30, 2026

Physician with relevant experience: Dr. Patrick Milligan (Infectious Disease Physician, Community Health Network)

Term: Ends Sept. 30, 2027

Rare Disease Caregiver: Laura McLinn (President of Best Day Ever Foundation and Caregiver of Son Living With a Rare Disease - Duchenne Muscular Dystrophy)

Term: Ends Sept. 30, 2027

Rare Disease Organization: Mindy Cameron (Muscular Dystrophy Family Foundation and Caregiver of Son Living With a Rare Disease - Duchenne Muscular Dystrophy)

Term: Ends Sept. 30, 2025

Rare Disease Patient: Dr. Doug Cipkala (Pediatric Oncology, Peyton Manning)

Term: Ends Sept. 30, 2026

Rare Disease Patient: Dr. Michael Busk (Physician, Ascension St. Vincent)

Term: Ends Sept. 30, 2026

Rare Disease Researcher: Dr. Santiago Schnell (Director, Notre Dame Center for Rare Disease)

Term: Ends Sept. 30, 2026

Registered Nurse with relevant experience: Lucy Paskus (CPNP at Peyton Manning)

Term: Ends Sept. 30, 2026

Director of Office of Medicaid Policy and Planning Designee: Dr. (Jeremy) Ty Sullivan (OMPP)

Term: Appointment does not expire

Commissioner of the Department of Insurance Designee: Cory Best (IDOI)

Term: Appointment does not expire

Indiana Minority Health Coalition chief operating officer: Carl Ellison (President of the Indiana Minority Health Coalition),

Term: Appointment does not expire

Summary of Activities and Progress

RDAC Fiscal Year 2024 Highlights

- First meeting was held on September 26, 2023 and meetings have occurred monthly since then. Beginning in July 2024, meetings will occur on the second Friday of the month. Beginning in October 2024, members elected to move to bi-monthly scheduled meetings.
- Bylaws and electronic attendance policy adopted by the RDAC.
- Presentations were made to the RDAC by the Indiana Department of Insurance (IDOI), the Indiana Department of Health (IDOH), the Indiana Family and Social Services Administration (FSSA), the Indiana Children's Special Health Care Services (CSHCS), and the Indiana PGG Advisory Committee.
- Continued development of a survey instrument for parents, clients and providers of survivors of pediatric cancer which will be modified for other rare disease conditions. This survey will allow the RDAC to understand the scope and challenges of rare disease in Indiana to guide future efforts to improve the quality of life al all those affected by rare disease in Indiana as set forth in IC 16-46-17-3(3-5, 7-8).
- Established subcommittees for pediatric cancer and rare disease resources. Subcommittees are made up of both members of the RDAC as well as members of the public (including advocates and parents of children with rare diseases and pediatric cancer) that have expressed interest in the topic.
- The resources subcommittee was formed to fulfill the requirements set forth in IC 16-46-17-3(6) stating "publish a list of existing, publicly accessible resources on research, diagnosis, treatment and education relating to rare diseases on the state department's website."
- The pediatric cancer subcommittee was formed to fulfill the requirements set forth in IC 16-46-17-3(7) stating "evaluate the current status and funding of pediatric cancer research taking place in Indiana and how the research interacts with the landscape of pediatric cancer research done nationally." Appendix 2, referenced and incorporated herein, of this report discusses the current state of childhood cancer research in Indiana.
- Letter was submitted during open comment period to FSSA stating the RDAC support continued funding for legally responsible individuals to serve as paid personal care attendant for medically fragile individuals with 12 ayes and 2 abstentions. See Appendix 1
- Developed a RDAC webpage.
- Abstract on "Use of integrated preclinical platforms in close coordination with early phase trials to identify new drugs for orphan diseases" submitted to the National Organization of Rare Diseases for presentation at NORD Rare Diseases and Orphan Products Breakthrough Summit which will occur October 20-22, 2024 in Washington DC.
- RDAC meeting minutes and agendas may be viewed on the official RDAC webpage: www.in.gov/health/cdpc/rare-disease-advisory-council/.

Recommendations

The following recommendations were developed with the considerable and varied expertise of the RDAC. They reflect the widespread varied needs of patients living with rare disease. RDAC members recognize that ongoing recommendations will need to be adopted to fully address the needs of rare disease patients. These recommendations were seen as priorities to propose during a budget year, to further the ongoing work of the RDAC, honor the directive that the RDAC was to explore funding and research around pediatric cancer during the first year.

1. **Fund a pediatric cancer research and treatment grant program with a priority on innovative research and treatments for pediatric cancer.**

Childhood cancer research nationally accounts for only 4% of federally funded dollars awarded for cancer research overall. Identifying meaningful new therapies for pediatric cancers requires overcoming a series of obstacles including: fewer patients available to enroll on clinical trials, lack of novel drugs available to children, an incomplete understanding of the biochemical function of the cancer-causing mutations of the various cancers, the lack of research depth within an institution/region to function in effective research teams that can bring novel therapies to the clinic, and the costs and varied expertise required to generate new drugs.

While approximately 12 drugs per year are FDA approved for adult conditions, there have been only 11 drugs developed for pediatric conditions since 1978. Despite these many challenges, the medical and bioscience community in Indiana has made significant advances to drive innovation in pediatric cancer both locally and nationally. These include the major expansion of clinic and laboratory-based cancer research at IUSM/Riley Hospital for Children, the emerging collaborations between the flagship research institutions in the State, and the exciting development of public/private partnerships, particularly the Indiana Biosciences Research Institute that has a focus on orphan cancers and orphan disease therapeutics and is actively collaborating with IU School of Medicine and also beginning collaborations with Purdue University and Notre Dame University.

Though national investment in pediatric cancer discovery is small relative to the investment in adult cancers, Indiana has the potential to be a true hot spot of innovation and particularly innovation in the Midwest for pediatric cancers and also other non-malignant rare diseases. The development of increasing research capacity is important both for the development of a robust bioscience enterprise in Indiana and for the many children in Indiana. Being active in innovation in pediatric cancer promotes the awareness and access to novel drugs early in their use. Having a robust laboratory and clinical research community in Indiana provides opportunities for care that benefit all Indiana children and particularly those in many working-class families that would not have resources to travel. Strategic pilot investment by the State that could lead to transformative extramural funding opportunities (20-100 million dollar grants from ARPA-H), or the expansion of novel preclinical/clinical phase 1 platform trials for currently incurable cancers could be of broad benefit to families in Indiana. Several other states have recently made similar investments (Kentucky, Nebraska, New Jersey, New York, Maryland, Virginia,

Pennsylvania). Appendix 2 highlights research opportunities in Indiana between Indiana flagship academic institutions and the bioscience community to pursue federal and private equity funds. Pilot state support in this space could have parallel success as broad research efforts in Indiana in other medical conditions, particularly Alzheimer's disease. Further, having an innovative medical community has a halo effect that promotes the recruitment of pediatric subspecialist trainees and pediatric subspecialists that are in an increasingly steep decline nationally.

2. **Establish a working group of pediatric oncology specialists whose goal is to meet with and provide recommendations to the state and insurers on issues related to treatments and diagnostic modalities that affect pediatric oncology. This working group should be placed under the RDAC.**

3. **For those cases that are subject to prior authorization and peer review, establish a requirement of the insurance provider to have a pediatric subspecialist in the area of disease expertise as the peer reviewer.**

Recommendations 2 and 3 are closely linked. Therefore, the following justification supports both recommendations.

Historically, prior authorizations (PAs) were established to ensure that the utilization of health care resources (surgical, diagnostic, and pharmacy) was cost effective by maintaining consistency with published standard of care guidelines.

Barriers to an efficient and effective PA system, particularly in the pediatric oncology setting, include the burden of providing (often by phone and fax and not electronically) relevant clinical documentation, a lack of universally established clinical guidelines for such rare diseases, rapidly changing standards of care established by collaborative pediatric oncology groups such as the Children's Oncology Group, and a lack of reviewers with any pediatric oncology experience.

Whereas the PA process is intended to assure that patients receive medically appropriate care and reduce costs by eliminating unnecessary care, there are studies to suggest that the process itself has significant costs, including patient suffering and stress when delays in or denial of therapy occur. Delays in therapy as a result of PAs and appeals, particularly in the pediatric oncology setting, can significantly affect the overall outcome and survival of the patient.[1] Lengthy PAs with appeals can add to the financial costs to the health care system. The added cost of physician and staff burnout leads to reductions in overall provider availability also impacts the care provided to the patient.

We appreciate the immense complexities related to the prior authorization process and its objective to minimize inappropriate health care dollars spent. With the goal of providing the state of the art, highest quality care for Hoosier children, recommendations 2 and 3 were adopted.

We believe that these recommendations will benefit pediatric oncology and rare disease patients with greater efficiencies in providing timely, up to date care for them. We expect, from a pediatric oncology standpoint, that streamlining the PA process will also lead to improved overall survival outcomes for the pediatric oncology patient with the potential for short and long term savings in expenditures.

REFERENCES
1, Trapani D, Kraemer L, Rugo HS, Lin NU. Impact of Prior Authorization on Patient Access to Cancer Care. Am Soc Clin Oncol Educ Book. 2023 May;43:e100036

4. Provide a state subsidized position for a Learning Specialist/School and Community Liaison at every health system (currently four) serving pediatric oncology and rare disease patients to provide enhanced educational support.

We propose a state-subsidized innovative position for Learning Specialist/School and Community Liaison at every health system serving pediatric oncology and rare disease patients to provide enhanced educational support for survivors and those affected by childhood cancer. Education is a key predictor of future employment, income, and integration into society therefore, educational attainment is considered a key measure of the quality of long-term survivorship. As well as the impact that treatment may have on cognition (Askins & Moore, 2008) the education of survivors may also be adversely affected by missing time in school due to treatment, thus falling behind on schoolwork Vance & Eiser, 2002).

The purpose of this role is to function at the expanding intersection of medical, educational, and community institutions. These specialists will promote collaboration among professionals serving pediatric cancer patients, navigate networks dedicated to ongoing medical, educational, advocacy, and research, act as a liaison between the patient's medical team, family, and school, inform educational plans to best support the patient's needs, determine homebound needs, provide education information and resources and ongoing assessment for school needs and support, dissect/summarize neuropsychological reports with patients, families, and schools, and offer transitional support by creating transition plans when medically appropriate so as to get students back to school in a safe and meaningful way.

Transitioning does not happen at one point in time but is a process composed of multiple transitions that occur over time, preparing the individual for the next phase of life (Sabet, 2019). These specialists will create and implement plans to raise awareness and increase the utilization of services for persons affected by cancer. They will build awareness and establish relationships with healthcare providers and other organizations that will increase their knowledge of and referrals to educational services.

We propose the creation of an Indiana state-wide tutoring program consisting of retired teachers recruited from the Indiana Retired Teachers Association who support and encourage volunteerism. Children suffering from a chronic medical condition, such as cancer, may

experience lifelong impacts on learning, achievement, and employment opportunities, hence hindering their potential economic, social, and human development. Seeking ways to promote educational support within the educational or home environment ensures the presence, participation, and achievement of all children. Schools often do not have the resources to provide the level of support these children need.

REFERENCES 1. Askins, M. A., & Moore, B. D., 3rd (2008). Preventing neurocognitive late effects in childhood cancer survivors. *Journal of child neurology*, *23*(10), 1160–1171. https://doi.org/10.1177/0883073808321065

2. Sabet, R. F. (2019). *Health disparities among sickle cell disease patients: A grounded theory model* [Doctoral dissertation, University of Miami].

3. Vance, Y. H., & Eiser, C. (2002). The school experience of the child with cancer. *Child: care, health and development*, *28*(1), 5–19. https://doi.org/10.1046/j.1365-2214.2002.00227.x

5. Require insurance coverage for fertility preservation of pediatric cancer patients, when medically appropriate.

In the United States, approximately 160,000 people between ages 0-44 are diagnosed with cancer each year. Due to improvements in treatment, about 85% these patients will survive. Some cancer treatments, however, can cause infertility. Chemotherapy, radiation, and surgery can damage reproductive cells (eggs and sperm), reproductive organs, and/or endocrine functioning; they can also impact the ability to carry a pregnancy. Because this damage is primarily treatment-based, it can affect patients with any type of cancer.

Patients with other conditions requiring similar therapies (e.g., sickle cell disease, lupus, and thalassemia, etc.) are also at risk. In this age group, concerns about family building are second only to mortality, and infertility after cancer can cause depression, anxiety, and a lower quality of life.

Fertility preservation is now considered part of the standard of care for age-eligible patients. Standard procedures available for preserving fertility include sperm, egg, embryo, and ovarian tissue banking; all these approaches are supported by all the relevant medical associations, including the American Society of Clinical Oncology (ASCO), the American Society for Reproductive Medicine (ASRM), and the American Medical Association (AMA).

Cost is the biggest barrier to fertility preservation. Nationwide, costs can range from several hundred dollars for sperm banking, to approximately $15,000 for egg banking. Without insurance coverage, these treatments are unaffordable for many patients. The costs are exacerbated by the short window of opportunity that patients have before starting potentially sterilizing cancer treatment. While the costs faced by an individual patient are high, the cost when spread across a population of insured people is extremely low. Independent analyses in states where coverage has been enacted have estimated costs (per member per month) ranging from a low of $.01 (California); to a high of $.10-$.24 (Maryland).

Over the past six years, 16 states and DC have implemented some coverage for medically necessary fertility preservation. Current coverage: California, Connecticut, Colorado, Delaware, the District of Columbia, Illinois, Kentucky, Louisiana, Maine, Maryland, Montana, New Hampshire, New Jersey, New York, Rhode Island, Texas, and Utah.

Fertility preservation services are Medically Necessary. Fertility preservation for iatrogenic infertility is not "elective" or "experimental," but rather a needed intervention to prevent potential sterility and/or reproductive damage. Patients cannot rationally defer or forego life-saving treatments to spare their fertility. Independent clinicians uniformly find fertility preservation medically necessary in the context of gonadotoxic threat. These services address a side effect of cancer treatment. Remedies for other side effects, such as breast reconstruction, chemo-induced anemia, wigs and prostheses, etc., are typically covered by insurance.

Studies show that significant numbers of patients make sub-optimal treatment decisions (e.g., stopping tamoxifen or choosing less gonadotoxic treatment) to minimize reproductive impact. These decisions may adversely affect both medical outcomes and treatment costs. Infertility causes distress, depression, anxiety; these have financial and medical consequences, and result in overall lower quality of life for survivors. The lack of insurance coverage disproportionally affects women and those of lower socioeconomic backgrounds. Loss of fertility is not merely a medical complication; it permanently affects reproduction and parenthood – basic human activities worthy of the highest levels of protection.

6. State appropriation for continued RDAC activities including dedicated staff support.

RDAC will be considering ways to sustain their efforts across time. Staff support will be important to vet and maintain a high-quality resource website, support RDAC and subcommittees, engage the public for comments, adapt and disseminate the current survey instrument to other rare disease providers and patients and many other staff. Term limits will mean new member recruitment and orientation will be a regular task. Although this will serve to reinvigorate the RDAC, supporting council members will need stable staff support.

Appendix 1: RDAC Letter to Family Social Services Administration RDAC 2/9/2024

TOPIC: Proposed changes to Medicaid Waivers, specifically the Aged & Disabled[A&D] Waiver soon to be the Health & Wellness[H&W] Waiver

Purpose: To support families caring for medically fragile children with significant disabilities (e.g pediatric cancer patients) by allowing the child's LRI[legally responsible individual - including a parent, guardian, or other relative legally responsible for a minor child] to be the child's personal care attendant [PCA] and to be paid through the A&D Waiver program.

Background: Medicaid Waivers allow Medicaid to pay for services to someone who would otherwise need the level of care provided in an institution. The Indiana Family and Social Services Administration is proposing new waivers for people with disabilities that would end the practice of allowing parents of minor children and spouses to be paid as a family caregiver. In December 2023, the state issued a new Medicaid forecast that was nearly $1 billion off from the April 2023 forecast. An analysis found several factors led to the shortfall, including but not limited to: More people than expected enrolling in the A&D Waiver and increased use of A&D Waiver services, including attendant care. To address the near billion-dollar shortfall, the state proposed making changes to waivers. The Family and Social Services Administration (FSSA) submitted new waiver amendments to the Centers for Medicare and Medicaid Services (CMS) for the proposed Health and Wellness (H&W) waivers – currently the Aged & Disabled (A&D) waiver including: *Starting July 1, 2024, LRIs on the Health and Wellness, (formerly A&D Waiver), will only be paid for providing Structured Family Caregiving services. LRIs will no longer be paid to provide attendant care.

*Maintaining, but not increasing, the number of individuals served on the A&D Waiver, soon to be the Health and Wellness Waiver *Following current waiver regulations more strictly

*Providing waiver coverage only after an individual is approved for Medicaid The changes being proposed for the H&W Waiver do not eliminate Attendant Care services. However, the proposal would prevent LRIs from being paid to provide those services. Of note there is a shortage of home nursing and attendant care services in most if not all Indiana counties. Without LRIs acting as PCAs for medically fragile & complex children there may be no other service providers available.

Standard of Care: While not authorized in the current A&D waiver, the practice has been to allow LRIs to serve as paid PCAs with CMS allowing states to pay LRIs through a Medicaid Waiver.

Impact: Children with significant disabilities have frequent medical appointments, therapy sessions, and require constant care. Skilled caregivers other than their parents simply have not been reliably available in many areas of the state. LRIs know their child and their child's needs better than anyone. Because of their child's complex needs, LRIs are not able to work outside of the home. The reimbursement they receive does not provide the same level of income they would receive in a job outside of the home, but it does help. Being able to be a paid PCA for their child keeps families together by allowing LRIs to be with their child and keeping children out of institutionalized settings.

The RDAC (Rare Disease Advisory Council) opposes proposed changes to the A&D waiver [H&W waiver, and supports the practice of LRIs serving as paid PCAs for medically complex and fragile children.

I submit this on behalf of Indiana's Rare Disease Advisory Council. Our council voted to have these comments submitted to the open public comment forum.

Sincerely,

Laura McLinn

Appendix 2: State of Childhood Cancer Research in Indiana

The two fundamental means of innovation to improve childhood cancer survival – clinical and laboratory-based cancer research – are described in the appendix. The state of pediatric research in Indiana has had significant growth over the past several years and there is a strong basic, translational, and clinical research presence in the national and international community. There are numerous tangible examples of this impact on children in Indiana and beyond. Importantly, this research growth and innovation provides the impetus for other outstanding laboratory and clinical faculty to move to Indiana and develop additional new programs. In addition, the recent emergence of the Indiana Biosciences Research Institute (IBRI) and the many close collaborations in which they participate provides a unique new capacity in the Midwest and energy to Indiana in the development of novel drugs, biomarkers, technologies and biotech start up companies to drive therapeutics for both malignant and non-malignant applications.

The second area of innovation in childhood cancer is the preclinical identification of new therapies for pediatric cancers. The laboratory-based Pediatric Cancer Research Program (PCRP) in the state of Indiana is primarily driven by faculty members in the Department of Pediatrics at Indiana University School of Medicine (IUSM). This Department is now consistently in the top 10 Departments of Pediatrics in the United States in terms of NIH funded research and is #4 of all pediatric public institutions in the United States. The total extramural research support of the Department of Pediatrics is approximately 105 million dollars/year and the total cancer research grant support specifically is over 21 million dollars. In addition to research funds in the Department of Pediatrics, the Indiana University, National Cancer Institute (NCI) designated Simon Comprehensive Cancer Center (IUSCCC, led by Dr. **Kelvin Lee**) plays a role in facilitating pediatric cancer research by providing support to shared core facilities, shared laboratory space, and through collaborations access to a much broader group of investigators and resources.

The basic and translational research within the department of pediatrics is conducted within the Wells Center for Pediatric Research (WCPR); a division of the department of pediatrics, led by Dr. **Reuben Kapur**. WCPR is comprised of 52 principal investigators, spread across 75,000 sq/ft of research space, including its own building, focusing on 10 distinct, disease-related research programs. The WCPR mission is to find new cures for complex and rare pediatric diseases to reduce disease burden for children within the state of Indiana and nationally. Of the 52 investigators in the WCPR, 13 primarily focus on researching basic, translational, and clinical aspects of both solid and liquid tumors/cancer. The hematologic malignancies program, led by Dr. **Kapur** has NIH supported efforts in childhood leukemia/lymphoma (B cell and T cell), acute myeloid leukemia (AML), juvenile myelomonocytic leukemia (JMML), bone marrow failure (BMF) syndromes (e.g., Fanconi Anemia), graft *vs.* host disease (GvHD), and hematopoietic stem cell transplantation (BMT)/expansion. The pediatric solid tumor program, led by Dr. **Kelley,** focuses on studying Neurofibromatosis type 1 and type 2 (NF1), sarcomas, and brain tumors, as well as Human Papilloma Virus (HPV). The composition of investigators who conduct pediatric cancer

research within these two programs include senior investigators (Full Professors), Drs. **Clapp, Kelley, Katzenellenbogen, Pollok** and **Kapur**, mid-level investigators (Associate Professors), Drs. **Mayo, Fishel** and **Zhang** and junior investigators (Assistant Professors), Drs. **Tran, Peltier, Singh, Rhodes,** and **Angus**. The investigators include both PhDs as well as MD/PhD scientists. The research conducted by pediatric cancer researchers is supported by extramural funding from highly competitive funding agencies including National Institutes of Health (NIH) and department of defense (DOD). Among the several prestigious grants awarded to pediatric cancer investigators, WCPR has the ***only*** pediatric focused SPORE (Scientific Program of Research Excellence grant (Dr. **Clapp** and his Team) in the country (61 total SPORES in US). This SPORE that is headquartered at IU and includes investigators at UCSF, Johns Hopkins, Memorial Sloan Kettering Cancer Research Center, Children's Hospital of Philadelphia, University of Virginia, and the Pediatric branch of the National Cancer Institute. Other important multi-investigator grants include a collaborative translational research grant with the Pediatric Branch of the National Cancer Institute, and a Cooperative Center of Excellence in Hematology (CCEH) grant, one of only 5 NIH funded centers in the entire country. Investigators in the WCPR cancer group, particularly Kapur, Kelley, and Clapp, have developed or are currently developing new drugs for the treatment of cancer and Kelley has an agent that is in 9 phase 1 or phase 2 trials for malignant and non-malignant uses. Kapur and Kelley have their own start-up biotechs in Indiana and Clapp is developing new drugs and biomarkers in collaboration with investigators at the Indiana Biosciences Research Institute (see below for description).

One example of how investigators at IUSM/Riley have used novel technologies to promote the development of novel therapies for children's cancers include therapies for pediatric nerve sheath tumors. These methodologies include: the generation of genetically engineered mice designed to replicate the development of human tumors, molecular methods to identify activated proteins that drive tumor progression in both human tumors and in the mouse models, and preclinical testing of drugs or drug combinations in mice prior to enrollment into human patients. The Clapp laboratory focuses on two diseases, neurofibromatosis type 1-and 2 Both conditions acquire tumors on spinal and cranial nerves that cause substantial morbidity and mortality. Prior to 2009, early phase 1-2 clinical trials were conducted in the absence of significant preclinical data. In NF1 trials alone 0/14 clinical trials had an observable biological impact. Subsequently, Dr. Clapp and colleagues at IU have led a national collaborative where there was a closely aligned preclinical-clinical trials collaborative that included the generation of genetically engineered murine models that closely mimic the human diseases. Using this model, mice were treated with the most promising drugs and the biochemical impact of the drug on all druggable proteins called "kinases" in the tissues of the treated mice were quantified. Results to date have resulted in 3/3 drugs chosen for NF1 tumors to have a positive result in tumor regression in patients ranging from babies to adults. One of those drugs is now FDA approved (*Lancet Oncology, Nature Medicine, New England Journal of Medicine*), in part due the work of **Dr. Weiss (clinical trial)**, another IUSM/Riley faculty member and the Clapp lab that did preclinical studies requested by the FDA that could not be accomplished in young human patients. A

fourth drug for NF2 tumors, caused by a different mutation, has also had success using a similar preclinical/clinical trial strategy and the clinical trial from that work was just accepted for publication at the *New England Journal of Medicine* that was preceded by the preclinical trial results published in *PLOS1*. Collectively, these 4 therapies are lifechanging for patients in terms of reducing major morbidities such as mobility, incessant pain, deafness, disfiguration, and death. The success of these trials in different diseases and different tumors illustrates the capability to combine technologies and expertise to rapidly move new therapies forward for previously incurable diseases. Ongoing work seeks to broaden this strategy to other sarcomas, brain tumors, and hematologic malignancies in both the preclinical and phase 1-2 trial setting. Based on our now established successes, we feel that we can leverage innovative chemical proteomic approaches to find therapies that are more effective and don't carry the significant long term risks of standard chemotherapy.

Indiana Biosciences Research Institute

In 2013 the State of Indiana, its major life science companies (Cook, Corteva, Lilly, Roche), the IUSM, IU Health, the Lilly Endowment and Biocrossroads saw the need for better health solutions in the local and global community and collectively facilitated the creation of the Indiana Biosciences Research Institute. The IBRI is now attracting outstanding research talent that work in collaboration with academic and industry scientists to enable innovation that could not be achieved if the groups worked separately. **Alan Palkowitz, PhD** is President and CEO of IBRI and he is also a faculty at the IUSM. He is a trained medicinal chemist with over 30 years of industry and academic experience in drug discovery and translational research. Under Dr. Palkowitz's leadership the IBRI has built broad organizational capabilities encompassing the breadth of discovery, translational research, and scientific resources to help entrepreneurs and researchers accelerate drug discovery, improve the effectiveness of targeting diseases, and drive innovative solutions to improve patient outcomes.

Relevant to pediatric cancers and other rare diseases in children, the IBRI has developed a research emphasis in orphan diseases and there are numerous ongoing projects between IU Pediatrics and the IBRI currently. One leader that has been recently recruited is **Lou Stancato**. Dr. Stancato is a pharmacological scientist who had 26 years of experience at Eli Lilly, has been a staunch advocate at Lilly for pediatric research and development and Co-led a 30 member European Union international consortium that is the world's largest publicly available pediatric cancer research platform. He is leading the IBRI efforts on a coordinated pediatric oncology platform in central Indiana and has consciously reached out to investigators at all of the flagship institutions. A recent letter to stakeholders from Dr. Palkowitz that highlights ongoing work and capabilities can be viewed **here**.