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A Brief History of the Department of Medical and Molecular Genetics-2022

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Introduction

Among genetic centers in the United States, the Department of Medical and Molecular Genetics is unique as the department is a separate department within the Indiana University School of Medicine. Most genetic centers in the country are divisions of other departments such as departments of pediatrics or internal medicine. The department is divided into four major sections including clinical and laboratory services, research and genomics. The faculty is diverse in their interests and activities, including Ph.D. researchers who work on diverse genetic diseases, M.D. clinical geneticists who provide clinical services, clinical geneticists who see patients and do basic and clinical research work, faculty who are directors of clinical laboratories, Ph.D. and M.D. faculty whose primary function is teaching, and genetic counselors who provide genetic counseling and teaching. As of 2022, there were 68 faculty members and over 490 employees in the department. Of particular note, during the department's 61-year history, there have been only six chairpersons – Dr. Donald A. Merritt who served until 1977, Dr. Joe C. Christian 1977-1990, Dr. Merrill D. Benson from 1991-1998, Dr. Kenneth Cornetta from 2002-2014 and Dr. Tatiana Foroud from 2015 to the present. Dr. Gail Vance served as interim chair between 1998-2002 and 2014-2015. Of particular importance for the department is one of Dr. Merritt's basic philosophies that the department should have a balance between research, teaching, and service. This philosophy persists to this day.

Early History

In 1960, Dr. Merritt established the Division of Medical Genetics in the Department of Internal Medicine at the medical school and was then the division head. Early faculty members included P. Michael Conneally, Ph.D.; Joe C. Christian, Ph.D., M.D.; Marion Ed Hodes, Ph.D., M.D.; David Bixler, D.S.D, Ph.D.; Walter Nance, M.D.; and Catherine G. Palmer, Ph.D. During the early years the division was primarily a research unit. Dr. Conneally was principally interested in population genetics with a specific goal to find the gene causing Huntington disease. In 1981 by using genetic linkage studies, he and his collaborators succeeded in doing so and discovered

the chromosomal location of the gene on chromosome 4, and then ten years later, the actual gene itself. The significance of these findings goes beyond the recognition of the gene. Other than for X-linked genes, Huntington gene was one of the first genes to be identified to a specific location on a specific chromosome. Following these discoveries, Kimberly Quaid, Ph.D., was hired in the department to provide predictive Huntington disease genetic counseling, i.e., risk counseling for couples at risk for one of them to have the Huntington disease gene or for having a child with the diseased gene. Dr. Christian's primary research interests were quantitative genetics of cardiovascular disease risk and the heritability of different traits, both investigations utilizing twin studies. For instance, he found that 50% of a child's head size is related to the parent's head size. Dr. Hodes did extensive research on genes located on the X chromosome and in doing so discovered the gene causing Pelizaeus-Merzbacker disease, an X-linked disorder associated with severe intellectual disability and regression. Dr. Bixler interests were in oral genetics and the genetics of multifactorial traits such as cleft lip and cleft palate. He described the Antley-Bixler syndrome, a syndrome associated with unusual facial features and fusion of the elbows. Dr. Nance did extensive twin studies looking for the etiology of complex traits. Dr. Palmer established the cytogenetics laboratory in 1963 and was primarily interested in the cytogenetics of leukemias. One of the important discoveries from her laboratory was that the chromosome 15 with a microdeletion that results in Prader-Willi syndrome essentially was always derived from the father. This discovery began the era of understanding and the importance of genetic imprinting. She ran the cytogenetics lab for 31 years. As with the department's chairpersons, the cytogenetics lab has only had three directors - Dr. Palmer, Nyla Heerema, Ph.D. from 1994 to 1998 and Gail H. Vance, M.D. from 1998 to the present. Two of the noticeable accomplishments of the department early on were the obtaining of an NIH Human Genetics Center Grant for research in the late 60s, one of approximately 12 center grants in the country, and a NIH training grant starting in the 70s. The training grant lasted through to the 90s and was used to train numerous Ph.D. geneticists.

Clinical genetics services in the department first started in 1961 and were provided by Drs. Christian, Nance, Bixler and Hodes. One of the earliest families seen then was of particular interest because there was X-linked intellectual disability transmitted through multiple generations. No diagnosis was established at that time. The family was again evaluated in the early 70s without a confirmed diagnosis. Subsequently in the early 1980s, the family was again

reassessed, and a diagnosis of fragile X syndrome was made, a then recently recognized disorder. This was the one first family in Indiana diagnosed with this condition. The department in the 60s and 70s had one half-day medical genetics clinic per week. The clinic was a general medical genetics clinic that evaluated and counseling children and adults for all types of genetic disorders including inherited diseases, birth defects, cancers, and metabolic conditions. Since then the clinical program has great expanded and now routinely conducts over 45 different medical genetics and subspecialty clinics per **week**. During these early times, the above physicians also provided inpatient consultations for the entire medical center, with most consultation requests coming for children admitted to Riley Hospital for Children.

In the mid-1960s, the Division of Medical Genetics separated from the Department of Internal Medicine and established itself as a separate department within the medical school. At about this same time the department moved into the basement, first floor and half of the second floor of the Research Wing of the Riley Hospital for Children. Here it remained until 1989. In 2006, because of the increased importance of molecular genetics, the department changed his name from the Department of Medical Genetics to the Department of Medical and Molecular Genetics. Currently the department has four major divisions. These include Division of Clinical and Biochemical Genetics (Director: Stephanie Ware, M.D., Ph.D.), Division of Diagnostic Genomics Clinical Laboratory Services (Director: Dr. Vance), Division of Molecular/Basic Research and Therapeutics (Director: Kenneth White, Ph.D.) and Division of Hereditary Genomics (Director: Tatiana Foroud, Ph.D.).

Subsequent Years

Clinical Services

In 1976, David D. Weaver, M.S., M.D., was hired to be the director of clinical services for the department. Over the next few years, he expanded the clinical services by establishing Genetic Counseling, Bone Dysplasia, and Fetal Alcohol Syndrome Evaluation Clinics. A year later, he established the first medical school sponsored outreach clinic, the Terre Haute Genetics Clinic, at Memorial Hospital in Terre Haute. Interestingly, because of limited space, the first clinics were held on the fourth floor of an essentially abandoned segment of the hospital. The clinic utilized old patient room with examinations being done on hospital beds. The clinic has been held every second or third month since then but stopped in 2020 because of the COVID 19 pandemic.

Subsequently to the genetic clinic in Terre Haute, the division started outreach clinics in South Bend, Bloomington, Evansville, Madison, and Muscatatuck State Hospital. The latter facility was located near Butlerville and was one of the state's residential facilities for intellectually impaired individuals. The basic concept behind establishing these outreach clinics was to allow access to genetic services for those who would not or could not travel to Indianapolis. The department no longer conducts clinics in South Bend, Evansville or Muscatatuck. The rest of these clinics had continued to provide services until the beginning of the COVID pandemic. During the 70s, 80s and into the 90s, we also provided inpatient consultations at Wishard Hospital, Methodist Hospital, St. Vincent's Hospital, and Community Hospital North. The department now does not provide genetic services to St. Vincent's as the hospital hired their own clinical geneticist in the 1990s. Current on-campus clinics conducted by the department include general Medical Genetics, Indiana Familial Cancer, Bone Dysplasia, Cardiovascular Genetics, Cardiomyopathy, Pediatric Arrhythmic, Pediatric and Adult Metabolic, Pediatric Pulmonary Hypertension, Ophthalmologic, Hearing Loss, and the Undiagnosed Rare Genetic Clinics. The last listed clinic is a clinic that does comprehensive molecular testing on individuals who have defied the establishment of diagnoses. The division also provided teratogen information services for the state in the early 1980s to 2016, at which time the service was defunded. The Division of Clinical and Biochemical Genetics also has had only three directors: Dr. Weaver from 1976 to 2005, Dr. Hainline from 2006 to 2016, and Dr. Ware from 2016 to the current time.

Metabolic Disorders

Fundamentally, metabolic disorders are disorders involving various enzyme deficiencies essential for biochemical reactions. All enzymes are produced by a gene or a combination of genes. Thus in a metabolic disorder, a mutated gene does not produce a functional or an adequate quantity of enzyme for normal chemical function. As there are hundreds of different genes producing enzymes, there are hundreds of different metabolic disorders associated with mutations in these genes. Fortunately, today many of these metabolic diseases can be treated. Thus, the field of metabolic disorders is not only involved in diagnosing but treatment of these disorders.

The first full-time faculty member involved in metabolic disorders at Riley Hospital for Children was Dr. Ira Brandt, who was hired by the Department of Pediatrics in the early 1970s. A few

years later, he was joined by Dr. Rebecca Wappner who had previous training in clinical genetics and then subsequently in biochemical genetics (metabolism) with Dr. Brandt. In 1976, Drs. Brandt and Wappner established the Biochemical Genetics Service within the department with the fundamental mission to identify and treat children and adults with metabolic diseases. Shortly after Dr. Wappner joined Dr. Brandt as faculty, the division was awarded an Indiana Department of Health grant to diagnose and manage patients with these conditions. These patients including not only those identified by newborn screening but also children and adults who were later found to be affected with metabolic disorders. Additionally, the division created the Biochemical Genetics Laboratory, which brought in the newest diagnostic technology including a gas chromatography/mass spectrometry to the medical school. In 1989, Dr. Brandt retired and in the same year, Dr. Bryan Hainline, a biochemical and molecular geneticist, was recruited from Washington University to replace him. Tragically, in 2006, Dr. Wappner died, leaving Dr. Hainline to deal with all of the service's metabolic patients. Shortly thereafter, Dr. Cornetta who was then the chairman of the Department of Medical and Molecular Genetics and Dr. Richard Schreiner, then chairman of the Department of Pediatrics, agreed to have Dr. Hainline transfer to the Department of Medical and Molecular Genetics and for the department to take over the management of all metabolic disorders at Riley Hospital. This arrangement worked well as some of physicians in the Department of Medical and Molecular Genetics were able to provide metabolic coverage for Dr. Hainline. Another plus for the arrangement was that all subsequent clinical genetics residents who trained in the department have received extensive metabolic training during their residency. And four of these residents have subsequently been retained as clinical faculty members in the department and also have provided metabolic care. Today, metabolic assessment and care continue today to be the purview of the genetics department.

Laboratory Services

Over the ensuing years, the department's laboratory services have expanded considerably. Initially in 1963, it was providing only cytogenetics evaluations but subsequently then extensive biochemical, molecular, and expanded cytogenetics evaluations were offered. By 1970s, there were two separate laboratories in the department - cytogenetics and molecular. In 2006 a biochemical lab, which subsequently closed, and in 2010 a pharmacogenomics laboratories were

added. In 2017, Marcus Miller, Ph.D., joined the department and reestablished the biochemical lab. He also upgraded the technology for the lab to include tandem mass spectrometry and liquid chromatography/mass spectrometry for urine organic acids, plasma and urine amino acids, carnitine and acylcarnitine analyses and other analytical methodologies not offered elsewhere on campus. Drs. Vance and Miller also established the Indiana University COVID 19 testing lab in 2020 to provide viral testing for all Indiana University personnel. In 2021, Dr. Marwan Tayeh and in 2022, Dr. Francesco Vetrini were recruited to develop a genomics laboratory utilizing high throughput sequencing for both somatic and germline disorders. Recently, all five laboratories have been combined into the Division of Diagnostic Genomics Clinical Laboratory Services headed by Dr. Vance. The division now has six full-time faculty members. Previous laboratory directors have included Dr. Hodes; Stephen R. Dlouhy, Ph.D.; Dr. Hainline; and Victoria Pratt, Ph.D.

Research Activities

Since its inception in the late 1960s, many of the research laboratories in the department have been involved in identify the genes and the mechanisms involved in single gene disorders such as Huntington disease and Prader-Willi syndrome, and in multifactorial traits such as mental illnesses, Alzheimer and Parkinson diseases. Specific areas in which these labs have been involved have included cancer research, looking for causes and treatment options; computational biology and bioinformatics; neuroscience; musculoskeletal; bone metabolism; and diabetes. Over the years, these research activities have been extremely well funded, have made numerous discoveries, and the scientists involved have published literally hundreds of articles on their studies. The department has been so successful in obtaining research grants that the department is now eighth in National Institutes of Health funding for genetic centers.

Education

Education also has been a major part of the departmental activities since its inception. From the 1960's, the department has trained numerous M.S. and Ph.D. students in multiple areas within medical genetic including cytogenetics, molecular genetics, and population genetics. Many of these students have gone on to become productive researchers and teachers throughout the nation while a number have stayed on as faculty members in the department. In 1976, Dr. Weaver also established a separate three-credit medical genetics course for medical students. Subsequently in

2018, this course was replaced by the current basic science survey course offered to the medical students, the Molecular-Cell-Tissue (MCT) Course. Stephanie Sharpe, M.D., a departmental full-time faculty member, is one of the course directors for this class. Further, since the 1970s, the department also have provided clinical and research medical genetics electives for junior and senior medical students, and for residents and fellows from throughout the medical school. Although most residents taking this elective have been pediatric ones, the department also has trained residents from other disciplines primarily medicine and obstetrics/gynecology. The department has also trained its own residents and fellows in clinical genetics and other subdisciplines within the department. Specifically, since the early 70s, the department has trained over 30 physicians as clinical geneticists. Interestingly, the department's residency program requires that the physicians applying for the program have a prior completed or to be completed residency in a different discipline before being eligible for the department's residency program. More recently and in conjunction with the Department of Pediatrics, the department offers a combined pediatric-clinical genetics residency. The resident spends a total of four years in training in both department and at the end of the training is eligible for board certification in both pediatrics and clinical genetics.

The residency training program in the department was directed by Dr. Vance from the mid-1990s until 2018 when Clair Francomano, M.D., assumed the duties. The department also sponsors a Laboratory Genetic and Genomic fellowship accredited by the ACGME. Since the beginning of the department, the research faculty also has offered postdoctoral fellowships in their research labs. All of the above training opportunities have resulted in multiple trained researchers in various aspects of genetics. In total, the department has trained more than 300 M.S. and Ph.D. students and fellows.

Genetics Counseling Training Program

Genetic counselors for the most part are individuals who have been trained in clinical genetics and genetic counseling. Most of these individuals have a master's degree in genetics and are employed in a wide variety of positions. These areas mainly include medical genetics centers such as the Department of Medical and Molecular Genetics, industry primarily companies doing molecular genetics testing and providing genetic testing information and counseling, teaching principally in genetic counseling training programs, and research. The concept of having genetic

counselors involved in providing genetic services first began in the early 1980s and the numbers of centers training counselors has continually increased in numbers since that time.

The first genetic counselor in our department was Dr. Peggy Davee. She got her Ph.D. in anthropology from the Department of Anthropology, Indiana University, Bloomington, IN. However, she fell in love with clinical genetics after participating in our clinical genetics training program in Indianapolis. She was hired as a genetic counselor in the department in 1988. The department's second genetic counselor was Lola Cook, who initially was enrolled in the department's Ph.D. program but finished her formal training with a master's degree from the department. She joined the staff of the department in 1989. In 1990, Dr. Davee, Lola Cook and Dr. Weaver established a genetic counseling training program in the department. Meeting the requirements for a genetic training program was relatively straightforward in that the department already taught most of the required basic genetic courses as part of its M.S./Ph.D. training program. In addition, there was a robust clinical service with a sizeable number of both in- and outpatient patients available. The program was officially started 1991 when the program accepted the first two students, Melissa King Weston and Elizabeth Leeth. Both completed their two-year training program in 1993. Elizabeth has had a distinguishing career in teaching in the Chicago area and beginning in 2012, Melissa was first the project coordinator and then the associate director of the department's genetic counseling training program, a position she currently holds. Over the pursuing 31 years since establishment of the program, the program has had only two directors. In 1993, Susan Sheley Romie, M.S., was appointed as the program's first director. She served until 2010 with the subsequent appointment of Paula Delk, M.S., in 2012. Paula still serves as the director. As of to date, the program has graduated 164 students, who now have positions throughout the country. The genetic counseling program, formally known as the Indiana University Genetic Counseling Program, is a subdivision within Division of Clinical and Biochemical Genetics.

Indiana Genetics Newborn Screening Program

Screening of newborns for genetic and endocrine disorders is an important part of Indiana's healthcare program. To be eligible for screening, a disorder must be treatable, and if not treated, will lead to significant medical or intellectual problems and/or death. In the 1970s, the state of Indiana required the newborn screening of only two conditions, phenylketonuria and

hypothyroidism. Testing was done by over 120 laboratories located throughout the state and even out of state. In the early 1980s, a number of healthcare providers including Drs. John Meany, the then director of the genetic section at the Indiana Department of Health; Brandt; Wappner and Weaver; and others, joined forces to change this unmanageable situation. As a result of their efforts, the state's legislature changed the law so that only one lab within the state could do newborn screening with no out-of-state testing, established a mechanism for adding new tests, required that all newborns to be screened and provided that both the screening testing and the follow-up treatment be paid for by a fee collected through the hospitals. Since that time, the number of screened disorders has gone from two to the present number of over 50 disorders.

Since the mid-1990s, the department has been intimately involved with the newborn screening program in that the departmental physicians have been involved in confirming diagnoses and providing treatment for individuals detected with these disorders. Most of these disorders are metabolic diseases and thus managed by the physicians in the Department of Medical and Molecular Genetics, the exceptions being hypothyroidism and congenital adrenal hyperplasia, which are handled by the physicians in the Division of Pediatric Endocrinology and Diabetology; cystic fibrosis cared for by the physicians in the Division of Pediatric Pulmonology, Allergy and Sleep Medicine; sickle cell and other hematologic disorders, and the congenital immune deficiencies managed by the Division of Pediatric Hematology/Oncology, all within the Department of Pediatrics at Riley Hospital for Children. These programs are all supported by grants from the Indiana State Department of Health. The expansion of the newborn screening program for genetic and endocrine disorders over the last 40 years has saved the health and lives of literally thousands of individuals.

The Department's Relationship with Riley Hospital for Children

Since the opening of Riley Hospital for Children in 1921, multiple Indiana University School of Medicine departments have provided patient care and teaching at Riley Hospital. Since its inception in 1960s, the Department of Medical and Molecular Genetics has had an intimate relationship with the faculty, staff and families at Riley Hospital. The location of the department in the Riley Research Wing of the hospital was most adventitious to these relationships as it afforded easy availability to the patients, families, physicians and other personnel at Riley Hospital. Further, other than for the outreach clinics, all of the department's outpatient clinics

were held in Riley Hospital, first in Clinic A, then in Clinic C and then the Riley Outpatient Center after its construction. For a short period, the division also had clinics for pediatric and adult patients in the University Hospital Outpatient Clinics during renovation of various clinics and the offices at Riley Hospital. Currently most of the department's clinics are held in the Pediatric Care Center, a separate building from Riley Hospital.

The close relationship while the department was in Riley Hospital was partly lost when the department moved to its new facilities in 1989. The move was necessitated by the department's significant increase in the number of staff and faculty over the years. There was literally no space left to operate. The new facility was in the Medical Research and Library Building, located two buildings east of Riley Hospital. The department then occupied three floors of the research section of building, which doubled the space of the department. Even though personnel in the department did not have same intimate relationship with those at Riley's staff and physicians, the department has continued to provide the same services to those at Riley Hospital.

A Partial Listing of the Services Provided by the Department

- Inpatient and outpatient genetic evaluations
- Inpatient and outpatient cancer genetics evaluations
- Inpatient and outpatient genetic counseling
- Inpatient and outpatient metabolic evaluations
- Inpatient and outpatient metabolic treatment and management including nutritional, pharmacologic and enzyme replacement therapies
- Complex biochemical genetic testing
- Adult genetics and metabolic clinics and services
- Chromosomal analyses-both karyotype and molecular (chromosomal microarray analysis)
- Other cytogenetic and cytogenomic clinical testing including fluorescence *in situ* hybridization
- Pre-mutation and full mutation fragile X gene analyses
- Cancer genetic typing
- Pharmacogenomic typing

- Genetic counseling in the Advance Lipid Clinic
- Medical management of patients with phenylketonuria (PKU) and other metabolic disorders
- Medical treatment for achondroplasia
- Evaluation for and treatment of patients with Ehlers-Danlos syndrome
- Specialty outpatient genetic clinics including Bone Dysplasia, Cancer, Lipid Clinic, Metabolic, general Medical Genetic, Hearing Loss, Ophthalmologic, Cardiovascular, Renal and Ehlers-Danlos Syndrome Clinics
- Outreach genetics clinic in Terre Haute, Bloomington and Madison
- Production of viruses for gene therapy
- Newborn screening follow-up and treatment of detected diseases
- Maintenance of a number of databases for specific genetic diseases
- Susan B Koman Cell Bank Repository
- Treatment of other metabolic/genetic diseases such as phenylketonuria (PKU)
- Clinical drug trials for PKU, Prader-Willi syndrome, and homocystinuria

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Photographs—Medical Genetics

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Query terms used are listed – links below show you the photos that come up:

query term – Medical Genetics:

<https://indianamemory.contentdm.oclc.org/digital/collection/IUPUIphotos/search/searchterm/Medical%20Genetics/field/all/mode/all/conn/and/order/title/ad/asc>

query term – Donald A. Merritt (note that the photo is listed as **A. Donald Merritt**):

<https://indianamemory.contentdm.oclc.org/digital/collection/IUPUIphotos/id/32692/rec/1>

query term – Joe Christian:

<https://indianamemory.contentdm.oclc.org/digital/collection/IUPUIphotos/search/searchterm/Joe%20Christian/field/all/mode/all/conn/and/order/title/ad/asc>

query term – Tatiana Foroud:

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