Pharmacogenomics Workshop: A Path to Individualized Medicine for Pediatrics
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***Eunice Kennedy Shriver* National Institute of Child Health and Human Development**
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Welcome and Introductions

Zhaoxia Ren, M.D., Ph.D., Medical Officer, OPPB, CRMC, NICHD, NIH

Dr. Ren welcomed the meeting participants, and asked the participants to introduce themselves. The purpose and goals of the workshop were to:

- Review current advances and clinical applications of pharmacogenomics
- Discuss limitations and obstacles in pediatric pharmacogenomics
- Identify gaps and opportunities in pediatric pharmacogenomic research
- Make recommendations for future research directions.

Role of the BPCA Program and OPPB in Pediatric Pharmacogenetics

Anne Zajicek, M.D., Pharm.D., Acting Branch Chief, OPPB, CRMC, NICHD, NIH

The BPCA Program is a partnership between the NIH and the Food and Drug Administration (FDA). Over the past 14 years, the FDA has made several attempts to add pediatric labeling. The history of the related legislations is as follows:

- 1994 Pediatric Rule—proposed the extrapolation of adult data to children; that is, the disease process and drug efficacy in adults could be extrapolated to children
- 1997 FDA Modernization Act (FDAMA)—proposed the concept of exclusivity; that is, if FDA requested a pediatric study from a pharmaceutical company, and the company conducted the study, it was granted an additional 6 months of exclusivity on the drug's patent
- 1998 Pediatric Rule—proposed that pediatric studies be conducted prior to FDA approval of the New Drug Application (NDA)
- 2002 BPCA—proposed the reauthorization of 6-month exclusivity and a process for studying off-patent drugs; the NIH became involved as a sponsor of off-patent drug studies
- 2003 Pediatric Research Equity Act (PREA)
- 2007 BPCA and PREA reauthorizations.

For BPCA 2002, a master list of all off-patent drugs that lacked adequate pediatric labeling was developed. In consultation with experts in pediatric practice and research, an annual list of drugs was developed, prioritized, and published. Considerations for prioritization included availability of safety and efficacy data, the need for additional data, the potential to produce health benefits,

and the need for reformulation. Newer legislation shifted the program's focus. BPCA 2007 directed the NIH to develop, prioritize, and publish an annual list of therapeutic areas and specific needs. In consultation with experts in pediatric practice and research, NIH scientists consider therapeutic gaps, the potential health benefits of research, and the adequacy of necessary infrastructure in developing the annual list.

From the priority list, the NIH writes and negotiates a Proposed Pediatric Study Request (PPSR) to the FDA as a draft Written Request (WR). The FDA issues a WR to holders of the NDA or abbreviated NDA. If the holder accepts the WR, it conducts the study. If the holder declines, the study is referred to the NIH, which develops a Request for Contracts or Request for Proposals and publishes a notice in FedBizOpps. Proposals are peer-reviewed, and contract(s) are awarded.

Ongoing BPCA studies are as follows:

- Lorazepam—clinical studies of sedation of children on ventilators in an intensive care unit (pharmacokinetics [PK], pharmacogenomics, safety, and efficacy)
- Lorazepam—clinical studies of treatment of status epilepticus (PK; safety and efficacy of lorazepam compared with diazepam)
- Nitroprusside—clinical studies to reduce blood pressure during surgery to reduce blood loss
- Lithium—clinical studies to define treatment of mania in children with bipolar disorder (PK and efficacy)
- Baclofen—clinical studies of oral baclofen to treat spasticity, most commonly from cerebral palsy (chart reviews, PK, pharmacodynamics [PD], pharmacogenomics, and formulations)
- Meropenem—treatment of serious intra-abdominal infections in infants
- Hydroxyurea—treatment of very young children with sickle cell disease
- Vincristine—studies to evaluate neurotoxicity and PK in children, in collaboration with the National Cancer Institute and the Children's Oncology Group (NCI-COG).
- Actinomycin-D—studies to evaluate hepatotoxicity/veno-occlusive disease, PK in children (with NCI-COG)
- Methotrexate—clinical studies to evaluate neurocognitive outcomes of pediatric patients with high-risk acute lymphoblastic leukemia (with NCI-COG)
- Daunomycin—PK, safety, and efficacy to treat childhood cancers and relationship to body weight (with NCI-COG)
- Morphine—PK, PD, and pharmacogenomic evaluations of the developmental and safety issues in treating pain in neonates
- Ketamine—preclinical studies to evaluate the scientific and safety concerns about use as an anesthetic in children
- Methylphenidate—preclinical and clinical evaluation of PK and safety to understand reports of cytogenetic toxicity.

The NICHD recently published a funding opportunity announcement (FOA) titled "Translational Research in Pediatric and Obstetric Pharmacology" with R01, R03, and R21 mechanisms.. This FOA encourages research grant applications to conduct studies to improve existing drug safety and efficacy and to develop new drugs for pediatric and obstetric populations. The primary goal of this FOA is to identify research opportunities in pharmacogenomics as it applies to children. The goals are to support:

- Pharmacological studies addressing the special differences of drug actions and responses among children at various developmental stages, between children and adults, and between pregnant and nonpregnant women
- Development of new drugs targeting children and pregnant women
- Multidisciplinary collaborations between basic and physician scientists to improve the use of therapeutics in obstetrics and pediatrics.

Session 1: Current Advances in Pharmacogenomics

Moderator: Richard Weinshilboum, M.D., Mary Lou and John H. Dasburg Professor for Cancer Genomics Research; Chair, Division of Clinical Pharmacology; Professor of Molecular Pharmacology and Experimental Therapeutics and Medicine, Mayo Clinic

Pharmacogenomics in the Postgenomic Era

Dr. Weinshilboum

Pharmacogenetics is the study of the role of inheritance in variation in drug response phenotypes. In the present "postgenomic" era, pharmacogenetics is rapidly evolving into "pharmacogenomics." That process involves a move beyond studies of single genes and one or a few single nucleotide polymorphisms (SNPs) to encompass PK and PD pathways and, ultimately, genomewide association (GWA) studies. In parallel with this process, and helping to drive it forward, are rapid changes in technology and in the organizational structure required to participate in and contribute to this important aspect of individualized medicine.

This evolutionary movement from pharmacogenetics to pharmacogenomics presents major opportunities and significant challenges. Pediatrics and obstetrics must participate in and contribute to this exciting and challenging series of scientific developments.

Pharmacogenomics is a critical component of "personalized" or "individualized" medicine. The clinical goals of pharmacogenomics are to avoid adverse drug reactions (ADRs), maximize drug efficacy, and select responsive patients. The scientific goals of pharmacogenomics are to link variation in genotype to variation in phenotype, determine mechanisms responsible for that link, and translate the link into enhanced understanding, treatment, and prevention of disease. Developments in the postgenomic era include next-generation (next-GEN) DNA sequencing, the 1000 Genomes Project, the ENCODE (the **Enc**yclopedia **O**f **D**NA **E**lements) Project, RNA-Seq (ultra-high-throughput transcriptome sequencing), and direct-to-consumer (DTC) genomics.

The FDA has been conducting hearings on pharmacogenetics and drug labeling for thiopurines (thiopurine methyltransferase [TPMT]), irinotecan (UGT1A1), warfarin (CYP2C9 and VKORC1), and tamoxifen (CYP2D6). Since the 1960s, the probability of overall survival of childhood acute lymphoblastic leukemia (ALL) has increased to the level (96–100 percent) that ALL is now considered curable in the majority of patients. Mercaptopurine is one of the drugs used to treat childhood leukemia. TPMT is an enzyme involved with the metabolism of mercaptopurine. Studies of Americans of Northern European extraction showed a trimodal distribution of TMPT genetic polymorphism. There are clinical consequences associated with this polymorphism. Low levels of TPMT result in increased thiopurine toxicity and increased

risk for secondary neoplasm. High levels of TPMT result in decreased therapeutic effect of mercaptopurine. This is one example of the use of genomics to "individualize" drug therapy.

Pharmacogenomic translational studies have evolved over the past several years in the following sequence:

- One gene, one or a few SNPs
- One gene, intragene haplotypes
- PK and PD pathways and haplotypes
- GWA studies.

The use of genome-wide techniques requires the study of large patient populations—a challenge for pediatrics. This fact also presents a challenge to funding agencies to find ways to create incentives for collaboration to make it realistically possible for large patient populations to be studied. However, we must not forget that the ultimate goal of pharmacogenomics is to help to identify and use the right drug at the right dose for every patient.

Pharmacogenomics: What Makes Children Different?

J. Steven Leeder, Pharm.D., Ph.D., Chief, Division of Clinical Pharmacology and Medical Toxicology, Children's Mercy Hospitals and Clinics; Professor, Pediatrics and Pharmacology, School of Medicine, University of Missouri–Kansas City

Understanding of the contribution of genetic variation to variability in drug disposition and response in adults has increased substantially over the past 25 years. However, the application of pharmacogenetic and pharmacogenomic principles to pediatric drug therapy has lagged well behind. Compared with adults, pediatric pharmacogenetics involves an added measure of complexity because variability due to developmental processes, or ontogeny, is superimposed on genetic variation. As a consequence, there are several important fundamental differences between pediatric and adult age groups that must be considered when integrating pharmacogenetic or pharmacogenomic principles into programs to optimize drug efficacy and safety in children.

First, context is important. During development, the primary function of "drug" biotransformation and transport pathways is the biosynthesis and catabolism of endogenous molecules responsible for normal growth and development. According to dogma, drug biotransformation pathways are "detoxification" systems to terminate biological activity and enhance elimination. However, these pathways play a role in maintaining physiological concentrations of small endogenous ligands involved in growth and differentiation, such as retinoic acid, thyroxine, vitamin D3, estrogens, DHEA, progesterone, testosterone, cortisol, prostaglandins, serotonin, and catecholamines. The biotransformation of drug and environmental toxicants co-opts some of the same pathways, involves others, and is superimposed on the essential developmental functions. Furthermore, the gene products do not operate in isolation but in tightly regulated pathways or networks.

Second, genotype–phenotype relationships may change during development. A specific phenotype may change over time between conception and senescence. In the context of drug biotransformation, fetuses and newborns may be phenotypically "slow" or "poor" metabolizers

for certain drug metabolizing pathways, acquiring a phenotype consistent with their genotype at some point later in the developmental process as those pathways mature (for example, glucuronidation and some cytochrome P450 [CYP] activities). It is apparent that not all infants will acquire drug metabolizing abilities at the same rate due to the interaction between genetics and environmental factors such as formula versus breast feeding, for example.

Functional drug biotransformation activity is acquired in gene-specific patterns. For example, CYP2D6 is not expressed in fetal liver to any appreciable extent. *In vitro* and *in vivo* phenotyping data indicate that genetic variation is the major contributor to variability in CYP2D6 activity beyond the first month of life. Variability in CYP2D6 activity can be applied in assessing the safety of cough and cold active ingredients because CYP2D6 is known to be or potentially involved in the biotransformation of dextromethorphan, diphenhydramine, chlorpheniramine, and brompheniramine. To better understand the relationship between dose and exposure in younger children, studies should be designed to pull from the genotypic extremes of the population, investigate the PK of CYP2D6 substrates in the extremes, look at the differences in exposure for the given dose, and try to capture the variability in drug clearance in children of different ages.

Third, patterns of drug response in adults do not necessarily predict patterns of drug response in pediatric populations. In some cases, adult experience is irrelevant for diseases such as persistent pulmonary hypertension of the newborn, Kawasaki disease, or Wilm's tumor, which have no adult correlate. Some pediatric and adult diseases have similar names and share some common characteristics, but there are important differences in disease presentation, treatment, and consequences of medication use, not the least of which is earlier age of disease onset. Ontogeny of drug response pathways is poorly understood. It is not known whether genetic variability affects pathway expression and ontogeny. Risk–benefit relationships may be altered if drug target and downstream pathway/gene network are not expressed.

Whether drugs developed to treat disease processes in adults can also be used to treat similar or unrelated diseases in children will depend on whether the drug target and the physiological context in which it operates are operative in the pathogenesis of the pediatric disease. Several ADRs occur exclusively in pediatrics (Reye's syndrome) or at a much higher frequency in children relative to adults (valproate hepatotoxicity, paradoxical reaction to fentanyl and midazolam), and the consequences of ADRs early in life may carry a life-long burden or morbidity. There are many challenges in the field of pediatric pharmacogenomics, but there is considerable opportunity to apply new tools and multidisciplinary approaches to improve drug safety and efficacy in children.

There are several reasons to study pediatric pharmacogenetics and pharmacogenomics:

- Most drugs are developed for "adult" disease. The impact or consequences of these drugs when introduced into a developing system is not known. It is not know whether these drugs are equally appropriate for the mechanisms responsible for pediatric forms of nominally the same disease.
- Sources of variability in drug response in children have an added measure of complexity: ontogeny.

- Adverse responses related to exposure of medications or environmental contaminants early in life can have life-long consequences.
- Children with diseases such as asthma, autism, attention deficit–hyperactivity disorder, and epilepsy become adults with these same diseases and disorders. Intervening early in the disease pathogenesis may change the patterns of adult disease.

Pharmacogenetics as a Biomarker of Drug Response

David Flockhart, M.D., Ph.D., Chief, Division of Clinical Pharmacology, Indiana University School of Medicine

Genomics is not the only biomarker. It must be seen in the context of other biomarkers, all of which interact. There are some basic principles for all biomarkers:

- Biomarkers are of no value if there is no variability in drug response.
- They must be valuable in the context of other available predictors.
- Biomarkers are of most clinical value when the genetic test allows alternative therapies to be distinguished.
- Biomarkers are of most economic value when a cheaper therapy can be substituted for an expensive one.

There are numerous reasons why pharmacogenomics should be used as a biomarker:

- To elucidate mechanisms
- To predict responses
- To deliver better therapy faster
- To identify new drug targets
- The availability of the Human Genome Map (free, on the Web)
- The availability of the Human HapMap (free, on the Web)
- The stability of DNA
- The ability to amplify DNA
- Cancer begins in DNA.

The clinical value of a pharmacogenetic test decreases when current clinical ability to predict is high. For example, it is easy to predict the response to a beta blocker such as propranolol. Because of this high predictability, there is little need or value for a pharmacogenetic test to predict propranolol's effect. The clinical ability to predict responses to antidepressants is low. Several drugs over a long period may be needed to achieve efficacy. A pharmacogenetic test to predict response to antidepressants would reduce morbidity and therefore be of value. Cancer chemotherapy is another area in which pharmacogenetic tests would be of high clinical value.

GWA studies can be used as a tool for predictive medicine, particularly when effect size is low. In these studies, there is an association between effect size and confidence interval around the mean odds ratio. As the effect size increases, so does the confidence interval. Some large effect sizes have been identified with GWA studies. The sample sizes to predict effect size are generally low.

There a number of clinical modifiers of genomics as a biomarker, including epigenomics (for example, histone methylation and acetylation), drug interactions, environmental modifiers (for example, toxins and diet), reimbursement, and compliance with therapy.

Drug interactions can modify genomic biomarkers. For example, in certain genotypes, CYP2D6 metabolizes tamoxifen to the active metabolite endoxifen. Drugs that inhibit CYP2D6 such as venlafaxine, sertraline, and paroxetine lower endoxifen plasma concentrations. CYP2D6 scoring is associated with relapse-free survival in women with breast cancer. Extensive metabolizers have lower rates of recurrence (about 2 percent). Poor metabolizers have higher rates of recurrence (about 32 percent).

Compliance with therapy is another clinical modifier of genomic biomarkers. For example, an adult observational community trial found a 67 percent adherence rate for tamoxifen after 2 years of treatment. CYP2D6 poor metabolizers are most likely to adhere to tamoxifen for 1 year. It is believed that poor metabolizers have fewer side effects but also less benefit from treatment. Extensive metabolizers were less likely to adhere, most likely because of more side effects. CYP2D6 activity score predicts adherence to tamoxifen therapy: The higher the CYP2D6 genotype score, the higher the dropout rate.

Reimbursement is the third clinical modifier of genomic biomarkers. For example, a study has shown that bevacizumab delays metastatic breast cancer recurrence but does not decrease mortality. A 6-month regimen of bevacizumab costs about $100,000–$150,000. Two VEGF SNP genotypes were isolated from bevacizumab patients who survived longer. Without these variants, bevacizumab patients derived no benefit. The clinical value of bevacizumab is of greater clinical value in patients with the VEGF SNP genotypes. There is a subgroup of patients treated with bevacizumab with lower survival rates. Bevacizumab may have no benefit in these patients and may actually be deleterious. Catalysts for test reimbursement include high impact journal publications, FDA label changes, practice guidelines, economic consequences, and patient, DTC, and wide genomic availability.

Because of the greater focus on postmarket evidence development under the Food and Drug Administration Amendments Act (FDAAA) of 2007, there is a new evidentiary paradigm for the genomic era. Elements of postmarket evidence development include:

- 100-million-person Sentinel network
- Access for advanced drug safety studies
- Getting at subgroup risks and benefits
- Flexible best evidence: observational methodologies before postmarket randomized clinical trials (RCTs)
- Graduated levels of regulatory action in response to evolving evidence.

Ways around the barriers to effective genomic biomarkers include:

- Use of new legislation (under FDAAA 2007, lack of efficacy is equivalent to toxicity)
- High-throughput next-GEN sequencing
- Robust bioinformatics
- Effective, validated modeling

- Focus on iterative improvement.

Exploring Systems Medicine Using Translational Bioinformatics

Atul Butte, M.D., Ph.D., Associate Professor, Medicine, Biomedical Informatics, and Pediatrics, Stanford Center for Biomedical Informatics Research

The nascent field of translational bioinformatics may help translate genome-era discoveries into clinical utility. There are several recent translational bioinformatics projects from the laboratory with direct implications for pharmacogenomics. These projects can be viewed from one of two perspectives:

- One disease across every vantage point
- One vantage point across every human disease.

The early results of the Human Genome Project found many of the genes associated with monogenic disorders. Since then, the focus has shifted to complex polygenic disorders. GWA studies have been proposed as a solution for studying these latter disorders. This approach is now feasible because of low costs of microarrays and the ability to survey 2 million DNA variants out of a potential 10 million SNPs. Despite the feasibility and vast potential, problems with GWA studies are beginning to surface, including inconsistent reproducibility across major studies and inconsistent patient selection leading to inconsistent results. For example, only two of three major GWA studies (Wellcome Trust Case Control Consortium, the Finland–United States Investigation of NIDDM Genetics [FUSION], and the Diabetes Genetic Initiative) found a positive association between the PPAR gamma candidate gene and type 2 diabetes (T2D). There are World Health Organization diagnostic criteria for T2D, but there are no criteria or standards for "normal." Thus, control subjects may not be consistent across studies. Genes may not fully explain complex polygenic disorders. With T2D, genetics can explain only 5–10 percent of the known heritable risk. The Wellcome Trust study concluded that for any given trait, there may be few if any large effects, an intermediate number of modest effects, and a substantial number of very small effects that increase disease risk. Combinations of approaches such as GWA studies, data-driven candidate gene sequencing, and functional data can be used to study one disease across every vantage point. Methods that take advantage of the enormous amount of publicly available genomic data will enable a first step toward solving "equation" for all genes, environmental factors, and phenotypes.

Modern-day use of DNA sequencing has enabled the reorganization of species in the taxonomical trees that date back to Linnaeus. Linnaeus was among the first scientists to suggest a taxonomical classification for diseases, or nosology. Sufficient publicly available genomic data now exist for modern scientists to consider building the first genomic-data driven nosology. It can be shown how such a nosology enables the discovery of new biomarkers for disease (such as inflammatory markers) and suggests novel roles for drugs in the treatment of disease. Existing drugs can potentially be used for new or different diseases and indications. There may be new uses for old biomarkers. In addition, microarrays of biomarkers could be built across tens of thousands of patients, which would expand and enhance the conduct of basic science.

In conclusion:

- The use of publicly available data can have an impact on medicine.
- Personalized medicine does not equal DNA; there is more. Environmental exposures and conditions play a critical role.
- Bioinformatics is not just about building tools. It includes using those tools and coming up with findings.
- There needs to be more emphasis on training in bioinformatics.

Canadian Pharmacogenomics Network for Drug Safety: Finding Drug Safety Solutions to Serious ADRs

Bruce Carleton, Pharm.D., Professor of Pediatrics and Pharmaceutical Sciences, University of British Columbia

ADRs cause significant morbidity and mortality:

- ADRs are the fourth leading cause of death in the United States.
- In the United States, ADRs cost between $137 billion and $177 billion annually.
- ADRs cause 7 percent of all hospital admissions.
- ADRs cause serious reactions in more 2,000,000 hospitalized patients (6.7 percent) each year in the United States.
- ADRs cause fatal reactions in more than 100,000 hospitalized patients each year in the United States.
- About 50 percent of newly approved therapeutic health products have serious ADRs, which are discovered only after the product is on the market.
- About 95 percent of all ADRs are unreported.

The ideal medication effectively treats or prevents disease and has no adverse effects. Clinical trials are conducted to provide evidence of efficacy and safety at usual doses in populations. However, physicians treat individual patients who can vary widely in their response to drug therapy. Individual variability in drug responses can have serious consequences. Genetic factors are responsible for 20–95 percent of the variability in drug response. Pharmacogenomics can help avoid ADRs and maximize drug efficacy for individual patients.

Active surveillance is likely more effective than voluntary reporting in identifying and collecting comprehensive case information for severe ADRs. To this end, Dr. Carleton and colleagues established the Genotypic Adjustment of Therapies in Childhood (GATC) Project, which includes:

- An active ADR surveillance network at eight sites across Canada
- A community-based ADR surveillance with the Canadian Pediatric Surveillance Program, a network of 2,300 pediatricians across Canada
- Collaboration with the Canadian "C-17" Oncology Network, a network of all pediatric oncology departments across Canada.

The anticipated outcomes of project include:

- Evidenced-based approach to individualized drug therapy in children
- Discovery of genetic factors underlying ADRs in childhood

- Genotyping to identify ADR-associated variants
- Increased reporting of ADRs
- Preventative strategies within 5 years.

The GATC Project helped to establish a drug safety active surveillance network with full-time clinical surveillors in 10 major pediatric teaching hospitals across Canada: the Canadian Pharmacogenomics Network for Drug Safety (CPNDS). The surveillors are all health care professionals—pharmacists, registered nurses, and physicians. CPNDS documents ADR cases with all relevant clinical data and identified drug-matched control patients. The CPNDS collects biomaterial to determine the role of genetics in the occurrence of specific ADRs.

Network surveillors identify children who have suffered ADRs (and matched controls) from inpatient, outpatient, and emergency departments at pediatric tertiary care hospitals in Canada. Biological samples are obtained from patients, parents, and grandparents for genotyping if available. Biomarkers of drug risk are identified via analysis of SNPs in genes controlling drug kinetics. Identified biomarkers are validated with PK studies.

National network development required 18 months and included collaboration at multiple levels, including senior administration, department heads, clinicians, and support staff. Other activities included recruiting and hiring of surveillors, addressing privacy concerns, securing local ethics approvals, developing protocols for ADR reporting, establishing sample collection processes, conducting remote project orientation, and gathering support. In 3 years, more than 2,300 ADR cases and 17,000 controls were enrolled. Biomarkers for three serious ADRs have been identified: anthracycline cardiotoxicity, cisplatin ototoxicity, and maternal–infant codeine central nervous system (CNS) depression.

Active ADR surveillance networks like CPNDS require extensive planning and ongoing support. CPNDS is effective for ADR reporting and drug safety biomarker research. Design of the network allows capture of a broad range of ADR cases and targeted surveillance of specific drugs or ADRs of principal concern.

Pediatric Pharmacogenetics Initiative at the Food and Drug Administration

Gilbert Burckart, Pharm.D., Associate Director for Regulatory Policy, Office of Clinical Pharmacology, Center for Drug Evaluation and Research (CDER), FDA

The conceptual foundation for FDA policies in genomic medicine and pharmacogenomics evolved from two initiatives:

- Personalized Health Care Initiative of HHS Secretary Michael Leavitt (2007)
- Critical Path Initiative of CDER Director Janet Woodcock (2005).

Although BPCA and PREA have made considerable strides in providing better clinical pharmacology information on new and old drugs used to treat children, less than 20 percent of studies under BPCA and PREA have labeling changes that provide a specific indication and a labeled dose for pediatric patients. A number of initiatives in the Office of Clinical Pharmacology have been and are being developed to address this need.

From a regulatory perspective, the inclusion of DNA collection and consideration of genotypes is addressed in the discussion of each WR (BPCA) and Pediatric Plan (PREA). A 21st Century Pediatric Review Pilot Program is being designed that will allow earlier consideration of the pediatric protocol during the review of an NDA.

Under the support of the Critical Path Initiative, a cooperative pediatric warfarin pharmacogenetic pilot study was initiated at three major pediatric centers. An additional pediatric project will examine the integration and modeling of pharmacogenomic, pharmacologic, and clinical information to predict outcomes in a large pediatric heart transplant population, in collaboration with a national consortium.

Genomic reviews of investigational new drugs applications and NDAs are incorporating recommendations for the inclusion of the pediatric studies when appropriate.

The Voluntary Genomic Data Submission and Biomarker Qualification programs are actively seeking the inclusion of information relevant to pediatric disease and drug treatment. The Office of Clinical Pharmacology is now promoting the inclusion of pediatric pharmacogenomic information in both regulatory processes and exploratory research. The pharmacogenomic information can include, but is not limited to, the following:

- Description of polymorphic enzymes
- Subpopulation-based information on prevalence or frequencies
- Positive and negative predictive values
- Clearance of the drug in relationship to the genotype
- Pharmacogenomic studies performed that provide evidence of genetically based differences in drug metabolism
- Changes in dose based on genotype.

In addition, there are three collaborative Web-based educational programs:

- American Medical Association/FDA Practicing Physician Training in Pharmacogenomics
- American College of Clinical Pharmacology/FDA Medical and Graduate Student Training in Pharmacogenomics
- FDA Patient Safety News Site on Genetic Testing.

In summary, the Office of Clinical Pharmacology Genomics Group is involved in every stage of drug development and drug use. The inclusion of pediatric pharmacogenomic information is a high priority in the program. The FDA is well positioned to work with consortia to facilitate the movement of pediatric pharmacogenomic information into clinical practice.

Session 2: Pharmacogenomics in Clinical Applications—Challenges and Opportunities

Moderator: Dr. Leeder

Pharmacogenetics of Opioid Toxicity in Young Children

Gideon Koren, M.D., Director, Motherisk Program, Hospital for Sick Children; Professor of Pediatrics, University of Toronto

A large number of neonates and young children are exposed to opioid analgesics, which have a narrow therapeutic index. During the last few years, clinicians have become painfully aware of pharmacogenetic risks of opioid fatalities in infants and toddlers exposed to common opioids.

Exposure of infants to codeine through breast milk may increase their risk of CNS depression when the mother is an ultra-rapid CYP2D6 metabolizer, producing substantially more morphine. Similarly, young children who are ultra-rapid CYP2D6 metabolizers and who are receiving codeine after painful outpatient procedures, such as tonsillectomy, are at an increased risk of apnea and death, as illustrated by a recently diagnosed case.

The Motherisk Program conducted a study to determine whether breastfeeding mothers who take codeine are at an increased risk of maternal and infant CNS depression if they are CYP2D6 ultra-rapid metabolizers and/or homozygous for UGT2B7*2. The study objective was to compare genetic and nongenetic characteristics of mothers and babies with or without signs of CNS depression following exposure to codeine while breastfeeding.

Telephone interviews were conducted with 171 mothers from the Motherisk Program. Of these, 99 mothers were excluded because they did not take codeine, cough syrup, or other CNS medications. The results showed that 17 (24 percent) infants exhibited CNS depression (that is, there was a major decrease in alertness during codeine compared with period without codeine). There was good concordance between maternal and infant CNS depression:

- In 71 percent of mother-infant pairs, both the infant and mother were CNS depressed.
- In 10 percent of mother-infant pairs, the mother only was CNS depressed.

Of the symptomatic mothers, 2 of 17 (11.8 percent) were genotype CYP2D6 UM *and* UGT2B7*2/*2 CYP2D. Of the 55 asymptomatic mothers, none had this genotype.

In summary, codeine cannot be considered a safe drug during breastfeeding for all infants. Maternal CYP2D6 UM/UGT2B7*2/*2 genotype was associated with serious adverse events including fatal poisoning in one infant. There is a dose–response effect between maternal codeine use and neonatal toxicity and a strong concordance between maternal and infant CNS symptoms. This research highlights the contribution of pharmacogenetic factors to maternal response and neonatal outcome.

Asthma Pharmacogenomics: A Plan to Personalize Asthma Treatment in Children

John Lima, Pharm.D., Director, Center for Clinical Pediatric Pharmacology, Biomedical Research, Nemours Children's Clinic

Asthma is a common, chronic, inflammatory disease of the airways caused by complex interactions between genetic and environmental factors that contribute to heterogeneous asthma phenotypes, including variable drug response. Asthma and variable drug response are thought to involve single or multiple variants on multiple genes that contribute modestly to asthma phenotypes.

Asthma imposes a significant burden on our society. It is one of the most common chronic childhood diseases in the United States. The prevalence of asthma among children is 9.1 percent (about 6.7 million individuals), and 60 percent of children with asthma experienced one or more asthma attacks in the previous year. The economic burden in this country from asthma is enormous, exceeding $16 billion in 2004, a large portion of which is attributable to avoidable emergency care and hospitalization. Although there are several drugs that are safe and effective in controlling asthma symptoms and in reducing asthma attacks, variable drug response is a major problem that contributes to morbidity.

Asthma drugs can be classified as either bronchodilators (short-acting bronchodilators, long-acting bronchodilators, and anticholinergics) or controllers (inhaled corticosteroids, leukotriene modifiers, theophylline, and mast cell stabilizers). Depending on the drug class and the severity and phenotype of asthma being studied, the proportion of nonresponders to drug intervention can exceed 75 percent in children with asthma. The basis for the interpatient variability in response to commonly used bronchodilators and controllers is largely due to genetic variability.

The long-range goal of asthma pharmacogenomics is to individualize drug treatment, which is expected to reduce morbidity and the economic burden of asthma. Numerous pharmacogenetic studies (including replication studies) document evidence supporting the genetic basis for response heterogeneity to bronchodilators and controllers. The genotype of the *ADRB2* Gly16Arg SNP associates with asthma worsening during continuous therapy with beta agonists. SNPs in four genes influence response to inhaled corticosteroids: *CRHR1*, *ACP*, *TBX21*, and *FCER2*. Polymorphisms in leukotriene pathway and transporter genes influence response to zileuton and leukotriene receptor antagonists, including *ALOX5*, *LTA4H*, *LTC4S*, *ABCC1*, and *SLCO2B1*. However, known variants explain only a small fraction of the variability in response to bronchodilators and controllers.

The following are necessary steps to personalizing asthma pharmacotherapy:

- Improve characterization of phenotypes; distinguish between responders and nonresponders
- Identify novel genes using GWA studies; confirm by replication in appropriate populations
- Determine mechanisms underlying genotype–phenotype associations
- Consider genotype-driven studies versus conventional studies
- Account for epistasis and epigenetics in formulating a predictive model
- Develop novel molecular biomarkers.

Interplay of Pharmacogenetics and Developmental Factors in Regulating Drug Metabolism

Ronald N. Hines, Ph.D., Professor, Pediatrics and Pharmacology/Toxicology, Medical College of Wisconsin; Associate Director, Children's Research Institute, Children's Hospital of Wisconsin

Profound changes in drug-metabolizing enzyme (DME) expression occur during development and affect drug efficacy and the risk of adverse events in the fetus and child. Current knowledge suggests individual hepatic DME ontogeny can be categorized into one of three classes. Enzymes belonging to the first class (for example, CYP3A7) are expressed at their highest level during the first trimester and either remain at high concentrations or decrease during gestation, but are silenced or expressed at low levels within 1–2 years after birth. Enzymes belonging to the second class, typified by SULT1A1, are expressed at relatively constant levels throughout gestation and minimal changes are observed postnatally. Enzymes in the third class (for example, CYP2D6, CYP2C9, and FMO3) are not expressed or are expressed at low levels in the fetus, usually during the second or third trimester. Substantial increases in enzyme levels are observed within the first 1–2 years after birth. Based on current data, the third class of enzymes represents the largest set.

Several cases suggest that developmental factors can dominate pharmacogenetic factors. For example, although CYP2D6 expression is detectable in hepatic tissue from many second- and third-trimester fetuses, genotype is not a significant factor influencing expression levels during gestation. Increases in CYP2D6 expression to adult or near-adult levels occur rapidly after birth. In postnatal samples both genotype and postnatal age significantly influence expression of this enzyme. Thus, a major challenge to applying pharmacogenetics to improve drug safety in children is determining at what age functional genetic variants identified in adults become a major determinant of expression in children. Compounding this challenge is the observation that even within a single developmental expression pattern class, there is considerable variability from one enzyme to another. For example, the postnatal increase in CYP2D6 expression to adult levels occurs relatively rapidly after birth. Both *in vitro* and *in vivo* data suggest maximum, constitutive expression levels within 2 weeks after birth. In contrast, FMO3 expression is rarely observed in the neonate but is detectable in most individuals by 1–2 years of age. However, prepubertal expression is generally only 30 percent of that observed in adults.

A second major challenge to the application of pharmacogenetics in children is the observation of significant interindividual variation in developmental expression patterns (windows of hypervariability) for a given enzyme. For example, in about 50 percent of individual neonatal liver samples examined, CYP2C9 expression levels were near adult levels. In contrast, for the remaining 50 percent of samples, CYP2C9 expression levels were no different than those observed in third-trimester samples. However, by 6 months of age, nearly all samples exhibited expression levels close to those observed in adults. Similarly, only 15 percent of the neonatal liver samples exhibited FMO3 expression. However, between the neonatal period and 1 year of age, and between 1 year and 11 years of age, 72 percent and 91 percent of samples exhibited FMO3 expression, respectively. Furthermore, case studies of transient trimethylaminuria that results from severe FMO3 deficiency are consistent with these *in vitro* observations. The extent to which genetic variability contributes to these interindividual differences in developmental

expression is not known. It is not known whether elucidation of these genetic differences would allow better prediction of drug disposition and response in children.

Challenges to elucidate the interplay between pharmacogenetics and ontogeny include:
- Age at which functional polymorphisms in adults become important determinants in children
- Variability among enzymes belonging to the same developmental expression pattern
- Interindividual variability in temporal expression patterns (windows of hypervariability).

Genetics and Pharmacogenomics of Complex Pediatric Disorders

Hakon Hakonarson, M.D., Ph.D., Associate Professor, Pediatrics, Director, Center for Applied Genomics, Children's Hospital of Philadelphia

ADRs are among the leading causes of death and disability in the United States:
- ADRs cause more than 100,000 deaths annually in the United States (fourth leading cause of death ahead of pulmonary disease, diabetes, AIDS, pneumonia, accidents, and automobile deaths).
- More than 1 in 9 emergency department visits are due to drug-related adverse events.
- ADRs cost $136 billion annually, which is greater than the total costs of cardiovascular or diabetic care combined.
- ADRs cause 1 out of 5 injuries or deaths per year to hospitalized patients.
- About two-thirds of patients' doctor visits result in a prescription.
- About 2.8 billion outpatient prescriptions (10 per person in the United States) were filled in 2000.
- ADRs increase exponentially with four or more medications due to drug–drug interactions.

Because genetic diversity contributes to both disease susceptibility and drug response variability, genotyping of patients has the potential of unveiling important variants that may predispose to ADRs.

The candidate gene approach has not been particularly effective in identifying genes that influence drug response. In contrast, the GWA study approach has increasingly gained popularity and has enabled scientists to associate specific variants with the predisposition for complex disease. The technology has stirred new hope for the mapping of genes and genetic variants that regulate drug response related to these conditions. Despite the early successes, researchers can explain only a very small fraction of genetic risk for most diseases.

To further understanding of the genetic variations underlying disease susceptibility and variability in drug response, the Center for Applied Genomics at Children's Hospital of Philadelphia is collaborating with more than 30 active disease projects in an effort to genotype 100,000 children as part of a large GWA study. To date, there are samples from about 50,000 children in the database. The database includes samples from about 6,500 disease-free controls.

One approach to individualized medicine is the application of pathway analysis to GWA study data. This approach can be used across disease areas because there has been very strong

replication of pathway findings across studies and high biological relevance. The rationale for this approach is as follows:

- Single-locus/single-marker studies may lack the power to detect genuinely associated loci.
- Different GWA studies on the same disease often detect different SNPs (heterogeneity).
  - There is a small effect size of any individual SNP.
  - Individual GWA studies are often relatively underpowered.
- A pathway-based approach considers multiple variants in related or interacting genes and analyzes the group for statistical significance between cases and controls.
  - Certain biological pathways may be more relevant in certain individuals.

Collectively, GWA studies support the notion that modern high-throughput SNP genotyping technologies, when applied to large and comprehensively phenotyped patient cohorts, may readily reveal the most clinically relevant disease-modifying and drug-response genes. Recent advances in the genotyping field have conclusively uncovered variants that underlie disease susceptibility and variability in drug response for common disorders. Although GWA studies and associated technologies are a having massive impact on gene discovery in complex human disease, there are challenges in the application of pharmacogenomics:

- There is an extremely high failure rate in drug development.
- Researchers first need to understand complex diseases mechanistically.
- Researchers need to understand the genetic network of disease genes in order to find the most optimal therapeutic drug target for intervention.
- GWA studies are the most robust tool researchers have to unveil these complexities.
- GWA studies have effectively uncovered unlinked biological disease pathways, including:
  - Strong association between HLA-B*5701 and hypersensitivity reactions to abacavir
  - Association between elevated ALAT and the MHC alleles DRB1*07 and DQA1*02 in patients treated with the thrombin inhibitor Ximelagatran
  - Multiple successes in diabetes, cardiovascular disease, obesity, metabolic disorders, inflammation, and cancer.
- Current technology is highly promising in the application of pharmacogenetics and pharmacogenomics.

Can "Individualized Drug Therapy" Be Successful, Given the Complexity of the Human Genome?

Daniel Nebert, M.D., Professor, Department of Pediatrics, Division of Human Genetics, Department of Environmental Health, University of Cincinnati Medical Center

It is not known whether the number of DNA variant sites (genotype) can be associated 100 percent of the time with the prediction of a drug response (phenotype). Ideally, a 100 percent level of success in genotype–phenotype association studies would be most desirable for "individualized drug therapy." Sequencing of the entire human genome, the mapping of common haplotypes of SNPs, and increasingly cost-effective genotyping technologies leading to GWA studies have demonstrated the requirements needed to separate true associations from the plethora of false positives. There are dozens of reasons why an unequivocal genotype, as well as an unequivocal phenotype, is virtually impossible to achieve in current limited-size studies of human populations. For example, multiple genomic phenomena can override a SNP. The

problem of insufficiently stringent criteria leads to decreased statistical power and, consequently, equivocal interpretation of most genotype–phenotype association studies.

The ENCODE Pilot Project covering about 1 percent of the human genome has led to a number of genomic breakthroughs but has shown that scientists are no longer even certain what a "gene" is. However, disease-related genes can be classified as human "monogenic" genes, "high-Penetrance predominantly Monogenic" (hPpM) genes, and "complex disease" genes. Comparing monogenic, hPpM pharmacogenetic disorders, and complex diseases indicates that the percentage that a gene might contribute to the phenotype varies: >90 percent, 15–20 percent, and <1 percent, respectively. Although there have been recent gene–disease association "successes" using GWA studies, there have been discrepancies across GWA studies. Epigenetics and epigenomics could explain some of these discrepancies.

Careful scrutiny of the mouse and human genomes indicates that only 12 of the about 20,500 shared protein-coding genes are actually exclusive to one or the other species. RNA-interference (RNAi) genes number into the thousands. Science has shown that genetic systems have evolved over millions of years to a point of maximum stability—in the face of genetic and environmental perturbation. Yet, waves of genetic change accompanying the origin of the *Homo* genus and subsequent migration around the globe have disrupted this stable equilibrium with an explosion in the past 6,000 years. Within the past 300 years or so, dramatic cultural changes (striking dietary shifts, tobacco smoking, air pollution, altered pathogen exposure, taking drugs [prescribed, over-the-counter, recreational]), and psychological stress have invoked epigenetic changes in the human genome.

Continuous discoveries of new surprises about the human genome have led scientists to question reviews declaring that "personalized medicine is almost here" or that "individualized drug therapy will soon become a reality." It is predicted that, although some ADRs/efficacy traits might follow hPpM (15–20 percent) inheritance, others likely follow complex diseases (<1 percent) inheritance. Researchers must appreciate that all drug responses are gradients, reflecting quantitative trait loci (QTLs). Accordingly, these responses can be evaluated by alterations in expression (eQTLs), metabolism (mQTLs), and perhaps protein (pQTLs) profiles. It is predicted that the future of individualized drug therapy will involve a combination of these, rather than DNA tests alone.

In conclusion, there are many problems with quantifying the phenotype, and especially the genotype. Epigenetics must play a big role in complex diseases, as well as ADRs. GWA studies, being done in human genetics, have now begun in pharmacogenomics (≥1 percent SNPs versus epigenetics). Some traits (for example, therapeutic failure) might be amenable to GWA studies, whereas others (for example, drug-induced obesity) might be more amenable to metabolomics. "Personalized medicine" and "individualized drug therapy" are a long way off.

BioVU: The Future of Pediatric Biobanking at Vanderbilt University

Louis Muglia, M.D., Ph.D., Vice Chair for Research Affairs, Department of Pediatrics, Vanderbilt University Medical Center

Two independent, but now interrelated, areas of biomedical research have converged to provide a unique model to realize the potential of personalized medicine. The first area is the technology to efficiently, cost-effectively, and reliably gather high-dimensional biological information such as genotype or gene expression (mRNA or protein) profiles. Nanogram amounts of human DNA can be used for association of a panoply of candidate genes, genomewide polymorphisms, or complete genome sequencing with rare or common complex disorders and response to drug therapies, for example.

Concomitant with the rapid acceleration in technologies for analyzing genes and other biomarkers has been an explosion in bioinformatics. Vanderbilt University has developed a unique, large-scale biobank—BioVU—that links DNA extracted from discarded blood samples to deidentified electronic medical records. BioVU has two major components:

- The Synthetic Derivative (SD), a deidentified image of the entire electronic medical record (EMR; 1.5 million records)
- DNA extracted from discarded blood samples (50,922 as of March 2, 2009, in adults) linked to the SD.

This EMR system contains health records spanning pregnancy, pediatric, and adult developmental windows that have been systematically extracted to form the SD database. The SD database is accessed through a user interface, and search queries can be performed using a range of fields, including keywords, free text, ICD-9 or Current Procedural Terminology codes, or medication lists. Because no Health Insurance Portability and Accountability Act (HIPAA) identifiers are available in the SD database, and projects cannot reidentify these records using the identified Vanderbilt University Medical Center (VUMC) database, those studies using the SD have been judged to meet criteria for non-human subjects research.

There are limitations in the project design. BioVU cannot be used for contact of individuals. Genome–phenome correlation capability depends on the quality of clinical data in EMRs. BioVU cannot currently be made into a public resource in its entirety due to unquantified but nonzero reidentification potential and the need to have enforceable acceptable use policies.

The BioVU DNA Databank, which extracts DNA using a novel "opt-out" model from individual blood samples collected as part of routine care that would otherwise be discarded, has rapidly changed the scale of DNA collections at Vanderbilt. BioVU was launched in February 2007 after 3 years of planning and extensive interactions with the ethics community, the Office for Human Research Protections, the university's institutional review board (IRB), the VUMC community, and the Nashville community. For initial feasibility and community acceptance, the sample collection was started only in adults. The resource is currently accruing about 500 adult samples per week. It is anticipated that pediatric accrual will be 15,000 samples per year beginning in summer 2009. The BioVU project is capable of generating a 250,000-sample collection in 4–5 years.

Expansion of BioVU to incorporate pediatric biobanking required resolution of the ethical considerations involved in the "opt-out" approach as applied to children. To address this need, additional pediatric-directed discussion incorporating the IRB, VUMC faculty and staff, and the community advisory board has occurred. Parent accessibility surveys established understanding, desire for participation, and overall acceptance of having samples, already acquired from their children in the course of clinical care and scheduled to be discarded, used in BioVU. A demonstration project—in which 21 SNPs were genotyped that had previously been implicated as common variants predisposing to atrial fibrillation, Crohn's disease, multiple sclerosis, rheumatoid arthritis, or T2D in the first 9,483 samples accrued into BioVU—will be presented as validation of this approach.

In summary, BioVU will provide an unprecedented resource for the following:

- Rapid confirmation of genetic markers identified by prospective, disease-focused studies
- Translation of genetic studies in model organisms to humans
- Previously unapproachable studies such as determining the spectrum of phenotypes that occur in the context of a given genotype (no specific inclusion and exclusion based on clinical characteristics).

Session 3: Working Group Breakout Sessions, Reports, and Discussion

Moderator: Dr. Weinshilboum

After the two presentation sessions, three working groups were formed to answer the following questions:

1. What are the limitations and obstacles in pediatrics pharmacogenetics research?
2. What are the challenges and opportunities for pediatric pharmacogenetics research?
3. What technologies are available for pediatric pharmacogenetics research?
4. What existing resources (DNA, biobanks) are available and how can they be used for pediatric pharmacogenetics studies?
5. How can pharmacogenetics be applied to pediatric clinical research, clinical trial design, and ongoing and future clinical trials?
6. What are the opportunities for collaborations with other pharmacogenetics programs or other stakeholders?
7. What are the major regulatory hurdles in pediatric pharmacogenetics research?
8. What are the training needs for pediatric pharmacogenetics?

Working Group A. The leader was Dr. Carleton. Group members included Drs. Flockhart, Hakonarson, Lima, Muglia, and Zajicek.

Working Group B. The leader was Dr. Hebert. Group members included Drs. Burckart, Leeder, Lubin, Nebert, Ren, and van den Anker.

Working Group C. The leader was Dr. Hines. Group members included Drs. Butte, Giacoia, Koren, Renbarger, Taylor-Zapata, and Weinshilboum.

Working Group Reports

The following are the combined reports for the three working groups.

1. Limitations and Obstacles in Pediatric Pharmacogenomic Research

Limitations and obstacles include:

- Accurate phenotyping
  - Diagnostics
  - Phenotypic descriptors
  - Difficulty with inability of children to communicate
- Access to pediatric patients in clinical trials (high costs, fewer clinical trials than observational cohorts, and no opportunity for replication)
- Infrastructure for large, high-throughput discovery efforts
- Patient numbers/adequate sample size and need for large, multicenter studies
- Trade-off with larger biobank studies (that is, not having phenotypic data)
- Lack of manufacturer-provided DNA (from clinical trials)
- Sample collection (for example, urine, blood, and saliva) from children, particularly in very young/small children
- Education
  - Some IRBs need education regarding pediatric studies. IRB concerns need to be addressed.
  - Communities need education about pediatric research.
  - Community mistrust of how research will be used needs to be addressed.
- Need for advocacy for awareness of major technological centers
  - Major genome and other centers' recognition of the need for pediatric studies
- Lack of pediatric clinical pharmacology–trained clinicians.

In addition:

- There is a need to include representation from children of diverse socioeconomic, racial, and ethnic backgrounds.
- Because of the necessary size of the studies and need for extensive infrastructure, high costs can limit pediatric pharmacogenomic research.
- Inadequate documentation in medical records that include all phenotypic descriptors is another limitation. Although some institutions use EMRs, they are generated from hand-written scanned documents. These EMRs are not searchable, which makes the collection of information for research difficult.
- Many disease-specific resources are available, but there is no registry of these resources.
- There is a lack of industry willingness to support pharmacogenomic studies.
- Most research budgets for genomics are predominantly for adult studies.
- There is a lack of reimbursement from insurance for genotyping.
- There is need for more fully developed/refined microarray-based gene expression profiling.
- There is a need to develop more robust GWA studies, using several targets.
- New molecular biomarkers of drug response are needed. Proteomic approaches need to be further developed.

2. Challenges and Opportunities for Pediatric Pharmacogenomic Research

Challenges include:
- The need to form collaborations and develop infrastructure
- Insufficient manpower (investigators, clinical staff, surveillors) to conduct research
- "Egos and silos" that segregate and impair collaboration
- The need for samples for a great number of ages (0–18 years)
- Unique diseases represented in the pediatric population
- Whether pharmacogenomic research can improve pediatric care
- Addressing the complexity of developmental changes in children
- Communicating through surrogates (parents, guardians)
- Social issues related to family structure and impact on ability to collect data.

Because of the large size of the studies, large number of co-investigators, and length of effort, a junior researcher or faculty member may not be a lead author of a resulting publication. The inability to be a lead author often affects promotion. This situation may discourage scientists from participating in pediatric pharmacogenetic research.

Opportunities are as follows:
- Because pediatric pharmacogenomics is an untapped area of research, any initiatives will basically be new and publishable.
- Research findings should ultimately be able to prevent ADRs and decrease health care costs.
- Genomic data can identify potential biological pathways and drug targets for pediatric diseases.
- Pilot studies can direct change in culture when physicians feel they are part of a research team and realize benefits to their patients.
- Bioinformatics platforms provide novel opportunities to gather high-dimensional information (that is, data mining).

Other opportunities include:
- Disease-specific research
- Rare disease resources
- Fetal exposures research
- Fetal/pediatric basis of adult disease
- Lactation research
- Elucidating developmental changes in genomics in early ages
- Developing partnerships and collaborations.

3. Available Technologies for Pediatric Pharmacogenomic Research

The following are some of the currently available technologies for pediatric pharmacogenomic research:
- Next-GEN sequencer
- DNA amplification

- Gene expression arrays
- Natural language algorithm
- SNP chips
- DNA patterns
- Metabolomics
- Nanotechnology
- Cytomegalovirus patterns
- Line blotting
- Online social networks (Twitter, Facebook) for community education
- EMRs
- Candidate gene approach
- "In between" approach (targeted SNP platforms)
- Epigenetics—methylation (focused or genomewide)
  - Approach more powerful with SNP variants
- Bioinformatics platforms.

4. Existing Resources and Potential Use for Pediatric Pharmacogenomic Research

Existing resources include:

- BioVU
- Patient databases (for example, Children's Hospital of Philadelphia, GATC/CPNDS, British Columbia's linked health database, the California newborn screening program's DNA bank, the U.S. Armed Forces DNA bank, Medicaid, and health maintenance organizations)
  - Personnel liaison necessary to access data
- The National Children's Study (NCS; n = 100,000, from planned conception to age 21)
- Newborn bloodspot collections
- National health registries in Denmark, the United Kingdom (National Health Service Biobank), and Norway
  - It is not known whether these registries include medication use data.
  - Data quality needs to be assessed.
  - Similarity in drug use is unknown (for example, pediatric oncology protocols).
- High-throughput screening with model organisms as a resource (for example, to examine teratogens and drugs with high occurrence of adverse outcomes)
- Cell lines or DNA as a public resource
  - Different genotypes, drug exposure experiments *in vitro*
  - Coriell Institute for Medical Research may have similar ability, but it is not known how material much is pediatric or age specific.
  - Children's Hospital of Philadelphia has frozen cells from children, with drug exposure data.
- Disease-oriented resources (for example, for sickle cell and rare disease foundations)
- Clinical and Translational Science Awards (CTSA) initiative
- Industry, NIH, and academic tissue banks, with registries.

5. Application of Pharmacogenomics to Pediatric Clinical Research, Clinical Trial Design, and Ongoing and Future Clinical Trials

Pharmacogenomics can be applied to pediatric clinical research as follows:

- Networking
- Establishing biobanks for all clinical trials, including the NIH and industry
- Designing PK trials to phenotype and genotype with consent to recontact for future studies, in a disease-specific manner
- Taking advantage of the CTSA network
- Educating the communities, parents, and physicians (perhaps through a Request for Applications [RFA])
- Creating a registry of biobanks.

Clinical trials need to:

- Focus on the efficacy of pharmacogenetics in pediatric therapy
- Have large sample sizes—large enough so that studies can be adequately powered.

There needs to be cooperative/collaborative groups and internationally based pediatric clinical trials to achieve these goals.

In addition:

- DNA samples need to be collected at time of trial (made part of the protocol).
  - IRB and consent issues need to be addressed.
- A metabolizing enzyme chip would be valuable for genotyping all children in a clinical trial.
- Genotype information should be used as selection or stratification criteria to ensure capture of data from individuals with different genotypes.
- RFAs need to specifically designate that these studies are important; review sections need to understand the importance of pediatric pharmacogenomic studies.

6. Opportunities for Collaborations with Other Pharmacogenomic Programs or Other Stakeholders

Opportunities for collaboration include:

- NCS
- PPRU network
- Obstetric Pharmacology Research Units (OPRU) network
- Pharmacogenetics Research Network (PGRN)
- GATC/CPNDS
- Databanks beyond these networks (biobanks available to all members of, for example, PGRN); would be helpful to have a pediatric component
- The 59 networks within NICHD (specifically, disease-related networks that could or do collect DNA)
- Centers for Disease Control and Prevention (for example, DNA banking for infectious diseases)

- Private-sector collaborations (for example, the Serious Adverse Event Consortium and the Pharmaceuticals Research and Manufacturers of America [PhRMA])
- Disease associations
- CTSA network
- International organizations such as the World Health Organization, the Gates Foundation, the Wellcome Trust, European networks, and cord blood networks
- Access to data and infrastructure for analysis.

7. Major Regulatory Hurdles in Pediatric Pharmacogenomic Research

The regulatory issues in pediatric pharmacogenomic research are not unique. There may, in fact, be fewer issues than for adult research in this area. Accreditation of programs could reduce some regulatory hurdles. Major regulatory hurdles include:

- HIPAA regulations
- IRB issues
  - Informed consent
  - Deidentified data
  - Changing rules and protocols
  - "Temporary" permission (that is, banking DNA for a finite period)
- Consumer genotyping
- FDA regulatory steps.

Although the FDA Office of Clinical Pharmacology has been supportive of pediatric pharmacogenomics research, clinical divisions have been more resistant to labeling changes (for example, oncology has been more resistant to changes from the standard RCTs approach). The regulatory steps should be clear in order to get better genetic information into drug labels. Issues include:

- No FDA label recommends genetic testing except for abacavir.
- There is a need for more than just genetic information in the label.
- Guidance and rules for pediatric pharmacogenomics research do not exist, making it hard to know what type of study is needed.
- There is a need to know what FDA is doing (that is, what regulatory changes are in process) in order to provide advice on pharmacogenomics.
- FDA wants to use credible data for labeling changes, but it is not always known what credible data are and where they can be gathered.
- Prospective RCTs are reasonable (for example, the St. Jude Children's Hospital study of TPMT plus white blood cell monitoring; the Motherisk Program, Hospital for Sick Children, codeine study).

8. Training Needs for Pediatric Pharmacogenomics

Training needs are as follows:

- NIH National Research Service Award (NRSA) Institutional Research Training Grants (T32 or K) awards for
  - Pediatric and obstetric–fetal pharmacogenomics

  - Pediatric and obstetric–fetal clinical pharmacology
- Pediatric residency training in pharmacogenomics
- Medical, pharmacy, public health, and nursing training in pharmacogenomics
- Postgraduate education (continuing medical education, continuing education) for pediatricians, pharmacists, and nurses on pharmacogenomics.

In addition:
- There is a lack of pediatric clinical pharmacology–trained clinicians and a need for a quantum leap in training opportunities.
- The CTSA network could serve as a training ground. CTSA includes:
  - Clinical and translational science awards
  - 60 funded sites
  - Specific language for training and pediatrics.
- Clinical pharmacology training could be added to the traditional areas of PK, PD, and pharmacogenomics. The National Institute of General Medical Sciences clinical pharmacology training programs could serve as a model. This curriculum could be used within the CTSA network.
- Pediatrics could be included in PK, PD, and pharmacogenomics coursework at medical schools.
- There is a need for NICHD-supported training grants and programs in pediatric clinical pharmacology, including pharmacogenomics.
- Pediatric pharmacogenomics would benefit from summer training institutes, which have been successful in other NICHD programs. These institutes raise awareness and generate interest.
- Ensuring that pediatric pharmacogenetics is addressed at major professional society meetings (for example, Society for Pediatric Research) will raise awareness and generate interest. The PPRU network has sponsored many sessions focusing on pediatric clinical pharmacology at such meetings.

There are some roadblocks to training:
- CTSA institutions train mostly physicians and people with doctoral degrees. Pharmacists are largely missing and would be important to include in training.
- Physicians in training generally do not like pharmacology (often because it does not focus on clinical pharmacology).
- There is no structure for including coursework in Clinical Research Curriculum Awards (for example, K30s).
- There are no mid career or senior investigator training opportunities.

Recommendations

Pharmacogenomics research should:
- Expand from just pharmacogenomics to include metabolomics, proteomics, and transcriptomics
- Expand to include obstetric–fetal pharmacology
- Include pediatrics and obstetrics into genomics bills and all legislation related to this area
- Be incorporated into health care reform to provide additional resources to NICHD

- Pursue nontraditional sources of funding such as public–private partnerships
- Look for opportunities to collaborate with organizations such as the Personalized Medicine Coalition.

In addition:
- Pediatric pharmacogenomic studies should take advantage of existing centers and programs and encourage collaborative efforts between pediatric subspecialties (for example, the PPRU network).
- Pediatrics should be included in all pharmacogenomic efforts involving other institutes and research efforts (for example, the NCS and biobanking projects).
- Pediatric pharmacogenomic research should take advantage of technologies at existing genome centers.
- Although EMRs are not designed as a source of research material, they are an available technology that could be used in pediatric pharmacogenomic research. Standardization of EMRs would enhance their value. Researchers need to advocate for the use of EMRs for pediatrics and pharmacological research.
- Clinicians and investigators should collect genetic materials from children with well-defined phenotypes. Establishing a culture that routinely collects genetic samples from well-defined phenotypes is an opportunity to expand pediatric pharmacogenomic research.
- There should be incentives for developing international collaborations as well as environmentally focused efforts such as the NCS.
- Researchers should explore the overlap between environmental toxicology and pharmacology. Overlap in technologies in these areas may foster collaborative efforts.
- Pilot studies may be worthwhile to provide insight into societal views of pediatric clinical research. For example, community feedback regarding a Children's Hospital of Wisconsin clinical pharmacogenomics study of seizures was very supportive and indicated that there may be less community concern about privacy than thought.
- There should be harmonization regarding interpretation and application of pharmacogenomic information across programs and studies. Studies would benefit from standardized reporting in medical records (for example, descriptions of phenotypes).

General Discussion

Several key themes were identified in the workshop:
- The need to incorporate pediatrics into studies that have been traditionally adult-based
- The need for education and training in pediatric clinical pharmacology and pharmacogenetics
- The importance of planning pediatric components in clinical projects—before projects begin
- The need to bring together pharmacogenomic researchers and pediatric pharmacology researchers
- The importance of bioinformatics in pharmacogenomics.

The following major issues and recommendations were discussed:
- Education and training in pharmacogenomics should be a top priority for NICHD.
- There is a need for cross-training and bridging disciplines (for example, bringing together pharmacogenomics and pediatric clinical pharmacology).

- Pharmacogenomics research requires investment in people (education and training), technology (mostly commercially driven), and environment (collaborations and infrastructure for studies).
- Although technology is rapidly advancing, key limitations are lack of phenotyping information and access to quality samples to overcome statistical limitation of power.
- Drug-response outcome measures need to be more clearly defined. There should be set of criteria for outcomes and harmonization of reporting.
- Funding mechanism should be created to provide incentives for multicenter trials.
- NICHD should help raise awareness in major genome centers about the need to include pediatric cohorts.
- Partnerships need to be explored and developed (for example, public–private: with academia, the Foundation for NIH, and professional societies; and among government agencies and institutes).
- NICHD should collaborate with projects such as Phenix and the Human Phenome Project to ensure inclusion of pediatric and maternal–fetal pharmacology and genomics.
- Consortia/partnerships could be created to develop phenotype databases.
- Phenotype data should be collected from BPCA and other NICHD clinical trials.
- Normal lab values for physiological measures should be defined to more clearly characterize phenotypes.
- Consortia/partnerships could be created to develop a database of normal lab values and parameters.
- NICHD needs to create funding vehicles to make technologies (for example, GWA studies, next-GEN sequencing) available in pharmacogenomic studies. R01 grants are not appropriate funding mechanism for these studies.

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