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Eunice Kennedy Shriver National Institute of
Child Health and Human Development
**Scientific Vision Workshop
on Diagnostics and Therapeutics**

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Workshop White Paper

by Workshop Organizers:
(in alphabetical order, by role)

A. James Barkovich, M.D. (Co-chair)
University of California, San Francisco

Stanley J. Szeffler, M.D. (Co-chair)
University of Colorado, Denver

Eric Olson, Ph.D.
Vertex Pharmaceuticals Incorporated

William Rymer, M.D., Ph.D.
Northwestern University

I. INTRODUCTION/OBJECTIVES/CROSS-CUTTING THEMES

The objectives of the NICHD Diagnostics and Therapeutics Vision Workshop were to:

- Use new techniques to diagnose and monitor drug response
- Identify biomarkers that can be assessed to evaluate disease and the effects of treatment, allowing clinicians to adjust or change treatments early and as needed
- Identify new approaches to measurements of impairment based on the emergence of new engineering and computer technologies
- Utilize a systems biology approach to identify new therapies for the management of disorders of interest to NICHD

To accomplish these objectives, the workshop organizing group developed four thematic sessions focused on: 1) Improving methods to diagnose and manage childhood diseases as a model; 2) Neurodevelopmental disorders; 3) Rehabilitation of neurological disability; and 4) Therapeutics development. The results of these sessions are presented in the below sections. Section II outlines the scientific opportunities, key questions to help facilitate the opportunities, and the research tools, methods, or approaches to achieve the anticipated outcomes for each of the four sessions. Section III describes how the scientific opportunities will advance the NICHD mission, Section IV addresses how the opportunities will affect public and global health, and Section V describes the training and workforce development activities needed to advance diagnostic and therapeutic sciences.

II. SCIENTIFIC OPPORTUNITIES

A. Improving Methods to Diagnose and Manage Childhood Disease

Co-Leaders: Robert Ward and Stanley Szeffler

Breakout Group Members: Peter Adamson, Gang Bao, Anne Blaschke, Leonard Dragone, Kevin Maher, Dianne Murphy, Michele Puryear, Paul Spearman, Kelan Tantisira, and Michael Watson

Introduction

New technologies provide new opportunities for diagnosing, managing, and monitoring diseases, such as nanotechnology for sickle cell disease, cancer, infectious disease, and cystic fibrosis; enzyme analysis for cardiovascular disease; or localized heat treatment for cancer.

Scientific Opportunities

In the area of diagnostics and monitoring, the scientific opportunities are to:

- Identify and utilize existing and new cohorts to access information combined with biologic samples to describe the normal so it can be differentiated from the diseased condition;
- Apply new technologies, such as nanotechnology, magnetic resonance imaging (MRI) spectroscopy, and automated polymerase chain reaction (PCR) analysis that can lead to rapid, specific diagnosis for targeted therapy;
- Link novel technologies, such as nanotechnology and functional studies with MRI spectroscopy, to imaging for detection of disease and prediction/evaluation of treatment response;

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- Improve disease management with the application of new generation genetic analysis and pharmacogenomics to detect susceptibility to a disease and improve the likelihood of successful drug therapy;
- Promote diagnostics through collaboration with industry, e.g., multiplex assays for biomarkers and pathogens as well as to assess exposure or develop models for new collaborations via funding mechanisms; and
- Evaluate clinical effectiveness through comparative therapeutic clinical trials.

Basic, Clinical, and Translational Questions Needed to Facilitate the Scientific Opportunities

In order to facilitate these opportunities certain basic, clinical, and translational questions need to be answered:

- What are the benefits and risks of new technology, such as nanotechnology?
- What is the potential for contamination in biomarker and microbiome research?
- How do we hasten the incorporation of new findings into clinical care?
- Can expanded newborn screening improve understanding of natural history of diseases and lead to early treatment that alters the course of disease?
- Can we develop better mathematical models of human disease, e.g., in silico models?
- How do we diagnose disease caused by microbial agents that cannot be grown in animals?
- How do we better understand normal and abnormal immune markers and functions in order to understand age-related vulnerabilities and identify abnormal patterns?
- Can we perform analysis by systems biology to link genotype and other biomarkers to clinical data to increase understanding of interacting factors and clarify phenotype?
- Can we establish a linkage for bio-banking systems to provide more robust background sample sizes for testing hypotheses?

What research tools, methods or approaches should be developed to achieve the anticipated outcomes?

The following research tools, methods, and approaches should be developed:

- Increased collaborative infrastructure development, e.g., expanding and linking clinical trials networks, to answer key questions to set and address priorities;
- Animal models should be explored and utilized carefully to aid in understanding disorders, developing hypotheses for treatment, and for screening treatment in preparation for human clinical trials;
- Nanotechnology and new generation genetic analysis should be examined for development of improved diagnostics and therapeutics;
- Genetic and epigenetic techniques should be refined to understand risk for disease development, level of severity, and level of treatment response; and
- Validated markers are needed to provide reliable outcome measures during clinical trials. This can be vital in the evaluation of expanded newborn screening. To do this, it will be important to profile research as an integral part of the clinical care environment.

B. Neurodevelopmental Disorders

Co- Leaders: A. James Barkovich and Robert McKinstry

Breakout Group Members: Peter Anderson, William Andrews, Mary D'Alton, Lex Doyle, Charles Dumoulin, P. Ellen Grant, Marit Sæbø Indredavik, Elysa Marco, Michael Msall, Duan Xu

Introduction

Despite many years of efforts, the anatomic, physiologic, and chemical causes of most childhood neurodevelopmental disorders are largely unknown. Even when causative genes are known, mechanisms are mostly postulated and fundamental questions remain unanswered. In the absence of knowledge of the causes, clinical decisions regarding intervention are made empirically, sometimes without a full understanding of the consequences of the action, and efficacy has been difficult to test due to the complexity of performing meaningful, long-term follow-up. Preterm birth is a poorly understood, but an increasingly common, cause of neurodevelopmental disorders (ND) that include sensorimotor disability, visual and visual processing disability, auditory impairment, disorders of cognition, and behavioral and psychiatric disorders. Currently, 12% of live births in the U.S. are premature; although most research has focused upon the subset with very low birthweight (slightly more than 10% of prematures), all prematurely born neonates are at increased risk for ND.

Scientific Opportunities

In the area of neurodevelopmental disorders, the scientific opportunities are:

- **Understanding the causes of premature birth and the causes of associated ND and abnormal long-term outcomes.**

Only a small percentage of preterm labor results in preterm birth (delivery prior to 36 gestational weeks), yet the effects of preterm labor upon the fetus (whether delivered prematurely or at term) are not known. To fully understand and potentially prevent ND, it will be necessary to study the fetus and fetal environment from the time of preterm labor and to determine whether the labor or its initiating factors have any effect upon the fetus. Studies may include analysis of the fetus, amniotic fluid, and placenta. It is important to recognize that, although the most vulnerable infants (the 10% born at very low birth weight, <1500 g) have the highest incidence of neurodevelopmental consequences (40-50%), more children born between 32 and 36 weeks gestation suffer neurodevelopmental disorders than those born at very low birthweight. Therefore, all fetuses that have experienced preterm labor (prior to 36 weeks), whether born prematurely or not, must be included in the study. Major deficiencies exist in our current knowledge of causes of neurodevelopmental disorders and in the clinical approach to neurodevelopmental disorders associated with prematurity. As to the former, neither the initiating cause nor the affected biochemical/developmental pathways affected are understood; a major reason for the latter is the significant delay in the assessment of the brain and a lack of long-term follow-up. Prematurely born neonates are subject to cardiovascular instability and respiratory problems; therefore, disturbing the neonate to assess the brain is delayed until other systems are stabilized. Unfortunately, the event(s)/condition(s) leading to altered neurodevelopment seem to have already occurred by this point. It is essential to develop methods to gently and powerfully assess the status of the brain soon (preferentially hours) after delivery to assess for and begin treatment for injury/disturbance of development. Similar methods should be used to assess treatments, which

should be developed as the results of early neurologic testing begin to unravel causes. Therapy for disturbances in brain development should begin as early as possible and be assessed by frequent testing during follow-up. Extended periods of follow-up are costly and difficult to perform at a single center because young families often relocate for economic/job-related factors; therefore, multi-institutional studies with potential for follow-up at all participating sites is a critical factor.

- **Development of a databank with biostatistical support that would include all laboratory, clinical, imaging, and follow-up data for all children in the study.**

To address potential disturbances with therapy (e.g., costs, follow-up care) and analyses thereof, the development of a databank, with biostatistical support, is proposed. This databank would include all assessments and clinical data from the mother and child from conception through adolescence (maternal factors, neo- and perinatal assessments, imaging, socioeconomic factors, developmental milestones, developmental testing, and neurobehavioral assessments). Centralizing the data repository will eliminate the need to replicate the data warehouse at each center, facilitate data sharing and build the foundation for mining long-term follow-up information from a larger number of children than any single center can hope to achieve. Furthermore, by making biostatistical support part of the databank, investigators can leverage the expertise gained through the community resource.

- **Collaboration among institutions to reduce costs and increase efficacy of studies during a time of diminishing funds.**

By having a centralized data repository, each grantee can budget for centralized biostatistical support resulting in cost-effective (revenue neutral to NICHD), focused expertise that can partner with the investigator to grow and innovate in the field of neurodevelopmental biostatistics. Said databank may also serve to stimulate collaboration among institutions as well as funding agencies to generate large collaborative studies that would allow for faster recruitment, more powerful scientific discoveries, and cost-effective identification of diagnostic strategies, biomarkers, and therapeutic interventions.

Basic, Clinical, and Translational Questions Needed to Facilitate the Scientific Opportunities

The study of ND in prematurely born neonates offers the opportunity to address many basic, clinical, and translational questions. Once provided with the necessary infrastructure of data on the mother, fetus, and premature newborn from multiple institutions and collected centrally, it should be possible to address the questions. The most fundamental question concerns the *causes of premature birth*.

Surprisingly little is understood about the environmental, maternal, and fetal factors that contribute to prematurity. Since it is likely that the best place for the fetus to develop is the uterus, it is important to understand the factors that lead to premature labor and birth and whether the cause of the preterm labor leads to the alterations of normal development or whether that is related to other factors during or after delivery. Currently, most investigations begin in the newborn period; quantitative assessments such as neuroimaging occur later, weeks to months after delivery. Studies of groups of mothers and fetuses at high risk for prematurity should be initiated. To better understand the maternal-fetal connection, the development of fetal MRI, which shows great promise, should be accelerated. *Technologies should be developed that allow early, safe, and innovative post-natal evaluation of the most vulnerable newborns*; these include (but are not limited to) affordable magnetic resonance (MR) compatible incubators to be used throughout the neonatal ICU (NICU), and MR scanners that can be safely and inexpensively deployed within the NICU. The diagnostic tools should be adapted so they can be used where they are

needed; this will eliminate the need to transport unstable children. The use of MR compatible incubators and NICU-based scanners will help to answer important and currently vexing questions, such as *what are causes* of disturbed neurodevelopment associated with premature birth? *When* do they occur? *How* does the disturbed development lead to the specific neurodevelopmental disorders, ranging from cerebral palsy to autism-related disorders to anxiety disorders, found later in life? Only after the causes are understood can adequate therapies be designed and tested. This raises more questions: Can the disturbed development or its effects be modulated? If we intervene in high-risk pregnancies, can we delay delivery? Will delay of delivery improve outcomes? Can short-term assessments using novel technologies in the NICU be used to modify the standard of care? Will this ultimately lead to a better life for affected children? Can we develop quantitative neurodevelopmental batteries that are practical to administer yet assess the neurodevelopmental trajectory powerfully enough to confidently assess the effects of our interventions?

What research tools, methods, or approaches should be developed to achieve the anticipated outcomes?

For realization of this vision, necessary research tools, methods, and approaches must be developed. These include: (1) the databank with biostatistical support; (2) a multi-institutional program to study the early detection and diagnosis of disturbances of normal development in prematurely born children; (3) development of safe, powerful diagnostic tools that can be employed prenatally (i.e., advanced fetal MRI acquisitions and analysis tools) and in the early postnatal period (affordable MR compatible newborn incubators and electroencephalography, or EEG; MRI; and magnetoencephalography, or MEG, in the NICU) for assessing the structure, physiology, plasticity, and integrity of the developing brain and the long-term anatomic and physiological consequences; (4) therapies aimed at processes identified by (3); and (5) long-term tests (neurodevelopmental, psychological, and imaging-based) to test the results of (4).

C. Rehabilitation of Neurological Disability

Leader: William Z. Rymer

Breakout Group Members: Paolo Bonato, Pablo Celnik, Leonardo Cohen, James Patton, David Reinkensmeyer, Douglas Smith, Carolee Winstein, Steven Wolf

Introduction

The theme of rehabilitation faces special challenges, because the research deals with disabling illnesses across the lifespan. Accordingly, the scope of interest ranges from rehabilitation of childhood neurological disorders (such as cerebral palsy and spina bifida) to traumatic injury of adults (e.g., traumatic brain and spinal cord injury) to degenerative diseases of aging adults, such as stroke and Parkinson's disease.

What is common to these themes, and potentially to other themes of interest to the NICHD, is the need for novel and accurate diagnostics, and for more precise, low-cost, and practical methods for tracking intervention outcomes, and especially for tracking the effects of novel cellular and immunological therapies. These therapies will almost certainly be used to promote key components of neural recovery, including motor learning and neural plasticity.

One major factor limiting our progress in restoring function after neurological disease or trauma is the lack of objective measures of impairment severity, and the associated difficulty in tracking changes in neurological function and status. This limitation holds both for an individual illness episode in one subject, and for tracking disease in impaired populations across the lifespan.

This plenary reviewed current approaches towards measurement of impairment, functional loss, and community participation in disabling neurological illness, and described potential new approaches towards such measurement, based on the emergence of new engineering and computer technologies.

Scientific Opportunities

In the area of rehabilitation of neurological disability, the scientific opportunities are:

- **Basic science vision**

The emergence of greater understanding of the mechanisms of neurological recovery, including neural plasticity and neural adaptation, provides a valuable framework to advance this field.

- **Basic Science Substrates for Neurologic Rehabilitation**

1. Mechanisms of neural plasticity – A gap exists between knowledge of the clinically observable phenomena of neuroplasticity (as manifested by using brain mapping techniques, for example) and their cellular substrates, such as axon sprouting and changes in receptor distribution and receptor properties.
2. Analysis of the injured brain – does it learn the same way as the intact brain?
3. Accurate animal models of human neurological disease must be developed. Many types of models will be needed to test ideas about rehabilitation therapies, largely because it will be impractical to test all the potential options in human subjects. These models could include animal models of neurologic disorders such as stroke and spinal cord injury, which could be used to test specific types of therapies as well as dosage schedules and therapy combinations.
4. Genetic and epigenetic causes of susceptibility to brain injury must be uncovered. For example, the clinical manifestations of brain injury appear to vary greatly according to the apolipoprotein E alleles present.
5. A better understanding of the genetics of drug action (pharmacogenetics) is needed to help planning for variations in patient response to rehabilitation drug therapies.

What research tools, methods, or approaches should be developed to achieve the anticipated outcomes?

The following research tools, methods, or approaches should be developed to achieve the anticipated outcomes:

- **Novel consortia to advance translational research**

- New consortia would be very valuable – these could follow several guidelines of the Cumberland Report, including:
 1. Interaction among patients, front-line clinicians, and clinical and basic scientists is essential so that they can explore their different priorities, skills, and unique concerns.

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2. These interactions can be facilitated by establishing **consortia** that include basic and clinical scientists, clinicians, engineers, therapists, and patient/caregiver representatives with funds targeted at those impairments that are major determinants of patient and caregiver outcomes. The consortia are designed to promote bidirectional exchange of information about patient and caregiver need and priorities, rather than simply serving as unidirectional conduits for research-related information.
 3. Such consortia would be instrumental in developing a lexicon of common methods, standardized outcome measures, data sharing, and long-term goals.
 4. Interactions of this sort would create a research-friendly, rather than only target-led, culture in front-line stroke rehabilitation services.
- **Need for new therapies**
 - Relatively few new drugs are available targeting disabling chronic neurologic illness.
 - Combined therapy designs (e.g., novel drugs coupled with physical therapy) must be developed and tested, although trial designs for combined therapies are difficult to implement effectively.
 - Advanced technologies (robotics; functional electrical stimulation, or FES) may provide controlled interventions, and allow precise measurement of outcomes at the same time as offering new therapeutic interventions.
 - **Need for better measurement tools of impairment, and of response to therapy**
 - Existing clinical assessment instruments lack reliability and sensitivity, and their relationship to mechanisms of recovery needs to be established.
 - Advanced technology/sensors must be developed to establish better tracking of compliance and clinical outcomes, at several ICF (International Classification of Functioning, Disability, and Health) levels.
 - New, low-cost, portable sensors may ultimately replace prevailing clinical instruments used for outcome assessments.
 - Use of patient-reported outcomes based on item response theory (IRT) may help us track response to rehabilitation therapies.
 - **Value of biomarkers in rehabilitation**
 - Use of biomarkers may allow better understanding of variability in natural history of neurologic illness and its response to therapy; e.g., brain imaging techniques (diffusion tensor imaging, or DTI; spectroscopy; functional magnetic resonance imaging, or fMRI) may help predict outcomes and guide therapeutic interventions.
 - **Value of health informatics**
 - Availability of extensive electronic medical data, potentially coupled with advanced sensor information, may allow rigorous retrospective analysis of patient response to treatment and patient outcomes. By this means, each *clinical* patient also serves as a *research* subject, maximizing our information recovery.
 - The findings would promote trial development, both explanatory and pragmatic.
 - Internet-based systems could be used to input, access, and mine common data elements.
 - **Need for novel clinical trial designs**
 - In rehabilitation research, adaptive trial designs are rarely used.
 - Given the constraints of small subject populations, adaptive or Bayesian designs are potentially well suited for testing rehabilitation interventions.

- Stratification techniques can better predict patient response to specific interventions.
- **Advantages of computational models**
 - Computational models may help to compensate for limitations in available data or in conceptual framework for understanding therapeutic mechanisms; e.g., a simple threshold crossing model is able to predict the outcomes of intensive hand therapy following stroke (Schweighofer) and a novel model of motor adaptation has been used to drive robotic therapy (Reinkensmeyer).
 - Models of motor learning will help clinicians to program treatment duration, frequency, and intensity, and predict long-term outcomes.

D. Therapeutic Development

Co-Leaders: Eric Olson and Steven Kern

Breakout Group Members: Radek Bukowski, Gary Hankins, H. William Kelly, Steven Leeder, W. Ian Lipkin, Alexandra Quittner, Michael Reed, Una Ryan, J. Peter Van Dorsten

Introduction

Therapies for diseases and conditions of interest to NICHD have largely arisen from migrating therapies for adult conditions to younger populations. Though there are exceptions (e.g., vaccines), the existing enterprise comprised of the public and private sectors encourages the biopharma industry to follow this “adults first” paradigm via support and incentives. This approach is flawed, however, and its problems have led to either inadequate therapies, delays in therapies, or inadequate information and guidance to physicians on how best to use a therapy. For example: (1) A molecular target, or a therapy that modulates that target for adults, may not be best, or even appropriate, for younger populations due to differences in the biological pathway being modulated; (2) The therapeutic goal of an intervention, which is the starting point for a drug discovery and development program, may differ among different age groups and stages of disease (e.g., the goal of treating a condition at its earliest stages or in very young children may be to delay or prevent symptoms or tissue damage, whereas the desired outcome of treating an adult is often to limit the signs and symptoms of an already progressed disease state); (3) Potential safety issues and dose selection are largely approached from an “adult framework” leading to a “looking under the lamp post” effect, or in other words, looking at a potential safety issue in children based on having seen it in adults, as opposed to a de novo approach; and (4) Outcome measures and biomarkers to assess a therapy in order to make decisions on further investment or eventually seek regulatory approval may change due to age groups or disease progression.

With these problems in mind, the following issues were considered:

1. **Dose selection:** Is there a need for improving dose selection during drug development and what emerging methodologies and approaches should be encouraged? Which pediatric groups are most problematic? Include small volume therapeutics, therapeutic drug monitoring, and pharmacokinetics/pharmacodynamics, or PK/PD. Also address animal and translational models.
2. **Drug delivery:** What are the needs and approaches to improve drug delivery (i.e., oral, inhaled, transdermal, injection)? Include formulation and devices.

3. **Vaccines:** What are the major unmet needs for childhood vaccines (i.e., preventive and therapeutic)? What new approaches are needed to improve safety, efficacy, and tolerability? What will be the role of vaccines in pediatric cancers?
4. **Safety assessment:** What are the scientific gaps that need to be filled to inform our approach to safety assessment of new therapies and those under development? Include animal models; developmental regulation of pathways involved in metabolism, transport, and drug distribution; and specific target organs that may be affected uniquely in children versus adults.
5. **Treating the fetus and pregnant women:** What are the hurdles in testing potential new therapies for the fetus, and what science is needed to overcome them?
6. **Patient reported outcomes:** What are the opportunities and challenges in developing and using quality of life instruments and patient-reported outcomes in pediatric drug development?

Scientific Opportunities

- Understand chronic diseases longitudinally, starting at the fetus and moving towards adulthood rather than the reverse, and turning these concepts into drug discovery and development:
 - Understanding the *in utero* development of children who go on to develop chronic disease could lead towards early intervention with substantial reduction or eradication of the condition in the population many years later.
 - Alternative trial designs, especially for pregnant women and young children, should be considered.
- Understand the mother-fetus interaction upon chronic conditions for the child and life-changing episodes for the mother:
 - Treating obesity epidemic and understanding long-term consequences to pregnant woman and child.
 - Understand and predict preterm birth, intrauterine growth restriction (IUGR), and preeclampsia in order to prevent and treat them.
 - Chorioamnionitis and the potential for neuroprotective therapies.
- Understand factors that start at birth and alter the impact of disease progression for life.
- Develop and evaluate behavioral interventions to improve adherence in children with chronic diseases.
- Develop patient-reported outcomes for children with chronic diseases and disabilities (currently used by the FDA in drug approval [guidance given in 2009]).

Basic, Clinical, and Translational Questions Needed to Facilitate the Scientific Opportunities

To facilitate these opportunities, certain basic, clinical, and translational questions must be answered:

- What is normal growth and development from birth to adulthood?
- What factors determine response to a therapy and why?
 - How does response to a therapy change longitudinally and what does that tell us about disease “maturation” or progression and therapeutic approaches?
- What will enhance our ability to predict therapeutic responders or identify important treatment subgroups?
- Identification of the optimal approaches to help ensure strong adherence to therapies:
 - How do we assess factors that impact adherence?
 - What interventions improve adherence?

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What research tools, methods, or approaches should be developed to achieve the anticipated outcomes?

The following research tools, methods, or approaches should be developed to achieve the anticipated outcomes:

- Structured information-gathering process on off-label medication use in pregnancy and childhood that will inform clinical practice;
- Structured sampling or adventitious sampling, e.g., analyzing discarded tubes of blood in the Neonatal Intensive Care Unit (NICU);
- Work with nurses and other clinical personnel to ensure that routine information-gathering is done in a way that will be useful for research;
- Standardized electronic medical records and national registries with a data dictionary;
- Standardization of data collection across NIH studies;
- Data sharing as a grant-closeout report activity;
- Large cohort studies; and
- Use of emerging trends in social media to support this effort; especially important as this is a pediatric-focused endeavor.

III. HOW THE SCIENTIFIC OPPORTUNITIES IN DIAGNOSTICS & THERAPEUTICS WILL ADVANCE THE NICHD MISSION

In support of the NICHD mission, future studies should determine the normal course of disease to aid recognition of variations from normal and lead to hypothesis generation. Opportunities exist for defining phenotypes using better tools and selected animal models that allow better disease characterization and testing of specific hypotheses. Particularly in pediatric therapeutics, biomarkers must be validated and then incorporated into diagnosis, treatment, and monitoring of response. NICHD has the unique opportunity to develop priorities for expanding newborn screening tests; the potential for this is theoretically infinite, but each expansion must be based upon an understanding of the frequency and severity of the condition, feasibility of treatment, and the accuracy of the proposed test.

Overall, the scientific opportunities outlined in this white paper will increase the knowledge base to help children fulfill their potential to live healthy and productive lives free from disease or disability. The opportunities will also increase the knowledge base concerning pregnancy and premature labor and, thereby, reduce the chance that women suffer as a result from the reproductive process.

IV. HOW THE SCIENTIFIC OPPORTUNITIES IN DIAGNOSTICS & THERAPEUTICS WILL AFFECT PUBLIC & GLOBAL HEALTH

The scientific opportunities discussed above can have a great impact on public and global health. First, the better understanding of normal growth and development will result in generation of hypotheses concerning the expression of disease and development of better treatment strategies. New and better tests for disease diagnosis and for monitoring disease activity could reduce the number (and hence the costs) of exams, leading to more selective management with less morbidity and fewer adverse outcomes. An example of this approach is a large study aimed at understanding the causes of prematurity and

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consequent neurodevelopmental disorders. The cost to society for caring for and educating prematurely born children is enormous. If the causes of prematurity were elucidated and the number of preterm births was decreased, these costs would be markedly reduced or eliminated. Similarly, decreasing prematurity would eliminate the lifelong impact of these neurodevelopmental disorders upon health and lifestyle outcomes of the individual, as well as the social and economic impacts upon the family and community.

Another area of great impact to the public's health is the use of electronic medical data. Analogous to the way economists can mine data from labor statistics, medical research could do similar data mining with medical information. Areas ripe for data mining are electronic medical records and national database registries. Electronic medical records can be used to capture, evaluate, and share information more efficiently and in larger scales than possible with paper records. Linking these medical records to large databases and research networks can reduce research costs needed to define baseline physiologic values for healthy children. For example, improving the understanding of chronic disease through the creation of national/global registries would allow single cohorts to be used multiple times for different studies and would create benchmarks for understanding of disease that could be used for assessing therapeutic advancements. Although easily achieved technologically, privacy concerns may create difficulties. To ensure maximum benefits for the public, checks and balances must be put into place for national registries. Issues that will need to be considered are who has access to the registries, how to access registries, and enforcement of privacy laws to ensure violators are prosecuted to maintain patient trust. Other issues to consider include whether registries can be made mandatory, as in neonatal testing, and how data can be collected in a way that is useful for the research.

The contribution of expanded newborn screening should also be explored to improve public and global health. A better understanding of differences between children and adults in terms of disease presentation and response to treatment would result from this work. This organized plan could help to understand features of diseases that are apparently increasing in incidence, such as atopy, obesity, autism, and gastroschisis, and the reasons for their increase.

By understanding solutions that work (or don't) across systems, cultures, and economies, we can improve the chances of developing diagnostic tests and therapeutics that are of greatest help to the public and global health.

V. WHAT INNOVATIVE TRAINING AND OTHER WORKFORCE DEVELOPMENT ACTIVITIES SHOULD BE PURSUED TO ADVANCE DIAGNOSTICS & THERAPEUTICS SCIENCE

The current economic and regulatory environment continues to put pressure on our educational system, jeopardizing the next generation of investigators. Therefore, **innovative training and other workforce development activities** should be pursued, possibly including expanded debt repayment. Specifically, multidisciplinary groups should be created with diverse research expertise to develop *Model Training Programs* that include maternal fetal programming, embryology, genetics, developmental physiology, cognitive psychology, physiological imaging, developmental pharmacology, and behavioral outcomes. Although no single trainee can become an expert in all aspects of development and developmental pathology, training within this multidisciplinary environment should produce a crop of investigators

with broader perspectives, greater appreciation for the complexity of the problems and a greater appreciation of the perspectives of other disciplines in searching for answers. A particularly pressing need is to foster biostatistics research for development of new models to analyze the disparate measures generated by multiple clinical and imaging exams, combined with longitudinal developmental assessments. It is crucial to move beyond standard models for assessing intervention. The developmental trajectory is complex, playing out over many years; factors affecting outcome begin prior to conception and continue throughout childhood. Current statistical training programs do not empower graduates with the tools needed to handle this complexity. We also need to educate the educators who instruct rehabilitation clinicians. Current instructors are not optimally prepared to train their students in scientific foundations and concepts necessary for optimal future clinical service.

Following these developments, methods must be developed to implement new diagnostic and monitoring procedures in clinical practice to rapidly move science to patient care. With an increased emphasis on translational research, study sections must be organized such that they are capable of reviewing a breadth of aims to support research that bridges clinical and basic research. In addition, efforts should be made to collaborate with FDA; a combined approach may lead to a better understanding of requirements which, in turn, might speed development of research tools into diagnostic tests and therapies. Financial incentives and innovative loan repayment programs should also be developed to support research career development in key areas of research.

Finally, it is important to develop improved understanding of the ethics and consequences of having both mother and child treated as “therapeutic orphans,” required to use adaptations of treatments developed for other patient groups due to fear of potentially harming them. Specifically, how should one train IRBs and researchers on these issues? What are ethics of a “no” to at-risk mothers and children from an IRB? It is suggested to train the next generation of pediatricians without them knowing they are being trained! This might be accomplished by improving the basic science and therapeutic knowledge foundations in clinical training and by adding to physicians’ toolkit through an integrative degree. Other improvements might be gained by training of patients, with intention to change patient behavior in order to improve therapeutic results, and by training clinicians and researchers in the basics of drug development.

VI. ACCOMPLISHMENTS

If this plan is followed, these accomplishments can be achieved in the next 10 years:

1. Establishment of normal values for pediatric immunological and biomarker tests;
2. Better understanding of the natural history and pathophysiology of targeted fetal, pediatric, and adult disabling conditions, specifically, areas of high prevalence, morbidity, and mortality, that fall within the mission of NICHD;
3. A significant impact on reducing childhood morbidity and mortality through diagnostic and monitoring techniques for clinical application early in development, including prenatal identification of disease and intervention;
4. A reduction in premature birth and the associated requirements for extensive health care, educational assistance, family counseling, and community assistance that accompany complications of prematurity;

5. Introduction of novel technology for diagnosis, treatment, and monitoring for asthma, autism, cognitive disorders such as Down Syndrome, congenital heart disease, mental illness, and obesity;
6. A careful assessment of the ethics of genetic testing and implications for treatment, for example genetic testing at birth to identify disease potential;
7. Enhanced clinical training to incorporate new advances in science and technology as applied to patient care;
8. Phenotype identification that will change our approach to clinical trials and therapy by using specific components to convert common diseases to rare diseases;
9. Targeted use of novel robotic and engineering systems to enhance the therapeutic capacity of the treating therapist;
10. Development of advanced diagnostic systems to quantify severity of neurological injury and to improve outcome prediction;
11. Development of a new generation of drugs targeting restoration of function and structural reorganization of neural tissue after injury or disease;
12. Re-appropriation of research support to develop cohesive infrastructures that will support advances in management of rare or complex diseases of children and adults;
13. Development of centralized large databases and biostatistical support that, along with integration of health records, will allow a better understanding of disease evolution in children.

VII. CONCLUSION

In summary, multiple opportunities exist for significant advances in health and prevention/treatment of disease in the next 10 years. This will require:

1. A combination of better training of pediatricians, obstetricians, and rehabilitation clinicians in basic science and research methods;
2. Broader, multidisciplinary education of clinician scientists;
3. A better understanding of fetal and childhood development and the stage of onset of disease, allowing earlier and, perhaps, more effective treatments to be designed; obesity, asthma, autism, congenital heart disease, and premature birth and its consequences would be especially important areas to investigate;
4. Development of treatments specifically for pregnant mothers and fetuses (this may require new methods of training for IRB members);
5. More large-scale trials to evaluate responses more rapidly and to validate new treatments;
6. Identification of new biomarkers to analyze responses to therapy for childhood illness rapidly, and for severe and disabling illnesses such as stroke or traumatic brain injury; and
7. New methods by which to analyze the enormous quantity and wide range of variables and outcome measures that affect treatment analyses.

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Participant List

Special thanks to the workshop participants, who contributed to the ideas in this white paper:

Peter C. Adamson, M.D.
University of Pennsylvania
Philadelphia, PA

Paolo Bonato, Ph.D.
Harvard Medical School
Boston, MA

Peter J. Anderson, Ph.D.
University of Melbourne
Melbourne, Australia

Radek K. Bukowski, M.D.
University of Texas Medical Branch
Galveston, TX

William Andrews, M.D., Ph.D.
University of Alabama at Birmingham
Birmingham, AL

Pablo Celnik, M.D.
Johns Hopkins Hospital
Baltimore, MD

Jamelle Banks, M.P.H.
Eunice Kennedy Shriver National Institute
of Child Health and Human Development
National Institutes of Health
Bethesda, MD

Leonardo G. Cohen, M.D.
National Institute of Neurological Disorders
and Stroke
National Institutes of Health
Bethesda, MD

Gang Bao, Ph.D.
Georgia Institute of Technology
Atlanta, GA

Mary D'Alton, M.D.
Columbia University
New York, NY

A. James Barkovich, M.D.
University of California, San Francisco
San Francisco, CA

Lex W. Doyle, M.D.
The University of Melbourne
Melbourne, Australia

Peter Basser, Ph.D.
Eunice Kennedy Shriver National Institute
of Child Health and Human Development
National Institutes of Health
Bethesda, MD

Leonard Louis Dragone, M.D., Ph.D.
University of Colorado, Denver
Denver, CO

Anne J. Blaschke, M.D., Ph.D.
University of Utah School of Medicine
Salt Lake City, UT

Charles L. Dumoulin, Ph.D.
University of Cincinnati College of
Medicine
Cincinnati, OH

P. Ellen Grant, M.D., M.Sc.
Children's Hospital Boston
Boston, MA

Gary D.V. Hankins, M.D.
University of Texas Medical Branch
Galveston, TX

Marit Sæbø Indredavik
Norwegian University of Science and
Technology
Trondheim, Norway

H. William Kelly, Pharm.D.
University of New Mexico Health Sciences
Center
Albuquerque, NM

Steven Edward Kern, Ph.D.
Novartis Pharma AG
Basel, Switzerland

Steven James Leeder, Ph.D., Pharm.D.
University of Missouri Kansas City
Kansas City, MO

W. Ian Lipkin, M.D.
Columbia University Medical Center
New York, NY

Kevin Maher, M.D.
Emory University School of Medicine
Atlanta, GA

Elysa Marco, M.D.
University of California, San Francisco
San Francisco, CA

Robert C. McKinstry, M.D.
Washington University School of Medicine
in St. Louis
St. Louis, MO

Michael Msall, M.D.
University of Chicago Medical Center
Chicago, IL

Dianne Murphy, M.D., FAAP
Food and Drug Administration
Silver Spring, MD

Eric Olson, Ph.D.
Vertex Pharmaceuticals Incorporated
Cambridge, MA

James L. Patton, Ph.D.
University of Illinois at Chicago/
Northwestern University Feinberg School of
Medicine
Chicago, IL

Michele Puryear, M.D., Ph.D.
Health Resources and Services
Administration
Rockville, MD

Louis A. Quatrano, Ph.D.
Eunice Kennedy Shriver National Institute
of Child Health and Human Development
National Institutes of Health
Bethesda, MD

Alexandra Quittner, Ph.D.
University of Miami
Coral Gables, FL

Michael Reed, Pharm.D., FCCP, FCP
Akron Children's Hospital
Akron, OH

David J. Reinkensmeyer, Ph.D.
University of California, Irvine
Irvine, CA

Una S. Ryan, O.B.E., Ph.D., D.Sc.
Diagnostics For All
Cambridge, MA

William Rymer, M.D., Ph.D.
Northwestern University School of
Medicine
Chicago, IL

Douglas Smith, M.D.
University of Pennsylvania
Philadelphia, PA

Paul Spearman, Ph.D.
Emory University School of Medicine
Atlanta, GA

Stanley James Szeffler, M.D.
University of Colorado, Denver
Denver, CO

Kelan Tantisira, M.D., M.P.H.
Harvard Medical School
Boston, MA

James Peter Van Dorsten, M.D.
Medical University of South Carolina
Charleston, SC

**Robert Marshall Ward, M.D., FAAP,
FCP**
University of Utah
Salt Lake City, UT

Michael S. Watson, M.S., Ph.D., FACMG
American College of Medical Genetics
Bethesda, MD

Carolee J. Winstein, Ph.D., PT, FAPTA
University of Southern California
Los Angeles, CA

Steven L. Wolf, Ph.D., PT, FAPTA
Emory University
Atlanta, GA

Duan Xu, Ph.D.
University of California, San Francisco
San Francisco, CA

Anne Zajicek, M.D.
Eunice Kennedy Shriver National Institute
of Child Health and Human Development
National Institutes of Health
Bethesda, MD