

# Sudden Unexpected Death in Fetal Life Through Early Childhood

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In March 2015, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development held a workshop entitled “Sudden Unexpected Death in Fetal Life Through Early Childhood: New Opportunities.” Its objective was to advance efforts to understand and ultimately prevent sudden deaths in early life, by considering their pathogenesis as a potential continuum with some commonalities in biological origins or pathways. A second objective of this meeting was to highlight current issues surrounding the classification of sudden infant death syndrome (SIDS), and the implications of variations in the use of the term “SIDS” in forensic practice, and pediatric care and research. The proceedings reflected the most current knowledge and understanding of the origins and biology of vulnerability to sudden unexpected death, and its environmental triggers. Participants were encouraged to consider the application of new technologies and “omics” approaches to accelerate research. The major advances in delineating the intrinsic vulnerabilities to sudden death in early life have come from epidemiologic, neural, cardiac, metabolic, genetic, and physiologic research, with some commonalities among cases of unexplained stillbirth, SIDS, and sudden unexplained death in childhood observed. It was emphasized that investigations of sudden unexpected death are inconsistent, varying by jurisdiction, as are the education, certification practices, and experience of death certifiers. In addition, there is no practical consensus on the use of “SIDS” as a determination in cause of death. Major clinical, forensic, and scientific areas are identified for future research.

Sudden unexplained death in early life, from the fetal period to early childhood, poses long-lasting burdens to affected families seeking explanations, and a significant challenge for those seeking to better understand and improve child survival. In 2013, there were 23 595 stillbirths (fetal deaths  $\leq 20$  gestational weeks) in the United States, according to the National Center for Health Statistics.<sup>1</sup> Although the proportion of unexplained stillbirth varies by classification scheme, a US population-based study did not identify a cause in 24% of stillbirths.<sup>2</sup> There were also 3422 sudden unexpected infant deaths (SUIDs)<sup>3</sup> (87.0/100 000

live births), with 45.6% reported as due to the sudden infant death syndrome (SIDS). SIDS is defined as the sudden and unexpected death of an infant  $< 12$  months of age that remains unexplained after a review of the clinical history, complete autopsy, and death scene investigation.<sup>4</sup> SIDS is the leading cause of postneonatal mortality, and the fourth leading cause of overall infant mortality in the United States.<sup>3</sup> Sudden unexplained death in childhood (SUDC), another category of unexplained death, occurs in children  $> 1$  year old lacking a determined cause of death after complete postmortem investigation, with an incidence of 1.3

## abstract



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Dr Goldstein drafted the initial manuscript; Drs. Kinney and Willinger reviewed and revised the manuscript; and all authors formed the core of the planning committee for the reported workshop on sudden death in early life and participated in the workshop, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

The opinions expressed in this article are those of the authors and do not necessarily reflect the views of the Eunice Kennedy Shriver National Institute of Child Health and Development.

**DOI:** 10.1542/peds.2015-4661

Accepted for publication Mar 7, 2016

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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**FINANCIAL DISCLOSURE:** The authors have indicated they have no financial relationships relevant to this article to disclose.

**FUNDING:** This study was funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development. Funded by the National Institutes of Health (NIH).

**To cite:** Goldstein RD, Kinney HC, Willinger M. Sudden Unexpected Death in Fetal Life Through Early Childhood. *Pediatrics*. 2016;137(6):e20154661

per 100 000 for children between 1 and 4 years.<sup>5</sup>

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development held a workshop March 23 to 24, 2015, entitled “Sudden Unexpected Death in Fetal Life Through Early Childhood: New Opportunities.” Its objective was to advance efforts to understand and ultimately prevent sudden deaths in early life, by considering their pathogenesis, at least in part, as a potential continuum with some common biological origins or pathways. Invited researchers shared work on biological factors relevant to sudden deaths from fetal life through early childhood, including intrinsic factors involved in unexpected death, underlying biological evidence of preceding conditions or circumstances that may contribute, or interactions between intrinsic vulnerabilities and adverse environmental factors in the pathogenesis of sudden death. A second objective was to highlight current issues surrounding the classification of SIDS in forensic practice, pediatric care, and research. Participants were also encouraged to consider new technologies and “omics” approaches to accelerate research. The Triple Risk Model for SIDS, proposing that SIDS occurs in infants with latent biological vulnerabilities, exposed to external threats during a critical period in development, served as a reference.<sup>6</sup> A similar model has been proposed for unexplained stillbirth.<sup>7</sup> This report summarizes the current state of knowledge, and promising approaches in different disciplines. Gaps in knowledge and future directions identified by participants are listed.

## ANTENATAL ORIGINS OF VULNERABILITY

Several factors reflecting an adverse intrauterine environment are seen in

both stillbirth and SIDS. These factors include placental abnormalities, poor fetal growth, and preterm labor. An estimated 25% to 40% of stillborns are small for gestational age,<sup>8,9</sup> also a risk factor for SIDS.<sup>10,11</sup> Pregnancies in an individual woman before and after a SIDS loss are more likely to be complicated by poor fetal growth and early labor.<sup>12</sup> Elevated levels of  $\alpha$ -fetoprotein in maternal serum are associated with preterm birth, in utero growth restriction, and stillbirth, perhaps reflecting impaired placental function.<sup>13</sup> There is a linear positive correlation between second trimester  $\alpha$ -fetoprotein levels and subsequent risk for SIDS, which remains significant after adjusting for gestational age, birth weight, maternal age, parity, socioeconomic deprivation, smoking, and infant gender. In utero exposure to cigarette smoke and alcohol increases the risk for both stillbirth and SIDS.<sup>14–19</sup> Yet, despite the number of noted associations, stillbirth rates have not declined like SIDS.

The influence of interventions promoting supine sleep position on reducing mortality from SIDS is well recognized.<sup>20</sup> Less recognized is that declines in SIDS are not solely due to modifications in the infant sleep environment. There is significant concordance between reductions in SIDS mortality rates and those of explained causes of infant death, particularly mortality due to congenital anomalies, respiratory distress of the newborn, and diseases of the circulatory system.<sup>21</sup> This concordance suggests that changes in perinatal factors or advances in medical approaches to the care of infants that have contributed to improvement in other causes of death, also likely contribute to declines in intrinsic vulnerability for SIDS. For example, widespread use of antenatal steroids and surfactant coincided with the promotion of Safe Sleep in the United States. Further, the prevalence of known SIDS risk

factors that may mediate intrinsic risk, changed over this period; for example, maternal smoking during pregnancy, teen pregnancy, and levels of inadequate prenatal care declined, and breastfeeding rates increased.

## PROGRESS TOWARD UNDERSTANDING UNDERLYING INTRINSIC VULNERABILITIES

### Neuropathology

Unexplained stillbirth and SIDS share common brain abnormalities, notably hypoplasia of the arcuate nucleus (considered the respiratory chemosensitive zone of the ventral medulla), gliosis of cerebral white matter and brainstem, and periventricular leukomalacia.<sup>22</sup> The latter 2 may be caused by prenatal hypoxia-ischemia and reflect adverse intrauterine environments.

It has been suggested that a significant subset of sudden deaths in early life involves dysfunction in limbic forebrain, to include the hippocampus and brainstem circuits, designated the “central homeostatic network.”<sup>23</sup> This purported neural network is involved in arousal, respiratory, autonomic, emotional, and cognitive homeostatic responses used to protect against stresses and potentially life-threatening challenges.<sup>23</sup> Similar hippocampal anomalies have been reported in cases of SIDS and SUDC.<sup>5,23–27</sup>

A range of brainstem neurotransmitter defects are found in SIDS.<sup>28</sup> The most robust abnormalities are observed in the serotonin (5-HT) network, composed of 5-HT neuronal aggregates in rostral and caudal brainstem domains.<sup>29–35</sup> Serotonin is released from brainstem neurons projecting to the dentate gyrus. Serotonin serves a trophic role on granule cell migration and proliferation, suggesting that 5-HT plays a role in the pathogenesis of this combined

developmental hippocampal and brainstem pathology.<sup>24,25</sup> Abnormalities are seen in the dentate gyrus of the hippocampus in ~40% of SUID, a fivefold increased frequency compared with infants dying of known causes,<sup>24</sup> and in ~50% of cases of SUDC,<sup>25</sup> also significantly increased when compared with children dying of known causes. The abnormalities are characterized by bilayering of granule cells in the dentate gyrus of the hippocampus, termed dentate gyral bilamination, previously reported in some cases of temporal lobe epilepsy.<sup>36,37</sup> Some researchers hypothesize that abnormalities in hippocampal regulation in at least some cases of sudden unexplained death lead to cardiorespiratory/homeostatic instability or autonomic seizures as a mechanism of sleep-related sudden death in infancy and early childhood.<sup>5,24–26</sup> Approximately two-thirds of SUDC cases with hippocampal pathology have a personal and/or family history of febrile seizures, suggesting that such seizures are a risk factor for sudden death in this circumstance.<sup>25</sup> Further, abnormalities in  $\geq 1$  “nodes” of the homeostatic network can cause sudden, sleep-related sudden death in early life.<sup>23</sup> Alternatively, hippocampal and brainstem findings may reflect 2 subsets of disorders within the central homeostatic network that manifest as sudden death in infants via a final common pathway.

### Cardiac Genetics

In addition to brain vulnerabilities, arrhythmogenic disorders of cardiac function are increasingly recognized in association with sudden unexplained death in early life. Genetic research has focused on identifying a subset of deaths due to loss-of-function or gain-of-function mutations in ion channels of the heart. Initial findings suggested that 2% of infants dying from SIDS carried gain-of-function mutations in the

SCN5A-encoded sodium channel.<sup>38</sup> Research is finding a further contribution of genes involved in cardiac channelopathies,<sup>39,40</sup> including pore-forming mutations in the calcium release channel that give rise to the ryanodine receptor and catecholaminergic polymorphic ventricular tachycardia,<sup>41</sup> and 4 additional long QT syndrome susceptibility genes involving channel interacting proteins and caveolin-3 mutations (which affect sodium channels).<sup>42</sup> Understanding the contribution of these cardiac channelopathies in fetal loss is ongoing, including a report of 3 long QT syndrome-associated mutations among fetal deaths.<sup>43</sup>

Whole exome sequencing is expanding the identification of mutations that may increase vulnerability to sudden death in early life. A rational approach to variants of unknown significance discovered through whole exome sequencing is an important concern. Functional validation is critical to demonstrate biological plausibility, and thus avoid undue family distress and unnecessary interventions. Functional validation is possible by site-directed mutagenesis in cell lines in culture and voltage clamp analysis demonstrating electrical current abnormalities; for example, defects in depolarization, or other whole animal functional validation models. Genetically based disorders may have different phenotypic expressions at different ages, presumably due to different developmental, environmental, and epigenetic factors across the age spectrum.

### Metabolic Disorders

Vulnerability arises from inherited metabolic disorders (IMDs) in 1% to 2% of SIDS deaths.<sup>44</sup> These disorders can be identified soon after birth, and death potentially prevented by interventions specific to the disorder. These metabolic disorders, primarily fatty acid

oxidation disorders, mimic the presentation of SUID, with little or no clinical prodrome.<sup>45</sup> Medium-chain acyl coenzyme A dehydrogenase deficiency is the most prevalent fatty acid oxidation disorder detected among SUIDs.<sup>44</sup> Newborn screening for medium-chain acyl coenzyme A dehydrogenase led to newborn screening now performed in all states and territories of the United States.<sup>46</sup> The adoption of advancing methodologies in newborn screening has shown that IMDs are more common than previously estimated by clinical presentation.<sup>47</sup> With focused attention to new disorders, unrecognized IMDs are likely to be discovered with the advent of new technologies, rapid genomic screening, and early detection with fetal screens.

### Fetal, Infant, and Maternal Physiology

Autonomic dysfunction is hypothesized to contribute to SIDS and stillbirth pathogenesis. Diminished high-frequency heart rate variability (HRV), a common measure of cardiac parasympathetic nerve activity,<sup>48</sup> and abnormalities in beat-to-beat dynamics of cardiac control have been observed in SIDS infants.<sup>49</sup> High-frequency HRV is also altered in infants with known risk factors for SIDS, including prematurity, prenatal exposures, such as smoking, and environmental exposures, such as prone sleeping.<sup>50</sup> Patterns of HRV change dramatically as a function of age and sleep state during prenatal and postnatal development.<sup>51,52</sup> Individual differences in HRV can now be quantified throughout the perinatal period, providing accurate measures of baseline autonomic nervous system maturity. It is also possible to assess functional responses to in utero challenges, such as those associated with maternal sleep position or intermittent hypoxia.<sup>53,54</sup>

Study of the development of brain activity provides a new focus for

determining early vulnerability to SIDS. The developmental asleep EEG profiles in the Collaborative Home Infant Monitoring Effort study show that healthy infants commonly display bursts of high-frequency activity during sleep, at rates of ~10 bursts per minute, until ~35 weeks to 44 postconceptional weeks, when bursts greatly diminish in number.<sup>55</sup> These bursts appear to be an important EEG feature during early development, potentially indicative of the functions of subplate neurons, a transient population underlying the cerebral cortex critical for establishing early connectivity in normal brain development.<sup>56</sup> Subplate injury in animal models eliminates bursts, and affects cortical development.<sup>57,58</sup> Research about the functional effects of prenatal alcohol and smoking exposure on brain development may eventually inform researchers about how these factors affect control of autonomic processes in the central homeostatic network, and responses to environmental challenges.

Researchers are investigating intrauterine stress to the fetus associated with the physiology and pathology of maternal sleep during pregnancy. Obstructive sleep apnea is present in 10% to 26% of pregnant women, with increasing prevalence approaching term, when most unexplained stillbirths occur.<sup>59</sup> Sleep-disordered breathing and obstructive sleep apnea cause recurrent fetal exposure to hypoxemia, oxidative stress, inflammation, and sympathetic activity.<sup>60</sup> Maternal sleep apnea is associated with preeclampsia, in turn a risk factor for both SIDS<sup>61</sup> and stillbirth.<sup>62</sup> Epidemiologic studies of stillbirth have focused on the role of maternal sleep position, including 2.54-increased risk for late stillbirth ( $\geq 28$  weeks' gestation) in mothers sleeping on their backs, and 1.74-increased risk in those sleeping on the right side, compared with sleeping on the left.<sup>63</sup> A study

of stillbirth at  $\geq 32$  weeks' gestation reported 6.24 increased risk of stillbirth for supine sleep compared with the left side.<sup>64</sup> Although the mechanisms underlying this association have yet to be delineated, growth restriction is more prevalent in stillbirths of women reporting sleeping on the back,<sup>65</sup> indicating a potential role of uterine blood flow.

### **ENVIRONMENTAL (EXTRINSIC) FACTORS**

Multiple studies have examined risk factors in the infant sleep environment for SIDS. Extrinsic factors associated with increased SIDS risk include prone and side sleep position, soft sleep surface and soft bedding over or under the infant, head or face covered during sleep, excess thermal insulation, bed sharing, and postnatal smoke exposure.<sup>20</sup> Factors associated with reduced risk of SIDS include pacifier use, breastfeeding, and room sharing without bed sharing. Campaigns to reduce prone sleep position have been successful with a concomitant reduction in SIDS, but similar effects have not been seen from reductions in related practices like bed sharing<sup>66</sup> or suspect bedding.<sup>67</sup> In addition, disparities remain in the incidence of SIDS and other SUIDs in American population subgroups, with highest rates found among American Indian or Alaska Native and non-Hispanic black infants.<sup>3</sup>

Research on maturational physiology of infant sleep has been vital to understanding contributing factors to sudden death in the young, as most deaths occur during a sleep period. Maturation of the autonomic regulation of both the respiratory and cardiovascular systems occurs during infancy.<sup>68,69</sup> Sleep induces a decrease in blood pressure, heart rate, respiratory rate, and muscle tone, importantly in the upper airways, and depresses protective reflexes to hypoxia and hypercapnia.

In the prone position, blood pressure<sup>70</sup> and cerebral oxygenation are reduced<sup>71</sup> and cerebral vascular control is impaired.<sup>72</sup> Additionally, between 2 and 4 months of age, the peak period for SIDS, healthy term infants have depressed arousal and baroreflex response in the prone position.<sup>73-75</sup> Preterm infants have lower blood pressure and cerebral oxygenation than age-matched term infants, most marked when in the prone position.<sup>76,77</sup> These observations provide evidence for the increased risk of sudden death in infants sleeping prone, and at critical developmental periods.

### **PROMISING APPROACHES FOR DISCOVERY OF UNDERLYING VULNERABILITIES**

Advances in neuroimaging, and mathematical approaches to imaging data reconstruction, are aiding the elucidation of brain mechanisms in the pathogenesis of sudden unexplained death in early life. MRI of the neonatal and preterm brain, for example, has been the basis for brain atlases that include calibration for postconceptional age.<sup>78,79</sup> Advanced imaging has been used to examine how functional sensorimotor connections are affected by prematurity and associated pathology when presented with a stimulus.<sup>80</sup> Noninvasive technologies to measure fetal autonomic development in real time and for extended periods to identify fetuses at risk are now available. Researchers are now also attempting to integrate genetics and function with human connectivity, in central homeostatic network<sup>23</sup> and in utero pathways. This integrative approach, for example, has been initiated with candidate genes and brain injury associated with preterm birth<sup>81,82</sup>

Currently, information regarding physiologic vulnerability and the cascade of physiologic events leading

to SIDS is limited. Advances in bedside recording in NICUs allow for the generation of vast amounts of longitudinal data in infants, including cardiac, respiratory, and neural parameters. The potential now exists for comprehensive data collection on samples of sufficient power to develop growth chart-like normative databases, to interpret altered physiologic development and responses in SIDS. Collaboration in this area holds new promise for the study of rare outcomes.

Breakthroughs in genomics, proteomics, transcriptomics, and metabolomics hold new potential to decipher vulnerabilities and pathways in sudden unexplained death in early life. “Omics” approaches, for example, are leading to a greater understanding of 5-HT in SIDS pathogenesis. In a proteomics study of the medullary 5-HT network in SIDS, for example, there was a significant reduction in the family of 14-3-3 signal transduction proteins in SIDS cases compared with autopsy controls.<sup>83</sup> This protein family has multiple cellular functions, including facilitating 5-HT activity through interaction with tryptophan hydroxylase-2, the rate-limit biosynthetic enzyme for 5-HT, and reduced 14-3-3 protein levels could result in less effective 5-HT activity. The application of transcriptomics to human brain development in postmortem specimens is in early stages, but appears feasible.<sup>84</sup> Currently, “omics” approaches are limited by technical interpretation of biologically relevant differences (signal-to-noise); the complexities of confirming “omics” findings by other methods (eg, confirmation by Western blotting of protein abundance differences detected by broad-based proteomics); and understanding primary versus secondary, including compensatory, changes.

Whole exome sequencing of infants and their parents in the NICU is

another area in which the mining and analysis of “big [omics] data” may reveal important aspects of underlying physiology and new disorders with susceptibility to sudden death. The Newborn Sequencing in Genomic Medicine and Public Health program is examining the impact of rapid exome sequencing on clinical care and discovery.<sup>85,86</sup> Highly penetrant, rare variants that are likely to disrupt protein function as determined by criteria from the American College of Medical Genetics and Genomics<sup>87</sup> are sought. Rapid exome analysis of 35 undiagnosed newborns in the NICU led to diagnosis in 57%, and 17% received a partial diagnosis. Sixty-five percent of the whole genome sequencing results revealed de novo mutations, whereas 31% were inherited; the remainders were somatic mutations or chimerism. The diagnostic rate of 57% is a significant improvement compared with 9% who were diagnosed based on traditional genetic tests.

The National Institutes of Health Undiagnosed Disease Network uses genetic testing for those individuals whose first-level testing (eg, family history, physical examination, clinical chemistry, and imaging) fails to diagnose a suspected metabolic disorder. As part of this effort, the Undiagnosed Disease Network has metabolomics core facilities to determine the normal ranges of metabolites in serum, plasma, cerebrospinal fluid, and urine in healthy individuals of different ages, gender, and races or ethnicities, including validating and quantifying metabolites identified from critical cellular pathways or processes. One of these core facilities is working to establish the normal relative ranges of metabolites for deceased individuals of different ages, gender, and races or ethnicities and at different postmortem intervals, with direct relevance to diagnosis and discovery in sudden death in early life.

## The Role of Animal Models in Research

Validation for purported mechanisms of sudden unexplained death in early life may be found in animal models. Human autopsy studies can characterize regional, chemical, cellular, and molecular pathology, but findings represent only a “snapshot” of the process at 1 point in time (“end stage” at death), and cannot demonstrate mechanisms. Whole animal models, as well as reduced preparations and cell culture systems, permit exploration of genetic and nongenetic (acquired and environmental) factors in sudden death. For example, the hypothesis that the underlying vulnerability is a failure in protective responses to hypoxia, hypercarbia, or hyperthermia in brainstem 5-HT pathways has been investigated by using several models of 5-HT brainstem deficiency.<sup>88-93</sup> These models include genetically engineered mice with reversibly “silenced” 5-HT neurons using the Designer Receptors Exclusively Activated by Designer Drugs technology.<sup>93,94</sup> In all of these 5-HT-deficient models, physiologic aberrations in responses to hypoxia, including in arousal and autoresuscitation, have been demonstrated, as have effects during sleep.<sup>95</sup> The effects of 5-HT deficiency in these models on the laryngeal chemoreflex is under investigation.<sup>96</sup> Physiologic effects also have been shown to be exacerbated by the risk factors of prenatal exposure to alcohol at a critical postnatal age,<sup>97</sup> cigarette smoke/nicotine,<sup>98,99</sup> hyperthermia,<sup>100</sup> and other epigenetic factors (S. Lee, E.E. Nattie, A. Li, unpublished data). Animal models are also of value in developing biomarkers of a particularly abnormality (eg, 5-HT deficiency), and development of treatment strategies, including drugs. The respiratory stimulant caffeine, used currently in neonatal nurseries for apnea of prematurity, for

example, improves autoresuscitation abilities in 5-HT-deficient genetic-knockout mice.<sup>92</sup>

## **INFLUENCE OF FORENSICS AND VITAL STATISTICS REPORTING**

Although a persistent cause of infant mortality, the diagnosis of “SIDS” has been the subject of skepticism. In recent years, some medical examiners have called for the elimination of SIDS as a diagnosis or determination on death certificates.<sup>101,102</sup> Indeed, there is no practical consensus about how the term “SIDS” is used.<sup>103</sup> External risk factors, such as prone sleep position or bed sharing, may at times be considered to explain cause, such as positional asphyxia or accidental suffocation. At the same time, methods and expertise in the taxed medical examiner systems prevent the kind of detailed autopsies necessary for rare discoveries. Investigations of sudden unexpected death vary by jurisdiction, as does the education, certification practice, and experience of death certifiers.<sup>104</sup> Consequently, surveillance and research are adversely affected

Death certificate data are mostly coded automatically by the National Center for Health Statistics Mortality Medical Data System.<sup>105,106</sup> The system applies codes based on *International Classification of Diseases* rules and a broad range of key terms. Death certificates that cannot be automatically coded require manual coding, particularly cases of accidental suffocation,<sup>106</sup> creating differences between assigned death codes and the intent of the death certifier.<sup>105</sup> Moreover, completion of a death scene investigation or autopsy is not considered in coding. In recent years, cases coded as “unknown cause” and “accidental suffocation” are increasing.<sup>107</sup> In 2013, approximately half of SUIDs were ultimately categorized as SIDS, including some cases when the death

certifier wrote “SUID” on the death certificate. Because cause-of-death reporting practices and coding are inconsistent, it is difficult to evaluate the current status of SIDS in the United States without also including unknown causes and accidental suffocation.<sup>107</sup>

The medical examiner system has been historically constrained in its ability to research vulnerability to risk for sudden death.<sup>108</sup> It is difficult for researchers to access human SIDS tissue via medicolegal offices, where mandated autopsies occur. Examples of programs bridging the gap include California, which allows research without consent on autopsy tissue from any infant younger than a year old who dies suddenly and unexpectedly, and New Jersey, which provides a system for delayed consenting of approved protocols.

## **THE TRANSLATION OF BASIC DISCOVERY TO CLINICAL PRACTICE**

Robert’s Program on Sudden Unexpected Death in Pediatrics at Boston Children’s Hospital is the first comprehensive program to apply the undiagnosed disease paradigm to sudden infant and early childhood death. Clinicians and pathologists become involved, with parental consent, while the forensic autopsy is ongoing for children dying at <3 years old without apparent explanation in Massachusetts. The combined academic-forensic review includes the autopsy, death scene investigation, enhanced assessment of personal and familial past medical history, pedigrees, collaborative pathology and neuropathology, whole exome sequencing involving parents and deceased child, and metabolomics. The academic team includes physicians expert in general pediatrics, genetics, metabolism, cardiology, neurology (epilepsy), pediatric pathology, and neuropathology. The academic

and forensic teams deliberate each case together at the end of their evaluations and cause of death is determined, with the manner determined by the medical examiners. Integral to the program is grief counseling, with the counseling and in-depth medical/forensic investigations advancing mutual objectives. Families are interviewed in depth after the death to get their perspective on why they think the death occurred and the circumstances surrounding the death. Although sufficient numbers of genetic results are just beginning to be analyzed, important findings have occurred, including further evidence for dentate bilamination and genetic findings not evident from pedigrees (R. Goldstein, H.M. Nields, H.C. Kinney, unpublished data). This promising approach requires significant resources, expertise, and infrastructure.

## **GAPS AND FUTURE DIRECTIONS**

Progress toward greater understanding of the biology of vulnerability for sudden unexpected death from fetal life through early childhood is occurring through contributions from many fields. The research presented at the workshop supported focusing on the intrauterine environment, the nervous system, and potential causative variants for a subset of deaths. Looking forward, workshop participants discussed gaps in knowledge and promising approaches in research, translation, public health, and training (Table 1). The availability of new imaging technologies, and the tools to collect and analyze large complex physiologic, imaging, and genomic databases independently and in concert, provide new opportunities for research. For example, with the common theme of an altered intrauterine environment as an important contributor to

**TABLE 1** Gaps and Opportunities

Research	<p>Characterizing interactions between intrinsic vulnerability and external factors that may trigger a lethal pathway.</p> <p>Integrating epidemiology into longitudinal studies that incorporate physiology and “omic” technologies.</p> <p>Documenting early markers of placental development and function to include the gene expression profiles and regulation of transcription in the placenta.</p> <p>Exploring the continuum and developmental trajectory of the physiology of homeostasis, including preterm and postnatal environmental influences, and differences by race/ethnicity.</p> <p>Determining gender differences in placental development, and fetal and infant homeostasis.</p> <p>Collaborating to develop a large database of a multicenter birth cohort that is intensively phenotyped and prospectively followed; NICU monitoring is a potential source.</p> <p>Characterizing the development and function of the human central homeostatic network in early life.</p> <p>Continuing to develop neuroimaging of the developing brain connectome, to include improvement in technology and bioinformatics from fetal life through infancy, with particular attention to linking imaging data to biologic function.</p> <p>Analyzing genomic cohorts of uniformly phenotyped SIDS, early childhood deaths, and unexplained stillbirth trios, to quantify the types and proportion of highly penetrant, rare causative variants and their associated phenotypes.</p> <p>Researching the influence of maternal sleep physiology, including uterine blood flow, on fetal vulnerability to sudden death (stillbirth).</p> <p>Better understanding the trajectory of, and ways in which, families of young children grieve, and how enhanced attachment, cultural, psychosocial dynamics, and other factors affect grief.</p>
Translation	<p>Developing noninvasive technologies to measure fetal development in real time and for extended periods, to identify fetuses at risk.</p> <p>Developing new testing strategies for early detection of metabolic disorders and other genetic disorders; improved point-of-service testing and rapid DNA diagnosis.</p> <p>Improving methods to identify poor placental function late in pregnancy among low-risk women to aid in timely delivery to prevent term stillbirth and infant mortality and morbidity.</p> <p>Applying the undiagnosed disease paradigm in programs staffed jointly by clinicians, researchers, and forensic professionals that actively integrate the latest technologies, research findings, fatality review, and counseling.</p> <p>Expanding effective interventions for safe sleep, particularly in high-risk populations.</p>
Public Health	<p>Using definitions and terminology for SIDS and other SUIDs that are mutually acceptable and uniform, by pediatricians and other child health providers, forensic practitioners, researchers, and public health advocates. This gap also has importance to research.</p>
Training	<p>Satisfying the requirement for a larger pool of trained perinatal and pediatric pathologists and pediatric neuropathologists.</p>

vulnerability for unexpected death, longitudinal studies using multiple modes of data collection, starting from fetal life through infancy, are now possible. The new omic technologies provide opportunities to examine transcriptional pathways, quickly assess metabolic disorders, and search for potential rare causative variants. Challenges were identified. The recognition that rates of late stillbirth and sleep-related infant deaths have not changed in recent years supports efforts to develop new and improved interventions. Also, the basic difficulty arising from lack of consensus about nomenclature of sudden deaths hampers surveillance, supportive care, and research. It is hoped that the deliberations of this workshop will contribute to future innovation in research and clinical care for sudden and unexplained death in early life, and ultimately prevention.

#### ACKNOWLEDGMENTS

The authors thank and acknowledge the following participants, who spoke and contributed to the workshop. Their presentations were reflected in this article.

Michael J. Ackerman, MD, PhD, Mayo Clinic, Rochester, MN; Gerard T. Berry, MD, Boston Children’s Hospital, Boston, MA; Susan Berry, MD, University of Minnesota, Minneapolis, MN; David Edwards, FMedSci, DSc, Kings College, London, UK; William P. Fifer, PhD, Columbia University, NY, NY; Alan Guttmacher, MD, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Bethesda, MD; Fern Hauck, MD, MS, University of Virginia, Charlottesville, VA; Rosemary Horne, PhD, The Ritchie Centre, Melbourne, Australia; Stephen Kingsmore, MB, ChB, BAO, Children’s Mercy Hospital, Kansas City, MO; Judette Louis, MD, MPH, University of South Florida, Tampa, FL; Roger Mitchell, Chief

Medical Examiner, Washington, DC; Michael Myers, PhD, Columbia University, New York, NY; Eugene E. Nattie, PhD, Geisel School of Medicine at Dartmouth, Lebanon, NH; David Paterson, PhD, Boston Children’s Hospital, Boston, MA; Mary Ann Sens, MD, PhD, University of North Dakota School of Medicine and Health Sciences, Grand Forks, ND; Carrie K. Shapiro-Mendoza, PhD, MPH, Centers for Disease Control and Prevention, Atlanta, GA; Gordon C. S. Smith, MD, PhD, DSc, FMedSci, Cambridge University, Cambridge, UK.

#### ABBREVIATIONS

5-HT: serotonin  
 IMD: inherited metabolic disorder  
 SIDS: sudden infant death syndrome  
 SUDC: sudden unexplained death in childhood  
 SUID: sudden unexplained infant death

**POTENTIAL CONFLICT OF INTEREST:** The authors have indicated they have no potential conflicts of interest to disclose.

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*Pediatrics* 2016;137;

DOI: 10.1542/peds.2015-4661 originally published online May 26, 2016;

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