Screening for Sudden Cardiac Death in the Young: Report From a National Heart, Lung, and Blood Institute Working Group


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Sudden cardiac death (SCD) in the young (SCDY) has a devastating impact on families, care providers, and the community and attracts significant public and media attention. Sudden cardiac death is defined as an abrupt and unexpected death due to a cardiovascular cause, typically occurring <1 hour from the onset of symptoms. Depending on the source, “young” is variably defined as those less than 25, 30, 35, or 40 years of age. Estimates of the incidence of SCDY (not including infants) vary broadly from 0.6 to 6.2 per 100 000 persons.¹–³

Sudden infant death syndrome (SIDS) may be related to SCD in some infants. Sudden infant death syndrome is defined as the sudden death of an infant <1 year of age that cannot be explained after a thorough investigation is conducted, including an autopsy, death scene evaluation, and review of the clinical history. The incidence of SIDS ranges from 50 to 100 in 100 000,⁴ and emerging data suggest that as many as 10% to 15% of SIDS deaths are associated with functional cardiac ion channelopathy gene variants.⁵

The most common diagnoses that increase risk for SCDY include hypertrophic cardiomyopathy (HCM), coronary artery anomalies of wrong sinus origin, myocarditis, arrhythmogenic right ventricular cardiomyopathy, and ion channelopathies.⁶ The latter category includes hereditary diseases such as the congenital long-QT syndromes (LQTS), catecholaminergic polymorphic ventricular tachycardia, and Brugada syndrome, among other less common channelopathies. These diseases are typically undetected before the SCD event. Estimated prevalence rates of these conditions range from 1 per 500 persons for HCM to 1 per 2500 for the LQTS. SCD related to these diagnoses has been documented in infancy and during competitive athletics. In addition, prescription stimulant use for treatment of attention deficit hyperactivity disorder (ADHD) has been postulated to be a trigger for SCD.⁷,⁸

Sudden cardiac death in the young is a critical public health issue. A young life cut short represents a devastating event for families, and is associated with many lost productive years. There is significant dissonance among experts in the field about the best approach to prevent SCDY in the United States. Some experts support the implementation of large-scale cardiovascular screening programs in infants, in athletes, or in all children to identify at-risk individuals in an effort to prevent SCDY. Cardiovascular screening for SCDY typically involves the addition of an ECG to the current standard of care of history and physical examination. Echo-cardiography and genetic testing represent alternative or additional screening modalities. Observational data from the Veneto region of Italy suggest that ECG screening can successfully identify at-risk cardiovascular diseases and dramatically reduce the incidence of SCD in competitive athletes.⁹,¹⁰ Proponents of ECG screening in the United States suggest that it can be effective, feasible, and cost-effective.¹¹ Critics of ECG screening cite a lack of evidence to support its effectiveness or feasibility in the United States; lack of clinical accuracy; cost implications; and the potential clinical, financial, and emotional consequences of false-positive screening test results.¹² Cost estimates for a national ECG screening program in the United States for
competitive athletes alone range from $300 million to $2 billion annually.\textsuperscript{6,13}

The debate over cardiovascular screening to prevent SCDY has fervent and well-intentioned supporters on both sides. However, this debate will continue unresolved until additional, compelling evidence is provided that either supports or refutes the utility of screening for SCDY.

In an effort to provide direction to determine what type of evidence is necessary and the best methodology to obtain such evidence, the National Heart, Lung, and Blood Institute (NHLBI) convened a Working Group meeting in April 2010 in Bethesda, MD. The charge of the Working Group was to develop a research agenda and identify resources to evaluate whether screening for SCDY would effectively reduce SCD and add overall healthcare value, where value was defined as improved clinical outcomes with an acceptable cost-benefit ratio. The Working Group consisted of experts in pediatric cardiology and electrophysiology, adult cardiology, epidemiology, biostatistics, sports medicine, child psychiatry, health economics, ethics, oncology screening, and newborn screening. The Working Group unanimously supported the development of a research agenda that would determine the best approach to reduce SCDY.

**Analytic Framework for Screening**

In their classic text, Wilson and Jungner\textsuperscript{14} outlined the key principles required to support the validity of a screening program. Before a screening program is adopted, the following criteria should be met: The targeted condition should be an important public health issue with a sufficiently long latent or early symptomatic stage; the screening test should adequately recognize the targeted condition in the appropriate population; the test should be acceptable, safe, and inexpensive; and treatment for the recognized disease should be available, affordable, acceptable, and effective.

More recently, these principles have been modified by the US Preventive Services Task Force\textsuperscript{15} and translated into an analytic framework for screening (Figure). To be considered effective, a screening program must improve specific health outcomes, such as mortality, quality of life, pain, or function. The numbered arrows in the graphic framework represent key questions that specify the evidence required to link a screening program with improved health outcomes.\textsuperscript{15}

Evaluating the issue of screening for SCDY in the context of the US Preventive Services Task Force’s analytic framework, the Working Group identified several gaps in current knowledge and the evidence base linked to the key questions presented in the Figure. First (key question 1), there is presently no direct evidence in a US population that an ECG or any other cardiovascular screening program will reduce the incidence of SCD in any of the patient populations thought to be at increased risk (eg, infants, athletes, and patients with ADHD). Specifically, there has never been a clinical trial in which cardiovascular screening has been compared with no screening/usual care with an end point of SCD. Furthermore, there are limited objective data supporting the other links along the chain of logic. Specifically, gaps in knowledge exist regarding the following:

- Descriptive epidemiology and etiology of SCDY (key question 2)
Performance of the screening methodology in the target population
- Perform pilot ECG screening studies to test the characteristics of the ECG in target populations
- Perform comparative effectiveness studies to determine the incremental value of various screening methodologies, including history and physical examination, ECG, echocardiogram, and genetic testing

Management of asymptomatic heart disease identified by ECG screening
- Develop evidence-based management strategies for asymptomatic patients
- Evaluate risk stratification, prevention, and therapeutic strategies
- Use novel study designs and innovative recruitment strategies when studying low-prevalence diseases

Impact of a screening program
- Evaluate the impact of a screening program on individuals and families using quality-of-life studies and patient-preference measurements
- Use decision analysis to evaluate overall effectiveness of a screening program, as well as cost and resource utilization

Other resources to facilitate research
- Redefine the diagnostic criteria for the long-QT syndrome in the genetic era
- Define ECG norms in the US population, taking into account demographic variability

SCDY indicates sudden cardiac death in the young; ECG, electrocardiogram.

- Performance of the screening methodology in the target population (key question 3)
- Optimal management of asymptomatic heart disease that will be discovered by screening programs for SCDY (key questions 4 and 8)
- Impact of an ECG screening program on the individual, the family, the community, and society (key questions 1 and 7)

Recommendations of the Working Group
The Working Group addressed these knowledge gaps by developing research proposals that considered various approaches, including observational studies, clinical trials, decision modeling, and recommendations for resource development. Targeted populations for screening included infants, athletes, the general pediatric population, and patients with ADHD. Recommendations developed by the Working Group are discussed below according to the knowledge gap they address, and specific considerations for these populations are mentioned within this context. A summary of these recommendations is provided in the Table.

Epidemiology and Etiology of Sudden Cardiac Death in the Young
The wide range of estimates of SCDY incidence may stem from differences in definitions of SCD, inconsistencies in classifying cause of death on death certificates, variable ages and types of study populations, and differing case ascertainment methodologies. Case ascertainment in the United States primarily has included review of death certificates, insurance reports, public media reports, and other available electronic resources. These methodologies are clearly susceptible to inconsistent or inaccurate classification or coding and incomplete case ascertainment.

Using a prospective clinicopathological registry in the Veneto region of Italy, Corrado et al9 documented an annual incidence of SCDY in competitive athletes of 3.6 per 100,000 persons. The study used a systematic approach to case ascertainment and involved pathological investigation. However, the relatively small (approximately 8% of the Italian population) and homogeneous target population of that region of Italy is not generalizable to the US population; thus, these results cannot be extrapolated directly to formulate recommendations specific to the US population.

Accurate estimation of incidence rates of SCDY is critical for understanding the scope of the problem, devising appropriate preventive strategies, and informing policy makers who allocate resources. Assumed incidence rates directly influence cost-effectiveness estimates for prevention programs, with lower incidence rates implying unacceptably low benefits relative to the resources consumed, whereas higher incidence rates imply such programs are cost-effective. More precise estimation of SCDY incidence is important for well-informed public health planning for prevention and resource allocation.

In recognition of the importance of accurately defining the incidence of SCDY in the United States, the Working Group recommended the development of a prospective, population-based SCDY registry. Circumstances surrounding the deaths should be captured by death scene investigation, along with medical record, family history, and autopsy review. Demographic data about the decedent, activity level at the time of event, drugs or medications used (including stimulants for ADHD, psychotropic and asthma medications, etc), antecedent symptoms, and family history of SCD or SCD-associated conditions will provide relevant information for the elucidation of associations with SCDY. Partnering with local medical examiners, especially forensic pathologists, may allow for standardization of autopsy protocols. Autopsies should include a comprehensive examination of the heart, including cardiac dimensions, weight, gross structure, coronary artery anatomy, and histological evaluation of the myocardium. A concerted effort to rule out noncardiac causes of sudden death is critical. For cases with no definitive cause on general autopsy, appropriately preserved biospecimens should be collected for molecular autopsy (postmortem genetic investigation). Through sequencing and genomic approaches, molecular autopsy may be able to identify pathological variants associated with the LQTS, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia, each of which predisposes to SCDY. Although primarily limited to research laboratories (health insurance does not currently pay for postmortem testing), molecular autopsy will be critical for full description of SCDY cases.

The Working Group recommended involving the Centers for Disease Control and Prevention in the development of the registry because of their surveillance expertise. The Working Group also recommended leveraging the resources and infra-
structure of the National Center for Child Death Review (supported by the Health Resources and Services Administration’s Maternal Child Health Bureau) and state-based child death review teams who seek to clarify how and why children die and to identify risk factors and targets for intervention. Forty-nine of 50 states have mandated or state-enabled child death review teams that perform comprehensive, multidisciplinary reviews of childhood deaths, although many teams are underfunded and have variable approaches. The National Association of Medical Examiners was also discussed as a valuable potential partner in this effort.

The Working Group also proposed further work regarding causes of SCDY. Recent data have suggested that pathological ion channelopathy mutations are associated with nearly 10% to 15% of SIDS cases and up to 30% of autopsy-negative SCDY cases (defined as an autopsy in which the gross and histological findings do not provide an adequate explanation for the cause of death). Although these data are compelling, a more definitive link between channelopathies and SCDY through comparative study has not been demonstrated thus far. Risk factors for SCDY are also in dispute. Although it is widely held that athletic activity results in a higher risk of SCD, a recent epidemiological study from Denmark raises some questions about that hypothesis, which suggests the need for further study. Furthermore, there is significant controversy concerning whether stimulants for ADHD, other medications, or dietary supplements may predispose to SCDY.

To address these knowledge gaps in the epidemiology and etiology of SCDY, the Working Group recommended a case-control study to facilitate comparisons of epidemiological, anatomic, and genetic variables associated with SCDY. Moreover, the coupling of a case-control study to the prospective registry would enhance the power of such a study design. Such a case-control study requires proper characterization of the cases, including genetic analysis, selection of suitable controls, and appropriate selection of matching variables without overmatching. Identification of incident cases using the registry would enable a thorough evaluation of the cases in close temporal proximity to the event to allow identification of event triggers. Also, within the defined geographic regions of the registry, the person-time pool of potential control subjects would be nearly identical to that of the case subjects. Various control types may be selected for different comparisons. For instance, accidental death victims may serve as controls when potential differences in cardiac anatomy are being evaluated. Control subjects from the same community and/or school as the SCD case subjects may facilitate comparisons of demographic factors, behavioral factors, and triggers such as physical activity, substance abuse, or stimulant use. Family-based control subjects, such as siblings or parents, may be useful for genetic studies.

Potential questions that could be addressed by such a population-based incident case-control study include:

- Is the prevalence of ion channelopathy mutations higher in case subjects with autopsy-negative sudden unexpected death than in control subjects?
- Is the prevalence of ion channelopathy mutations higher in SIDS cases than in control subjects?
- Is the use of currently prescribed drugs for ADHD associated with SCDY?
- Is participation in competitive athletics or other vigorous activity a risk factor for SCDY?
- Are there significant environmental or contextual differences between case subjects and control subjects, such as socioeconomic status, race, history of drug exposure, family history, or other factors?

Performance of the Screening Methodology in the Target Population

Understanding the performance of the screening test in the targeted population is a critical element in the chain of logic that links a screening program with improved health outcomes. The most commonly discussed (and widely debated) cardiovascular screening test is the ECG.

To date, the performance of the ECG as a screening test has not been evaluated adequately in the United States. Previous screening studies have generally had small patient populations. A notable exception to this is the work by Schwartz et al., who evaluated ECG screening in large populations of neonates in Italy. This work has not been replicated in the United States; therefore, the ability to generalize results to the more diverse US population remains unclear. ECG screening studies also have suffered from a lack of comparison to a gold standard, which prevents accurate determination of the sensitivity and specificity of the test. In addition, there is some controversy as to where to set the cutoff criteria for deciding what is abnormal in measures of continuous scales (such as the QT interval). These determinations will have a major impact on sensitivity and specificity.

The Working Group recommended pilot ECG screening studies to determine the test characteristics of the ECG in target populations. An adequately sized cohort would undergo ECG testing and the appropriate gold standard testing for specific diseases of interest. Choosing the appropriate gold standard may be a challenge, because diseases may evolve with age (eg, HCM), ECG changes may precede imaging findings, and advances in molecular/genetic research may alter the standard of diagnosis for certain diseases (eg, ion channelopathies, HCM). Sensitivity and specificity would be determined for the ECG compared with the gold standard. The study should include a sampling frame that is representative of the ethnically and geographically diverse US population. The study should also have standardized study methods and protocols, with centralized ECG interpretation and a priori determinations of criteria for abnormal ECG findings based on literature review and expert consensus.

Age-specific issues need to be addressed relative to the characteristics of the test and the diseases of interest. For instance, a screening study in infants might compare the QT interval at 2 days old and 2 weeks old to determine whether the testing characteristics of the ECG vary with the electrophysiological transition of the newborn. Studies in infants would focus on ECG findings in LQTS, whereas ECG findings for HCM would be studied primarily in older children and adolescents. Sex and race/ethnicity are also
likely to be important considerations in the design of screening studies, because they are associated with genetic variation or gene expression and ultimately SCD risk. In addition to defining the sensitivity and specificity of the ECG in specific populations, an ECG screening study would also help evaluate feasibility, resource requirements, reliability, reproducibility, and potential harmful effects of screening. The screening tool itself may be optimized through refinement of criteria for abnormalities. Such a study might also define parameters for the design of a larger clinical trial.

The Working Group noted that the history and physical examination, the current standard for screening for SCDY risk (especially as part of the preparticipation evaluation for athletes), has been poorly characterized as a screening test. Studies to better understand the performance (sensitivity, specificity, etc) of the history and physical examination as a screening test and studies that seek to improve that performance have the potential for immediate clinical impact. Comparative studies will help determine the ideal screening methodology by determining the incremental value of the addition of such tests as ECGs, echocardiograms, and genetic testing to the current standard of care. Novel screening methodologies developed in the future also will require comparative testing. For instance, genomic research may identify genetic variants or a combination of variants that identify high-risk patients.

Management of Asymptomatic Heart Disease Identified by ECG Screening

Incidental identification of disease in asymptomatic patients is an unexpected by-product of an effective screening program, yet early detection of disease does not always result in improved outcomes. Some disease identified by screening tests may be subclinical and may never lead to symptoms. In an asymptomatic patient, initiation of treatment, with its attendant potential for side effects and complications, may lead to greater risk of harm to the patient. Currently, evidence-based guidelines are lacking for the management of asymptomatic patients with some diseases associated with increased risk of SCD.

In patients with Wolff-Parkinson-White syndrome, sudden death may be the first presentation of the syndrome. This is generally associated with atrial fibrillation, for which athletes may be at higher risk. The incidence of sudden death has been estimated to be 0.15% to 0.39% over 3 to 10 years of follow-up. Catheter ablation can eliminate the risk of sudden death, and is currently recommended for symptomatic patients (recommendation Class IIa, Level of Evidence B); however, ablation does carry a complication rate of approximately 2%. The use of prophylactic catheter ablation in asymptomatic individuals therefore remains controversial. Several studies have explored the natural history of Wolff-Parkinson-White syndrome in children and adults and, to clarify which patients would benefit from catheter ablation, have attempted to identify predictors of life-threatening arrhythmia events. At this time, the optimal management of asymptomatic patients remains unclear, and we are left to weigh the risk of sudden death against the risk of complications related to ablation until more rigorous clinical trials are performed.

HCM, the most common cause of SCDY in the United States, has a reported annual risk of death of ≤1%. In symptomatic patients, treatment with antiarrhythmic medications does not completely protect against SCD. As such, implantable cardioverter-defibrillators have become a reliable strategy for prevention of sudden death in high-risk patients. To identify patients at high risk of sudden death who may benefit from an implantable cardioverter-defibrillator, efforts have focused on risk stratification based on family history, episodes of syncope, degree of left ventricular hypertrophy, presence of documented ventricular tachycardia, abnormal blood pressure response to exercise, and malignant genetic mutations. Yet, risk stratification is limited by a low positive predictive value, dynamic changes in signs and symptoms over time, and the ability to extrapolate data to children. Studies using animal models of HCM have identified potential therapeutic options (angiotensin II type 1 receptor antagonists, L-type calcium channel blockers, and N-acetylcysteine) that may lead to decreases in the degree of hypertrophy and may attenuate the development of disease. Such future therapies may be ideal for asymptomatic patients identified by a screening modality, but their clinical value has not yet been demonstrated.

To address knowledge gaps in the approach to management of asymptomatic disease, the Working Group recommended the development of evidence-based management strategies for asymptomatic patients identified by an ECG or other screening program. The Working Group encouraged further attempts to stratify patients according to risk and to develop standardized management plans for asymptomatic patients.

Because of the low prevalence of the target diseases, the Working Group recognized that novel study designs and innovative recruitment strategies will be necessary, such as the use of HMO databases to perform large observational studies and the use of the Internet and direct-to-consumer targeting as recruitment tools to increase sample sizes for clinical trials. Potential studies might include a comparative study of management strategies for asymptomatic Wolff-Parkinson-White syndrome in adolescents or a clinical trial of an agent to slow progression of mild HCM.

Impact of a Screening Program

The Working Group recognized the need for research to assess the impact of a screening program on the individual and family. It is a given that false-positive diagnoses occur as a result of screening examinations, yet it is not known how false-positive findings impact individuals and families within the context of an ECG screening program. Determination of child, parent, and physician preferences with regard to screening in general, sports restriction, ADHD therapy, and treatment for asymptomatic heart disease will be important for a robust understanding of the impact of a screening program. Quality-of-life studies and patient preference measurements, by use of validated health status instruments and preference-based valuation methods, may help fill in this knowledge gap.
The impact of a screening program on society is often measured by cost as well as efficacy. Before a significant public health investment in large-scale ECG screening is made, it would be ideal to empirically demonstrate a link between screening and improved health outcomes (key question 1). It would also be important to determine the expected cost of such a screening program and to ascertain whether this is a cost-effective use of resources for families and society as a whole. The attainment of direct evidence may occur alongside a randomized, controlled clinical trial. Because of the relatively low incidence rate of SCDY, an adequately powered clinical trial would require a very large sample size. For instance, assuming the rate of SIDS is 100 per 100,000 and that 10% of SIDS cases are attributable to the LQTS, even if the reduction of LQTS-associated SIDS were 100% with ECG screening and treatment, a study with 80% power would require 3 million subjects. More conservative parameters or a lower incidence of SCD (as seen in older children or young adults) would further increase the required number of subjects. A clinical trial this large would clearly be both logistically challenging and extremely costly.

In the absence of a definitive clinical trial, the Working Group acknowledged the usefulness of decision analytic simulation modeling to evaluate both the overall effectiveness of a screening program and its cost. The advantage of simulation modeling is that it synthesizes data from all available sources and types of studies. In particular, it links estimates for each relationship in a causal chain so that both the clinical outcome (eg, salient event incidence, quality of life, and overall mortality) and economic outcomes (eg, costs, resource utilization) of a program can be projected in the absence of a single empirical trial. Simulation models can also help to identify assumptions that contribute the most uncertainty to the model’s overall projections. In this way, uncertainty analysis can be used to prioritize limited research resources by identifying areas of uncertainty that, when resolved, would most improve the model’s precision. Modeling can also be used to compare the value of alternative prevention strategies. For instance, decision modeling can be used to compare alternative screening strategies (ECG plus history and examination versus ECG alone versus echocardiogram alone) or to compare screening to management strategies, such as the placement of automatic external defibrillators in schools.

Other Resources
The Working Group made additional recommendations that may facilitate future research, including the formation of expert panels to (1) redefine the diagnostic criteria for LQTS in the genetic era and (2) define ECG norms in the US population, taking into account demographic variability (eg, age, race, ethnicity, and sex). Before genetic testing, the diagnosis of LQTS was based on ECG findings and clinical parameters. On the basis of these variables, Schwartz et al developed clinical diagnostic criteria that could be used to predict a probability of disease. With the advent of genetic testing, the utility and accuracy of these criteria have been questioned. However, clinical criteria still have use, such as in the screening of relatives of probands, the evaluation of patients with negative genetic tests but with high clinical suspicion of disease (phenotype positive), and the evaluation of gene-positive patients with low clinical likelihood of disease (phenotype negative).

Although recent efforts have been made to improve the standardization and interpretation of the ECG, generally accepted norms, especially for children, are based on outdated and nonrepresentative data for a heterogeneous population. Before a study of ECG screening is undertaken, efforts to define norms and establish criteria for abnormal findings, especially in the neonatal and young athlete populations, will be crucial.

Ethical Issues
The broad ethical challenge is to balance the potential benefits and risks of preventing SCD in an environment in which there is uncertainty about its causes, measures to evaluate risk, and the effectiveness of interventions to reduce risk. Many of the proposed studies pose complex ethical and regulatory issues.

Creation of a registry would require investigators to seek informed consent from family members of a child, adolescent, or young adult shortly after an unexpected death, when they feel most vulnerable. Family members would be asked to answer sensitive questions during bereavement about their loved one’s lifestyle (eg, drug or alcohol use) and would be asked to permit the collection of biological samples for genetic analysis.

A case-control study might require investigators to seek such consent not only from parents of children who died of SCD but from parents whose children died of other causes. Some of those causes (suicide, homicide, drunk driving) may be difficult issues for parents to discuss, and the study would offer no direct benefits to the participants. Alternatively, such studies might be designed to be conducted in a deidentified manner, which would reduce the burden on the surviving families, and institutional review boards might allow waiver of consent in such circumstances.

A prospective study of the efficacy of different approaches to screening for cardiac disease would be the most challenging ethically and logistically. Such a study would require very large numbers of patients, long-term follow-up, and carefully explained informed consent and assent of appropriately aged children. Because ECGs are not themselves experimental interventions, some physicians may be unwilling to have their patients randomized in a trial, parents might be reticent to enroll their children, and institutional review boards may raise questions about what is, or ought to be, the standard of care.

Conclusions
Disagreement over the best approach to preventing SCDY is fueled in large part by lack of evidence. Moving the field forward will require the rigorous application of research to fill in the knowledge gaps identified by the Working Group. The Working Group suggested various research approaches to address these gaps and identified needed resources and potential ethical barriers. The ultimate goal of the Working Group’s recommendations is to transform
the debate over screening for SCDY into a conversation about the evidence needed to help answer the important questions raised by SCDY. Such a conversation will put us on a path to developing a sound evidence base for the prevention of SCDY.

Appendix

Additional participants in the meeting included: Diane Bild, MD, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD; Adolfo Correa, MD, MPH, Centers for Disease Control and Prevention, Atlanta, GA; Peter Denchev, PhD, National Institute of Mental Health, National Institutes of Health, Bethesda, MD; Darryl Gray, MD, Agency for Healthcare Research and Quality, Rockville, MD; Barnett Kramer, PhD, MPH, National Institutes of Health, Bethesda, MD; David Lathrop, PhD, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD; Michael Schoenbaum, PhD, National Institute of Mental Health, National Institutes of Health, Bethesda, MD; Xin Tian, PhD, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD; and Benedetto Vitiello, MD, National Institute of Mental Health, National Institutes of Health, Bethesda, MD.

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