Developing the 2011 Integrated Pediatric Guidelines for Cardiovascular Risk Reduction

abstract

This article reviews aspects of development of the recently released “Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents” for pediatric care providers that remain in the area of human judgment. Discussed will be the context in which the guidelines were developed, the formal evidence review process, a consideration of how quality grades were established, key social/ethical issues that the panel confronted, and a critique of the final work with recommendations for future guideline development. Lessons learned are that both a formal evidence review process is essential to developing a credible document, and human judgment is critical to producing a meaningful result. Guideline development is a dynamic process that must be continuously self-critical as new evidence is acquired and sociopolitical and environmental contexts evolve. Pediatrics 2012;129:e1311–e1319
Commissioned in 2006, the 2011 “Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents” are the first guidelines addressing cardiovascular disease (CVD) risk factors from the National Heart Lung and Blood Institute (NHLBI) to be driven by an evidence-based, rather than a consensus-based process. Subsequent guidelines will follow this process. Previous CVD risk reduction guidelines sponsored by NHLBI have addressed a single topic and have usually been consensus opinions developed by expert panels, based on careful interpretation of available evidence.

For the new guideline, sufficient pediatriac research related to CVD risk had been conducted to allow the development of evidence-based recommendations. The guideline process adhered to recommendations in existence in 2006 such as those developed by the AGREE network, including consideration of scope, a formal evidence review, key stakeholder involvement, scientific rigor, clarity of presentation, and editorial independence. The Institute of Medicine (IOM) document, “Clinical Practice Guidelines We Can Trust,” was released in 2011, after completion of guideline development. In retrospect, the Expert Panel process closely mirrored those standards, as shown in Table 1.

Despite defining a rigorous evidence evaluation process, it became clear to the panel that, no matter how carefully the evidence evaluation process was defined, human judgment would be necessary at key decision points. This article will review those human elements. We will first discuss the context in which the guidelines were developed. The formal evidence review process will be described, with particular attention to how the final evidence-grading paradigm was established. A discussion of key social and ethical issues that the panel confronted in translating the evidence review into recommendations will be presented. We will conclude with a critique of the final work and recommendations for future guideline development.

### THE SOCIOPOLITICAL CONTEXT OF THE 2011 INTEGRATED GUIDELINES FOR CARDIOVASCULAR HEALTH AND RISK REDUCTION FOR CHILDREN AND ADOLESCENTS

The Expert Panel was charged with developing evidence-based guidelines addressing all of the major risk factors to assist pediatric care providers (pediatricians, family practitioners, nurses and nurse practitioners, physician assistants and registered dietitians) in both the promotion of cardiovascular (CV) health and the identification and management of specific risk factors from infancy into young adulthood. This charge itself created the first major problem. Although children with extremes of CV risk exist, these children will form a distinct minority of those who go on to develop CVD in the future. The majority of children who develop CVD acquire risk factors in childhood, mostly through adverse behaviors such as poor nutrition, tobacco use, and sedentary lifestyle. Success in modifying these behaviors requires a prevention-oriented, public health approach, which can only be supported by physician guidance, as opposed to pharmacologic or other prescribed treatment interventions.

A guideline solely devoted to the extremes of CVD risk, strictly calibrated to the identification of those requiring medical intervention, would not fulfill the general purpose of promoting CV health and CVD risk reduction. Those with some or intermediate risk, as much as 85% of the adult population, would be underserved.

<table>
<thead>
<tr>
<th>TABLE 1 NHLBI Expert Panel Process Versus the IOM Standard</th>
<th>Integrated CVD Guideline</th>
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<tr>
<td>Establish transparency COI process</td>
<td>Guideline development process funding by NHLBI explicitly stated. EP members disclosed all potential COI before appointment. All COI discussed before EP work began. Potential COI reviewed again before guideline release. Chairman had no significant COI.</td>
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<tr>
<td>Guideline development group composition</td>
<td>EP membership multidisciplinary, including scientific experts and clinicians. Public involvement encouraged by formal public comment review.</td>
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<td>Guideline-systematic review intersection</td>
<td>EP and systematic review team worked closely to define the scope, approach, and output of the evidence review. Complete evidence tables available on line at: <a href="http://www.nhlbi.nih.gov/guidelines/cvd_ped/index.htm">http://www.nhlbi.nih.gov/guidelines/cvd_ped/index.htm</a></td>
</tr>
<tr>
<td>Evidence review foundation and rating system</td>
<td>Standard grading system of the American Academy of Pediatrics selected. Full guideline report includes a summary of relevant evidence for each recommendation including quality, quantity, and consistency.</td>
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<tr>
<td>Articulation of recommendations</td>
<td>Each recommendation graded based on the quality, quantity, and consistency of the evidence. Strength of each recommendation explicitly provided.</td>
</tr>
<tr>
<td>External review</td>
<td>All recommendations provided in a standardized form by age group by using the format of the American Academy of Pediatric “Bright Futures” standards for pediatric preventive care. Extensive external review process with public comment review period, invited review by multiple stakeholders, and formal review by Health and Human Services. Written record of response to each review.</td>
</tr>
<tr>
<td>Updating</td>
<td>Regular monitoring of the literature by NHLBI planned at the outset of guideline development to determine the need for updating.</td>
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COI, conflict of interest; EP, expert panel.
Therefore, the recommendations in these guidelines would need to address the role of pediatric care providers in both the prevention of risk factor development (primordial prevention) and the prevention of future CVD by effective management of identified risk factors (primary prevention).

The CVD risk reduction guideline development process has evolved significantly over the past 50 years. The earliest guidelines for adults emerged in the 1960s in the context of a CVD epidemic, the recent identification of important risk factors (tobacco use, hypercholesterolemia, and hypertension), and sufficient epidemiological, clinical, and basic research for experts to recommend risk factor control. As experience with both the value and pitfalls of guidelines developed, and as more research findings became available, objective evidence evaluation assumed increasing importance in providing credibility for recommendations. In fact, several groups were developed to review the medical literature in an unbiased fashion to determine if specific medical practices were indeed supported by current research findings. These considerations led to the second critical challenge for the Expert Panel: formulating new guidelines that successfully navigated through the Scylla of existing consensus-based guidelines and the Charybdis of published evidence-based meta-analyses and systematic reviews on relatively narrow topics that had not been incorporated into a complete and comprehensive guideline. The final product had to provide clinicians with a useful algorithm for the many different medical contexts that pediatric risk reduction presents, in the absence of complete evidence for many of these scenarios. The clinical context of the more typical patient with multiple risk factors for CVD, or risk for multiple competing morbidities other than CVD, had to be addressed.

DEVELOPING THE EVIDENCE-GRAADING MODEL

The specific steps in the evidence evaluation process are completely described in the guidelines. These follow the path of formulating critical questions for the evidence review to address, defining search criteria to identify literature related to these questions with defined inclusion and exclusion criteria, recording the findings of selected studies in evidence tables, grading the included studies based on an a priori defined grading system, and using the results of the evidence review to formulate specific recommendations. Recommendations were graded by the Expert Panel based on the entire body of relevant evidence.

In 2006, no specific evidence review process encompassed the large scope of the panel’s charge. At its early face-to-face meetings, evidence evaluation schema and potential modifications that might be needed to accomplish the panel’s charge were discussed. Two existing evidence-grading systems seemed best suited: the US Preventive Services Task Force (USPSTF) general analytic framework (Fig 1) and the American Academy of Pediatrics (AAP) algorithm (Tables 2 and 3) currently used for evaluation of evidence in AAP guidelines and recommendations. Each had been previously used to address pediatric CVD prevention questions. The importance of the USPSTF algorithm is the guarantee that both unintended as well as intended consequences of screening and treatment are considered in any recommendation.

The nature of atherosclerosis itself was considered in finalizing an evidence-grading system. Considerable research now exists on the development of atherosclerosis linking the presence of risk factors in childhood and adolescence to the presence and severity of the atherosclerotic process as assessed by both pathologic and imaging studies. The Bogalusa Heart Study was able to directly link risk factors measured in youth to the presence of atherosclerosis determined pathologically at accidental death. Conversely, evidence exists linking the absence of CVD risk factors in childhood and young adult life to the absence of atherosclerosis or CVD morbidity in adulthood. The panel agreed that this evidence represents the most convincing rationale for the development of these guidelines and is needed to be given appropriate weight.

This consideration of atherosclerosis raises a related quandary: the relative importance as an end point of atherosclerosis development per se versus...
CVD event reduction. Research on CV risk reduction in children and adolescents can only address the process of atherosclerosis, because the clinical end point of manifest CVD almost always occurs much later in life. Without atherosclerosis (or rare pathologic conditions of the coronary arteries), CVD events do not occur in childhood. Realistically, it is only the development of atherosclerosis that can be prevented by efforts directed at children. The evidence review for the guidelines strongly suggests that retarding atherosclerosis development is a meaningful goal. The development of measures of subclinical atherosclerosis provides new tools for assessing the evolution of atherosclerosis.

However, atherosclerosis by itself is not equivalent to an event: its presence only increases the likelihood that an event will ultimately occur. Thus, prevention of atherosclerosis does not necessarily provide a guarantee of long-term health, particularly if morbidities are incurred by screening or treatment in the process of prevention. Logistical and ethical difficulties preclude initiation of a clinical trial in childhood for the prevention of CV events, so alternative types of evidence addressing the development and progression of atherosclerosis must be considered and weighed. The long natural history of atherosclerosis development provides the opportunity for research assessing many intermediate steps beginning in fetal life and extending through childhood into young adulthood. This concept is demonstrated in Fig 2, which shows the pathway from birth to CVD events and the many influences, biological and environmental, that relate to the development of atherosclerosis over that time course. It is evidence from research regarding modification of these intermediate steps that constitutes the prime substance of a pediatric report.

It is important to emphasize that it is the presence of risk factors and the likelihood of their persistence into adulthood that provides the rationale for pharmacologic treatment in youth, not the presence of subclinical atherosclerosis. Even in adults, only coronary calcium on computed tomography scan (not present generally until the third or fourth decade of life) provides sufficient evidence for risk reclassification. As discussed below, the evaluation and grading of evidence for risk persistence and its relationship to both atherosclerosis and outcomes in epidemiological and genetic studies was paramount for the panel.

The primacy of well-conducted randomized clinical trials was recognized as the highest level of evidence (Table 2). However, this preeminence places certain limitations on a pediatric evidence-grading system. Randomized trials are best conducted with a narrowly defined problem, a single intervention, a well-defined population in which the adverse condition has a reasonable incidence or prevalence, and in which the desirable outcome can be ascertained in a reasonable period of time. None of these conditions exists with regard to pediatric prevention of CVD. There are multiple risk factors for CVD, there are multiple interventions (diet treatment, behavior modification, medications), most of the population is at risk, and the proximate desired outcomes are intermediate (ie, smoking cessation or lipid lowering as opposed to event reduction). It remains a curious fact that, in randomized trials, the achievement of smoking cessation by itself is considered an unqualified success even with high remission rates, whereas the safe lowering of low-density lipoprotein cholesterol (LDL-C) in a patient with familial hypercholesterolemia, despite the higher proximate risk of an event, requires a CVD event reduction trial in the general population for some to endorse this treatment.

It was at the second level of evidence, below the level of randomized clinical trials, that use of the AAP system needs to be clarified and where a specific kind of evidence has particular relevance to the development of CVD. As shown in Table 1, “overwhelmingly consistent evidence from observational studies” is included in this second level of evidence. There is a remarkable consistency in the findings of many observational natural history studies of the evolution of CVD risk from childhood or young adulthood into adult life with regard to tracking risk factors across decades, factors that impact worsening of risk (eg, development of obesity), and the importance of risk measured early in life to either various morbidity or mortality end points measured later in life. Maintenance of a low CVD risk state is associated with the absence of CVD end points later in life.

Consideration of the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study is an effective example. PDAY is perforce cross-sectional, because it compares pathologic measures of atherosclerosis in the coronary arteries and abdominal aorta measured postmortem in 15- to 34-year-olds dying accidentally with CVD risk factors measured postmortem, as well. Thus, the highest quality end point measurable in children and young adults, the pathologic extent of atherosclerosis, is linked to risk.
measures ranging from highly accurate (BMI), to surrogates (renal arterial wall thickness as a measure of hypertension), to blood measures potentially impacted by resuscitation efforts and other postmortem complications (serum lipids, thiocyanate levels). Findings are likely underestimates of the relationship of risk to atherosclerosis. Nonetheless, results from PDAY demonstrate strong relationships between atherosclerotic severity and extent, and the presence and intensity of known risk factors including higher age, higher non–high-density lipoprotein cholesterol, lower high-density lipoprotein cholesterol, hypertension, tobacco use, diabetes mellitus (glycohemoglobin), and obesity, the last only in males. There was strikingly higher atherosclerotic severity and extent as the number of risk factors increased. The usefulness of the PDAY findings has been buttressed by studies showing that PDAY risk assessments accurately predict subclinical atherosclerosis in living individuals and studies comparing risk distributions in the PDAY cohort with contemporary living individuals, suggesting the likelihood of hemodilution impacting serum and plasma measures.\cite{6,17,20} Consistent evidence from multiple observational and epidemiological studies like PDAY was of major importance in developing these guidelines and was graded as B, per the AAP grading system.

Mendelian randomization is a concept developed to take advantage of the random assignment of genetic abnormalities in a population as a tool to provide additional insight into the natural history of risk exposure. Having a genetic trait implies sustained lifetime exposure, overcoming limitations of single-exposure assessments such as in observational studies. This was felt to be critical evidence, so genetic natural history studies as examples of “Mendelian randomization” were added to the second level of evidence category.\cite{21} For example, in homozygous hypercholesterolemia where LDL-C levels exceed 800 mg/dL beginning in infancy, coronary events begin in the first decade of life, and lifespan is severely shortened. In heterozygous hypercholesterolemia, in which LDL-C levels are minimally 160 mg/dL and typically >200 mg/dL beginning in infancy, 50% of men and 25% of women experience clinical coronary events by age 50 years.\cite{22} In contrast, genetic traits associated with low cholesterol (eg, PCSK9, familial hypobetalipoproteinemia) are associated with longer life expectancy. In affected individuals, the genetic variation identifies the risk status controlled for environmental exposure, because affected and unaffected siblings grow up in similar environments.

**TRANSLATING EVIDENCE INTO GUIDELINES**

It is important to emphasize that this is also the point at which the panel process diverged significantly from similar historic processes. In a consensus guideline, once recommendations are agreed upon, they are buttressed by studies showing that PDAY risk assessments accurately predict subclinical atherosclerosis in living individuals and studies comparing risk distributions in the PDAY cohort with contemporary living individuals, suggesting the likelihood of hemodilution impacting serum and plasma measures.\cite{6,17,20} Consistent evidence from multiple observational and epidemiological studies like PDAY was of major importance in developing these guidelines and was graded as B, per the AAP grading system.
review was complete. Superficially, applying evidence grades would seem to be the most objective task in guideline development. However, many considerations made human judgment critical. Defining comparability of studies was important, given the considerable variation in design, duration, and setting of different trials and the high level of return to pretrial behaviors in studies of lifestyle change. Many different behavioral intervention strategies have been tested, so success rates needed to be matched to specific strategies. Because the 2011 Guidelines were specifically for primary care settings, should randomized trials in schools or other nonmedical sites be considered? Did more recent studies supersede well-conducted studies from the past? Primary end points varied widely; in infant tobacco exposure studies with mothers as the target of intervention, end points ranged from maternal tobacco use to tobacco smoke levels in the home.

For every recommendation in the 2011 report, there exist 2 components: the evidence grade and the strength of recommendation. Although a high evidence grade for multiple studies almost certainly implies a high strength of recommendation, a strong recommendation could be provided in the absence of the highest grade of evidence. Conversely, a number of interpretive factors could compromise a high evidence grade, limiting the strength of recommendation. A summary of considerations in linking an evidence grade to strength of recommendation follows.

### Efficacy/Effectiveness

Efficacy means that, in a specific setting, an intervention works (eg, statins lower cholesterol in clinical trials). Effectiveness means that, in practice, primary care providers will reliably prescribe the recommended intervention, that patients will actually implement it, and that the predicted benefit will occur. Whereas in the adult literature effectiveness research often parallels clinical trials, there is no comparable effectiveness literature for pediatric CVD risk reduction by the use of pharmaceuticals. For behavioral interventions, many were conducted in clinical practice settings, but generalizability beyond the participating practices was often not tested. For the panel, the demonstration of efficacy was considered sufficient to make a recommendation; however, if effectiveness seemed highly unlikely, a recommendation may have been tempered or withdrawn.

### Risk/Benefit

This distinction is critical in any pediatric guideline, because there are elements of both risk and benefit that simply cannot be assessed, because these events are so far downstream. One could easily argue that the initiation of pharmacologic treatment to lower blood pressure or cholesterol would have much greater benefit if initiated earlier than later in the atherosclerotic process; conversely the impact of side effects from decades of use of a pharmacologic agent, the possibility of increased costs for insurance coverage, or social stigma attached to chronic

### TABLE 3 Guideline Definitions for Evidence-Based Statements

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<tr>
<th>Statement Type</th>
<th>Definition</th>
<th>Implication</th>
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<tr>
<td>Strong Recommendation</td>
<td>The Expert Panel believes that the benefits of the recommended approach clearly exceed the harms and that the quality of the supporting evidence is excellent (grade A or B). In some clearly defined circumstances, strong recommendations may be made on the basis of lesser evidence (grade C or D) when high-quality evidence is impossible to obtain and when the anticipated benefits clearly outweigh the harms.</td>
<td>Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.</td>
</tr>
<tr>
<td>Optional Recommendation</td>
<td>The Expert Panel believes that the benefits exceed the harms, but that the quality of the evidence is not as strong (grade B or C). In some clearly defined circumstances, recommendations may be made on the basis of lesser evidence (grade D) when high-quality evidence is impossible to obtain and when the anticipated benefits clearly outweigh the harms.</td>
<td>Clinicians should generally follow a recommendation but remain alert to new information and sensitive to patient preferences.</td>
</tr>
<tr>
<td>No recommendation</td>
<td>There is both a lack of pertinent evidence (grade D) and an unclear balance between benefits and harms.</td>
<td>Clinicians should not be constrained in their decision-making and should be alert to newly published evidence that clarifies the balance of benefit versus harm; patient and family preferences should have a substantial influencing role.</td>
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medication use from an early age might negate these benefits.

There are also unusual scenarios that develop when there is no perceived risk to an intervention. For example, anti-tobacco counseling has no risk and a small benefit demonstrated in randomized trials. However, in the context of the time available to a practitioner for a health maintenance visit, is the potential tobacco-counseling success rate sufficiently high to compromise other important counseling opportunities that might be lost if the focus of the visit is tobacco?

**Specific Circumstances**

Although evidence that a particular intervention is highly successful might exist, that intervention may not be generalizable to a pediatric setting. Tobacco again provides a useful example, because successful behavioral and pharmacologic interventions exist in young adults with evidence that is grade A; however, comparable trials may not have been performed in adolescents or in specific pediatric age ranges.

**Social Role of Physicians**

Finally, and impossible to evaluate in an evidence paradigm, is the social role physicians play in health promotion. The absence of a proven effective treatment by a randomized trial for a recognized health problem does not mean that patients will not still present with this concern and expect well-informed medical guidance. For example, behavioral interventions to address obesity in a primary practice setting are often ineffective in trials; however, the fault may not be with the specific intervention but with the ability of the patient and family to comply. Thus, the panel felt compelled to provide information as part of the report on potentially efficacious treatments despite the fact that implementing these strategies may often be difficult.

**CRITIQUE OF THE CURRENT GUIDELINE**

The guideline development process ended in October 2008, and guideline publication has taken a considerable time since the formal work was concluded. Some of this delay was anticipated, because a period of time for public comment was part of the formal evaluation process. However, delays related to additional governmental review were unanticipated. One positive aspect of the extensive review process is the fact that few of the reviewers, now numbering well into the hundreds, have suggested altering the basic recommendations. This suggests that, with regard to CV risk prevention, there is consensus about what needs to be accomplished with lingering questions relating to the timing and intensity of risk modification required, the role of public health policy versus physician practice, and identification of the best methods to achieve desired goals. It is now reasonable to ask what could have been done differently and how could the process be improved.

Critical to guideline development from an evidence base is the formulation of the initial questions for evidence review. The cost-benefit of proposed recommendations was not included initially, because there is not a large literature on cost of CVD prevention beginning in youth. Thus, an additional section on issues related to screening for CVD risk was included. It is hoped that publication of the report will stimulate research specifically addressing cost or cost-benefit analysis.

There is now a substantial time gap between the closure of the evidence review and publication of the report. Fortunately, subsequent research reports have supported the recommendations in the guidelines. An example is the National Institute for Health and Clinical Excellence guideline from Great Britain on familial hypercholesterolemia. In Europe, recommendations for managing familial hypercholesterolemia, a genetic disorder affecting ∼1:500 in the general population are considered separately from population-based guidelines for lipid management. The National Institute for Health and Clinical Excellence guideline includes a cost-benefit analysis of management of genetic dyslipidemia. This perspective is different than the perspective considered in US guidelines and in this evidence review, which is based purely on lipid levels without considering underlying causes. In addition, the new guidelines limited the evidence review with regard to blood pressure. This was because, in 2006, when development of these guidelines began, the fourth report on blood pressure in childhood had just been released. Even though this was not an evidence-based document, clinical trial information on blood pressure treatment was evaluated in the report. A full evidence-based review of blood pressure treatment will be necessary in the future.

The prevalence of diabetes mellitus, both type 1 and type 2, is increasing in the United States, and much recent research has been devoted to associated CV morbidity. Future guidelines will need to consider diabetes more explicitly than previously.

A critical question relates to whether nutrition, physical activity, and family history should have been considered as risk factors by the panel. Recommendations regarding these factors could have been included within the context of treatment of other risk factors. It can be argued that these factors fall in the realm of public health rather than medical practice. The panel felt that, in the absence of a coherent public health strategy effectively addressing these issues, pediatric care providers are the primary source for information on these subjects for children and families. This approach was used despite the
fact that it was impossible to directly relate diet or physical activity to important end points such as premature atherosclerosis.

An ongoing process of evidence review is essential because atherosclerotic CVD remains the leading cause of death in North America; evidence that this process begins in childhood and is accelerated by the presence and intensity of known risk factors continues to appear; and there is an increasing body of evidence addressing CV risk reduction in childhood. Continuing surveillance of the literature will allow guideline recommendations to be updated as evidence develops. The evidence review could be sustained by using a revision of the current critical questions. The Expert Panel could be maintained with an established process for rotating membership and adding new representatives to sustain the high level of expertise, diversity, stakeholder representation, and energy that characterized development of the current guidelines. The panel could meet annually to review the accumulated evidence, add new areas for inclusion in the evidence review and/or new critical questions, and determine when new recommendations are needed. Disbanding the current panel will necessitate a completely new evidence review process for development of future recommendations.

SUMMARY
This article has reviewed aspects of development of evidence-based CVD prevention guidelines for pediatric care providers that remain in the area of human judgment probing issues related to construction of an evidence evaluation paradigm and post hoc issues that arise where competing considerations must be weighed before final recommendations can be developed. Tables 4 and 5 provide a synthesis of guidance from this article for both practitioners and those developing guidelines. There are 3 main lessons from this experience. First, in the contemporary era, a formal evidence review process is essential to developing a credible document. Second, even with a formal and objective review of the evidence, human judgment is critical to produce a meaningful result. Third, and implicit to the discussion, is recognition that guideline development is a dynamic process that must be continuously self-critical: new evidence is acquired, new sociopolitical and environmental contexts evolve, and human judgment is fallible.

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The online version of this article, along with updated information and services, is located on the World Wide Web at:
/content/129/5/e1311.full.html