

# Decision-making process for conditions nominated to the Recommended Uniform Screening Panel: statement of the US Department of Health and Human Services Secretary's Advisory Committee on Heritable Disorders in Newborns and Children

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**Purpose:** The US Secretary of Health and Human Services provides guidance to state newborn screening programs about which conditions should be included in screening (i.e., the "Recommended Uniform Screening Panel"). This guidance is informed by evidence-based recommendations from the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children. This report describes the Advisory Committee's revised decision-making process for considering conditions nominated to the panel.

**Methods:** An expert panel meeting was held in April 2012 to revise the decision matrix, which helps to guide the recommendation process. In January 2013, the Advisory Committee voted to adopt the revised decision matrix.

**Results:** The revised decision matrix clarifies the approach to rating magnitude and certainty of the net benefit of screening to the

population of screened newborns for nominated conditions, and now includes the consideration of the capability of state newborn screening programs for population-wide implementation by evaluating the feasibility and readiness of states to adopt screening for nominated conditions.

**Conclusion:** The revised decision matrix will bring increased quality, transparency, and consistency to the process of modifying the recommended uniform screening panel and will now allow formal evaluation of the challenges that state newborn screening programs face in adopting screening for new conditions.

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The US Department of Health and Human Services Secretary's Advisory Committee on Heritable Disorders in Newborns and Children ("the Advisory Committee") provides guidance to the Secretary of Health and Human Services ("Secretary") about which conditions should be included in newborn screening. The conditions recommended for screening by the Advisory Committee and subsequently endorsed by the Secretary comprise the Recommended Uniform Screening Panel (RUSP). The RUSP initially included 29 core conditions, selected on the basis of the opinions of an expert panel convened by the American College of Medical Genetics and Genomics. Although the report recommending these conditions was first published in 2006,<sup>1</sup> the RUSP did not become official until 2010, when it was endorsed by the Secretary. Since this time, there have also been significant advances in

the methods used for evidence synthesis and the subsequent decision-making process.<sup>2</sup>

To improve the decision-making process, the Advisory Committee developed an explicit approach to making recommendations based on evidence-based assessment of conditions nominated to the RUSP. Central to this approach is the development of an evidence report by an outside group for each condition under consideration,<sup>3</sup> which summarizes the available direct evidence and the indirect chain of evidence from published and unpublished data regarding the benefits and harms of screening for the nominated condition. The Advisory Committee would make a determination about the addition of the condition to the RUSP on the basis of the magnitude and certainty of net benefit to the population of screened newborns that could result from

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screening.<sup>4,5</sup> The Advisory Committee would assess net benefit by considering the importance of the health outcomes, the estimated health benefits that could result from testing, the harms associated with testing for the condition, and the efficacy and effectiveness of testing and subsequent follow-up as compared with usual clinical practice. The Advisory Committee could make one of four possible recommendations on the basis of the assessment of net benefit: add the condition to the RUSP; do not add the condition to the RUSP but request further studies to resolve important and specific areas of uncertainty; do not add the condition to the RUSP on the basis of current knowledge of the anticipated net benefit of screening; or do not add the condition to the RUSP.<sup>4</sup> Using this approach, the Advisory Committee has added two conditions to the RUSP: severe combined immunodeficiency and critical congenital heart disease. Four additional conditions were referred for evidence review but were not recommended for inclusion in the RUSP: hemoglobin H disease, Krabbe disease, neonatal hyperbilirubinemia, and Pompe disease.

Missing from this evidence-based approach is a formal assessment of the capability of newborn screening programs to provide comprehensive screening, as suggested by the federal legislation that authorizes the Advisory Committee. In April 2012, the Health Resources and Services Administration supported a meeting of experts (see Appendix) to develop strategies to strengthen the evidence review process and to address this gap. In January 2013, the Advisory Committee voted to adopt a revised approach that explicitly considers newborn screening capability in its decision-making process. In addition, the revised approach expands the formal process for assessment of net benefit to provide greater specificity and clarity in the recommendations from the Advisory Committee. This report highlights the revised approach to evidence review, specifically highlighting the assessment of newborn screening program capability for conditions nominated to the RUSP, and how these findings will be used to develop the recommendations.

**ASSIGNING THE MAGNITUDE AND CERTAINTY OF NET BENEFIT**

The evidence base for the conditions nominated to the RUSP will rarely be complete, i.e., demonstrating that population screening directly leads to improved clinical outcomes for affected infants and to minimal harms for those not affected. Common barriers include: the rarity of the conditions and their variable genotype–phenotype correlation, the variable technical approaches used in screening algorithms, and the often broad spectrum of clinical phenotype in relation to diagnosis, treatment, and responses to therapy. As in the previous Advisory Committee approach, the process of condition review begins with the identification of key questions related to screening and diagnostic validity for the condition, treatment outcomes as they relate to clinical utility of population-based screening, followed by a synthesis of published and unpublished data related to each of these key questions.<sup>3</sup> The systematic review will now also be supplemented by a decision analytic model. This model will illustrate the estimated upper and lower ranges of predicted net benefit and harm to the population associated with newborn screening as compared with usual care with clinical identification.<sup>6</sup>

After review of the evidence report, the Advisory Committee will now assign one of five ratings to nominated conditions (Table 1) on the basis of consensus regarding the magnitude and certainty of population net benefit. The most difficult decision anticipated for the Advisory Committee will be in determining an A versus B rating. An A rating indicates high certainty throughout the chain of evidence represented by the key questions to reasonably believe that screening would lead to a significant net benefit for the population. In contrast, a B rating of the evidence indicates moderate certainty that screening would lead to a significant net benefit. The term moderate as used here indicates that the Advisory Committee believes that further research could change the magnitude or direction of findings within

**Table 1** Classification system used by the Advisory Committee

Net benefit to the population of newborns screened		States' capability to offer comprehensive newborn screening	
Rating	Description	Rating	Description
A	High certainty that screening for the targeted condition would lead to a significant net benefit	1	Screening has high to moderate feasibility <sup>a</sup> and most newborn screening programs are ready for comprehensive screening
B	Moderate certainty <sup>b</sup> that screening for the targeted condition would lead to a significant benefit	2	Screening has high to moderate feasibility and most newborn screening programs have developmental readiness for comprehensive screening
C	High or moderate certainty that screening for the targeted condition would lead to a small to zero net benefit	3	Screening has high to moderate feasibility and most newborn screening programs are unprepared for comprehensive screening
D	High or moderate certainty that screening for the targeted condition would lead to a negative net benefit	4	Screening has low feasibility
L	Low certainty regarding the net benefit of screening		

<sup>a</sup>High to moderate feasibility is based on the Advisory Committee's determination that there is an established and available screening test that can be adopted, a clear approach to diagnostic confirmation, and a treatment plan that is acceptable to clinicians and affected individuals and their families, and plans for long-term follow-up can be established. <sup>b</sup>Moderate certainty indicates that the Advisory Committee believes that further research could change the magnitude or direction of findings within any of the key questions such that the assessment of net benefit would be small to zero or even negative.

any of the key questions such that the assessment of net benefit would be small to zero or even negative. Because of the challenges inherent in examining most of the conditions nominated to the RUSP, there will nearly always be uncertainty within the key questions. The Advisory Committee will determine whether the degree to which this uncertainty implies an A or B rating. The other ratings relate to: conditions for which screening would be unlikely to lead to net benefit (C), conditions for which screening may be harmful overall (D), and conditions for which the evidence base is sufficiently limited that the Advisory Committee cannot evaluate the net benefit (L).

**ASSIGNING THE CAPABILITY TO SCREEN**

The Advisory Committee will now include review of the capability of state newborn screening programs to implement comprehensive screening, including short- and long-term follow-up, for nominated conditions by considering feasibility and readiness. The assessment of state newborn screening programs is intended to evaluate the entire integrated system needed for implementation of comprehensive newborn screening, not just the ability to provide laboratory testing. This assessment will include: authority, laboratory testing, interpretation, reporting, tracking, and systems for assurance of diagnostic evaluation and evaluation of outcomes. The key features of feasibility are: availability of valid and reliable screening tests with adequate throughput to meet the needs of population-based deployment; availability of systems to ensure quality implementation of the screening test, including the assured availability of quality reagents and quality data-reporting systems; availability of quality-control and proficiency-testing samples, a centralized quality-assurance program; adequate training programs for new technologies; an established approach for diagnostic confirmation available

to newborn screening programs; and an established approach to long-term follow-up, including treatment, available to newborn screening programs. The key features of readiness are: availability of resources for screening, diagnostic confirmation, and long-term follow-up, including financial resources; availability of laboratory equipment, data systems, and expertise; access to specialty care and treatments; systems for data collection; and authorization for screening. Although overlap exists between issues of feasibility and readiness, the Advisory Committee does not need to fully distinguish these concepts when evaluating capability for screening. Instead, this framework helps to assure that all aspects of implementation are considered. The Association of Public Health Laboratories has agreed to prepare for the Advisory Committee a separate report describing key factors related to feasibility and readiness for each condition under consideration. This report will be based on surveys of state newborn screening programs and will consider the unique elements needed for comprehensive population-based newborn screening.

The Advisory Committee will classify feasibility into two categories: high or moderate versus low. High or moderate feasibility indicates that there is an established and available screening test that can be adopted, a clear approach to diagnostic confirmation, and a treatment plan that is acceptable to clinicians and affected individuals and their families, and plans for long-term follow-up can be established. Readiness will be classified into three categories: ready, developmental readiness, or unprepared. “Ready” implies that most newborn screening programs could implement screening within 1 year after the state makes the decision to include the condition and funding is made available. “Developmental readiness” suggests that most newborn screening programs face barriers that would require 1–3 years to address. “Unprepared” implies that most newborn screening programs would take longer than 3 years to implement, even

Net benefit		Feasibility	Readiness		
			Ready	Developmental	Unprepared
Significant benefit	High certainty	High or moderate feasibility	<b>A1</b>	<b>A2</b>	<b>A3</b>
		Low feasibility	<b>A4</b>		
	Moderate certainty		<b>B</b>		
Zero to small benefit	High or moderate		<b>C</b>		
Negative benefit	certainty		<b>D</b>		
	Low certainty		<b>L</b>		

Figure 1 The Advisory Committee decision matrix.

with the decision to add the condition and the availability of funding to begin comprehensive screening.

The Advisory Committee will assign one of the four ratings (Table 1) for the capability to screen based on consensus regarding feasibility and reliability. In general, feasibility is the primary factor used in assigning capability. Those conditions with high to moderate implementation feasibility will then be rated 1, 2, or 3, on the basis of readiness. A rating of 4 represents low feasibility, regardless of readiness. Overemphasis of readiness in rating capability could delay adoption of new beneficial screening activities. However, assessment of readiness can help the Advisory Committee develop recommendations to facilitate adoption of conditions into state newborn screening panels that could have significant net benefit. Capability does not need to be assigned for those conditions not associated with significant net benefit (i.e., not rated A). However, the Advisory Committee may assign a capability rating if it determines that this would help clarify future activities related to screening for the condition.

### RECOMMENDATION PROCESS

The Advisory Committee will now employ a revised decision matrix (Figure 1) that combines the ratings for net benefit and capability to make recommendations regarding conditions nominated to the RUSP. Those nominated conditions with an A1 or A2 rating will be recommended by the Advisory Committee to the Secretary for inclusion in the RUSP. Those with a rating of A3 or A4 may be recommended at the discretion of the Advisory Committee. All recommended conditions will include specific guidance to support timely implementation. In the event that a condition rated A3 or A4 is not recommended to the RUSP, the Advisory Committee will advise specific steps to improve feasibility or readiness. Those conditions rated B, C, D, or L will not be recommended to the Secretary for inclusion in the RUSP. However, the Advisory Committee will provide guidance regarding the type of research needed to resolve the key areas of uncertainty. Conditions rated as C or D will be reconsidered only if new evidence emerges to suggest the possibility of a significant net benefit of screening. Conditions rated L could be considered in the future, but only with an improvement in the evidence base. These refinements to the Advisory Committee's review of nominated conditions will bring increased quality, transparency, and consistency to the process of modifying the RUSP. Thus far, all considerations related to modification of the RUSP have been related to addition of new conditions. However, a similar process could be used to evaluate specific conditions currently included in the RUSP, which could potentially lead to removal of the condition from the RUSP. Future work will continue to refine the metrics used to evaluate population-based net benefit and the capability of state newborn screening programs to offer comprehensive newborn screening for nominated conditions.

### APPENDIX: PARTICIPANTS IN APRIL 2012 EXPERT MEETING, LISTED ALPHABETICALLY BY MAIN ORGANIZATION REPRESENTED

#### Agency for Healthcare Research and Quality

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Services or of the individual members of the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children.

### DISCLOSURE

The authors declare no conflict of interest.

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