

**The Advisory Committee on Heritable Disorders in
Newborns and Children (ACHDNC):
Policies and Procedures for Operation and the Development
of Recommendations for Screening Newborns and Children
for Heritable Disorders and
for the Heritable Disorders Program**

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A. Authority

Section 1111 of the Public Health Service (PHS) Act, 42 U.S.C. 300b-10, as amended in the Newborn Screening Saves Lives Act of 2008 (Attachment A). The Advisory Committee on Heritable Disorders in Newborns and Children is governed by the provisions of Public Law 92-463, as amended (5 U.S.C. App. 2), and 41 CFR Part 102-3, which sets forth standards for the formation and use of advisory committees.

B. Purpose

Title XXVI of the Children's Health Act of 2000, "Screening for Heritable Disorders," enacts three sections of the PHS Act: sections 1109, 1110, and 1111. This Act establishes grant programs to improve the ability of States to provide newborn and child screening for heritable disorders (section 1109) and for evaluating the effectiveness of screening, counseling or health care services in reducing the morbidity and mortality caused by heritable disorders in newborns and children (section 1110). On April 24, 2008, this Act was reauthorized and programs and activities were expanded by the "Newborn Screening Saves Lives Act of 2008" and added Sections 1112, 1113, 1114, 1115 and 1116. Section 1112 establishes a clearinghouse of newborn screening; Section 1113 establishes a program for laboratory quality; Section 1114 establishes an Interagency Coordinating Committee on Newborn and Child Screening (ICC); Section 1115 establishes a national contingency plan for newborn screening; and Section 1116 establishes the Hunter Kelly newborn screening research program.

The Secretary of Health and Human Services (the Secretary, HHS) is directed under section 1111 of the PHS Act to establish an Advisory Committee on Heritable Disorders in Newborns and Children. The Committee provides to the Secretary advice about aspects of newborn and childhood screening and technical information for the development of policies and priorities that will enhance the ability of the State and local health agencies to provide for newborn and child screening, counseling and health care services for newborns and children having or at risk for heritable disorders. The Committee also makes recommendations, gives advice, or provides information to the Secretary about the grant program established under Section 1109 of the Act. Activities carried out under Sections 1112-1114 and 1116 are undertaken in consultation with the Committee.

According to its charter, the ACHDNC shall review and report regularly on newborn and childhood screening practices, recommend improvements in the national newborn and childhood screening programs, and shall engage in the following activities:

- (1) provide advice and recommendations to the Secretary concerning grants and projects awarded or funded under section 1109;
- (2) provide technical information to the Secretary for the development of policies and priorities for the administration of grants under section 1109;
- (3) make systematic evidence-based and peer-reviewed recommendations that include the heritable disorders that have the potential to significantly impact public health for which all newborns should be screened, including secondary conditions that may be identified as a result of the laboratory methods used for screening;
- (4) develop a model decision-matrix for newborn screening expansion, including an evaluation of the potential public health impact of such expansion, and periodically update the recommended uniform screening panel, as appropriate, based on such decision-matrix;

- (5) consider ways to ensure that all States attain the capacity to screen for the conditions described in paragraph (3), and include in such consideration the results of grant funding under section 1109; and;
- (6) provide such recommendations, advice or information as may be necessary to enhance, expand or improve the ability of the Secretary to reduce the mortality or morbidity from heritable disorders, which may include recommendations, advice, or information dealing with—
- follow-up activities, including those necessary to achieve rapid diagnosis in the short-term, and those that ascertain long-term case management outcomes and appropriate access to related services;
 - implementation, monitoring, and evaluation of newborn screening activities, including diagnosis, screening, follow-up, and treatment activities;
 - diagnostic and other technology used in screening;
 - the availability and reporting of testing for conditions for which there is no existing treatment;
 - conditions not included in the recommended uniform screening panel that are treatable with Food and Drug Administration-approved products or other safe and effective treatments, as determined by scientific evidence and peer review;
 - minimum standards and related policies and procedures used by State newborn screening programs, such as language and terminology used by State newborn screening programs to include standardization of case definitions and names of disorders for which newborn screening tests are performed;
 - quality assurance, oversight, and evaluation of State newborn screening programs, including ensuring that tests and technologies used by each State meet established standards for detecting and reporting positive screening results;
 - public and provider awareness and education;
 - the cost and effectiveness of newborn screening and medical evaluation systems and intervention programs conducted by State-based programs;
 - identification of the causes of, public health impacts of, and risk factors for heritable disorders; and
 - coordination of surveillance activities, including standardized data collection and reporting, harmonization of laboratory definitions for heritable disorders and testing results, and confirmatory testing and verification of positive results, in order to assess and enhance monitoring of newborn diseases.

The ACHDNC is the only entity in the Federal government which makes such recommendations. The target audiences for the Committee recommendations are State-based newborn screening programs and public and private health providers who provide services to newborns and children with heritable disorders, public health and non governmental officials who make newborn and child screening policy, and the public.

A. Support

Coordination, management, and operational services are be provided by the Maternal and Child Health Bureau, Health Resources and Services Administration (HRSA).

B. Membership

The Committee consists of 15 voting members, including the following voting *ex-officio* members: the Administrator of Health Resources and Services Administration (HRSA), the Directors of the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), and the Agency for Healthcare Research and Quality (AHRQ), the Commissioner of the Food and Drug Administration (FDA) or their designees. The ACHDNC members are selected based on their expertise and qualifications necessary to contribute to the accomplishments of the Committee's objectives. Through its recommendations regarding newborn and child screening programs, the ACHDNC plays a leading role in the promotion of public health in the United States. Therefore, the Committee members appointed by the Secretary should include:

- medical, technical, or scientific professionals with special expertise in heritable disorders, or in providing screening, counseling, testing or specialty services for newborns and children at risk for heritable disorders;
- individuals with expertise in ethics and infectious diseases who have worked and published material in the area of newborn screening;
- members of the public having special expertise about or concern with heritable disorders

Departmental policy provides that Committee membership be fairly balanced in terms of points of view represented and the Committee's function. The Department will give close attention to the membership of the Committee to ensure that it reflects a distribution of the experience and expertise needed to understand and serve the diversity of the population served.

Members shall be invited to serve for overlapping terms of up to 4 years. However, any member appointed to fill a vacancy of an unexpired term shall be appointed for the remainder of such term. Members may serve after the expiration of their term until their successors have taken office, but no longer than 120 days. A quorum for the conduct of business by the full Committee shall be a simple majority (8) of the appointed voting members.

The Committee may also include nonvoting liaisons or organizational representatives as determined to be necessary by the Secretary, to fulfill the duties of the Committee. In addition, the Committee is encouraged to work closely with other relevant HHS entities that focus on reviewing scientific evidence and making recommendations on clinical preventive services. The Secretary shall be able to call upon special consultants, assemble ad hoc working groups, and convene hearings as necessary to assist in the work of the Committee.

1. Consideration for Nomination

Committee members serve as individuals, not as representatives of organizations or interest groups. Each person is selected based on his or her expertise as noted above.

The Secretary's goal in appointing members to the ACHDNC is to achieve the greatest level of expertise while minimizing the potential for actual or perceived conflicts of interest and assuring public confidence in the integrity of the Committee's advice. This can be achieved in large part by focusing on the types of expertise needed on the Committee, the ways in which individuals attain that expertise, and the value of maintaining such contacts during their tenure on the committee. Applying such an analysis, the Secretary has concluded that particular personal financial interests may create conflicts, or perceptions of conflicts. When the expertise of the individual contributes little unique or additional knowledge to the Committee and the financial interests create either an actual or apparent interest in the success or failure of the products of a

genetic or newborn screening test manufacturer, such interests should disqualify an individual from membership on the Committee. Disqualification is especially important if the individual personally will benefit financially from a decision that the Committee may make. Therefore, individuals with certain financial genetic or newborn screening-related interests generally will not be considered for appointment to the Committee. These conflicts would include employment by a genetic or newborn screening test or therapy manufacturer. Members are prohibited from serving as a consultant or advisor to a genetic or newborn screening test or therapy manufacturer and from accepting honoraria or travel reimbursement from a genetic or newborn screening test or therapy manufacturer during Committee tenure.

2. Solicitation for Nominees

Each year, suggestions for members are sought, generally through a federal register notice, from a variety of sources including, family organizations, professional medical, scientific or public health societies, current and former ACHDNC members, and the general public. These individuals are encouraged to contact members of their institutions, professional organizations, and peers to develop a broad slate of candidates. During the year, suggestions for membership to the Committee are received from various sources. These submissions are compiled for consideration along with those received from the solicitation.

3. Selection of Nominees

A listing of individuals suggested for nomination for appointment to the Committee is prepared by the Executive Secretary of the ACHDNC and forwarded to the federal ex-officio members for review.

The final nomination package is submitted to the Secretary, HHS, who appoints the member(s) to the Committee. When the appointment is confirmed by the Secretary, the new member serves for a term of up to 4 years. A member may be reappointed to serve up to an additional 4 years at the request of the Secretary. A member who is unable to fulfill the full term on the Committee may resign by submitting a letter of resignation to the Executive Secretary, ACHDNC. If a member resigns, a new member is appointed to fill the remainder of the unexpired term. The Chair is chosen by the Secretary.

C. Financial Interests – Financial Conflicts of Interest

Federal law (18 U.S.C. §208) prohibits Federal executive branch employees, including Special Government Employees (e.g., members of Federal advisory committees such as the ACHDNC), from participating, personally and substantially, in particular matters which have a direct and predictable effect on financial interests, to their knowledge, held by themselves, their spouse, minor child, general partner, organization in which they are serving as officer, director, trustee, general partner or employee. Members may have potential financial conflicts of interest because members are chosen for service based on their expertise and experience in the areas in which advice is sought by the government. Congress has recognized the need for service by these experts on Federal advisory committees, despite the inherent potential for conflicts of interest, by providing for waivers of the conflict of interest prohibition for particular matters of general applicability, under 18 U.S.C. §208(b) (3) when “the need for the individual’s services outweighs the potential for a conflict of interest created by the financial interest involved.”

The Secretary is sensitive to concerns about potential conflicts of interest by members serving on the ACHDNC. To assure the integrity of the Committee, steps have been taken to assure that there is compliance with the ethics statutes and regulations regarding financial conflicts and the appearance of financial conflicts of interest. As described in Section C of this policy, limited 208(b)(3) waivers for particular matters of general applicability are considered for members utilizing that statute's standard of the need for the individual's services outweighing the potential for a conflict of interest created by the financial interest involved [18 U.S.C. 208(b)(3) may be viewed at this site: http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=browse_usc&docid=Cite:+18USC208]

ACHDNC members must file OGE Confidential Financial Disclosure Reports, Form 450, as required by OGE regulations and the HRSA policy "Financial Disclosure for Federal Advisory Committee Members Appointed as Special Government Employees." The Designated Federal Officer (DFO)/Executive Secretary individually evaluates and considers for waiver the related financial interests of each ACHDNC member in accordance with the OGE regulations at 5 CFR Parts 2635 and 2640.

D. Organizational Representatives

Appointments by the Secretary of organizational representatives are based upon written requests from organizations, the Committee, and according to Secretarial needs. Requests from organizations should document the commitment of the organization to providing expert input into the ACHDNC decision-making process, travel and per diem support to their representative, and active dissemination to their membership about ACHDNC activities and recommendations. A request for organizational representation suggested to the Committee should be prepared and forwarded to the Executive Secretary /DFO for review and approval by the Committee. Because of space and time limitations at meetings, representatives must represent organizations that show interest in the Committee's work through active involvement and participation at Committee meetings, have broad interests in relevant fields (e.g., primary care, newborn screening, genetics and other relevant specialty expertise) and represent large constituencies relevant to the Committee's needs. Groups that represent more narrow interests or small constituencies (e.g., interest in a single disease) are invited to participate in ACHDNC activities on an ad hoc basis whenever issues of interest and concern are being discussed rather than requesting liaison representation. The Committee will evaluate requests for particular organizational liaisons in an ongoing manner and will consider the commitment of specific organizations to the Committee's charter and involvement of those organizations in Committee activities. Up to 12 liaison representatives will be permitted.

E. Voting

For Committee meetings, the Committee shall not take a vote unless a quorum of at least eight voting members is present. Voting members are specified by the charter. Only Committee members and ex-officio members may vote. Liaison members and organizational representatives may not vote.

All members, including *ex-officio* members, are expected to announce any conflicts of interest, as described within Federal law (18 U.S.C. §208) prior to any voting to determine if they can vote. For subcommittee meetings, only subcommittee members who are members of the Committee may vote.

F. Meetings

Regularly scheduled meetings are held at least two times a year, at the call of the Executive Secretary. Meeting dates are announced 6-12 months in advance. Meeting dates and the location of the meetings are posted on the ACHDNC web site as soon as the dates and location are selected. At least 15 days prior to the meeting, the meeting date, items to be discussed, and location are published in the Federal Register. Meetings traditionally are held in Washington, D.C. metro area. Except as noted otherwise in these policies and procedures, the Chair will use Roberts Rules of Order (Ninth Edition) as a guide when conducting Committee meetings.

If there is a need to consult ACHDNC members on an urgent or emergency basis, the Executive Secretary may request that the Chair establish an “emergency consultation workgroup” consisting of ACHDNC members, to discuss the nature of the emergency and possible responses to it. The workgroup will report its findings and recommendations to the full Committee for their deliberation.

ACHDNC meetings are generally open to the public for their entire duration. However, there may be occasions when the nature of the information is such that a closed meeting is required. All provisions of the Federal Advisory Committee Act and Government in the Sunshine Act regarding closed sessions will be followed. All ACHDNC proceedings shall be published on the Committee web site.

▪ Public Comment

ACHDNC holds open discussions and reserves meeting time for public comment. In some limited circumstances, a formal comment period is scheduled during the deliberation of a specific agenda item. Comments from the public may be received during open discussions depending on the amount of time available. These comments may be restricted in order to keep within the time allotted for the Committee to complete the agenda. Opportunity to make public comment orally on specific agenda items should be requested in advance. Members of the public who wish to address the Committee should contact the ACHDNC Executive Secretary to request public comment time. Brief comments will be allowed and in the event of a large volume of requests, the time allowed for each speaker may be specified in advance. It is recommended that oral comments also be submitted in writing. Public comments may be submitted to the Committee in writing, even when an individual cannot attend the meeting. Written comments are provided as handouts to the Committee and to the attendees, but are not read aloud during the meeting. The Committee may request that written comments be concise in order to facilitate the Committee’s ability to properly review and consider all comments received.

G. Working Groups and Subcommittees

ACHDNC is authorized to establish subcommittees. ACHDNC subcommittees: 1) must include two or more ACHDNC members, 2) must include the DFO/Executive Secretary or his or her designee, and 3) may include as consultants, organizational representatives. On occasion, technology or disease experts who are not government employees, ACHDNC members, *ex officio* members or organizational representatives may be asked to serve as consultants to a subcommittee. Only appointed voting members may chair a subcommittee. Members with a potential financial conflict of interest cannot serve on a subcommittee. All subcommittee

findings are presented to the ACHDNC in open meeting, and this information is openly deliberated. Subcommittee members serve for a term of up to 4 years. A member may be reappointed to serve up to an additional 4 years at the request of the ACHDNC Chair.

ACHDNC utilizes subgroups or working groups of the Committee, to review research data, published literature and expert opinion and develop options for presentation to the full Committee. The ACHDNC working groups are used as a resource for gathering, analyzing, and preparing information for the Committee. The Committee Chair appoints working group members and these members need not be Committee members. All working group findings are presented to the ACHDNC in open meeting, and this information is openly deliberated. Working group members serve for a term of up to 4 years. A member may be reappointed to serve up to an additional 4 years at the request of the ACHDNC Chair.

H. Member Responsibilities

1. Attendance at Meetings

Except in the event of an emergency, members of the ACHDNC assume the responsibility of attending all meetings. At the discretion of the Executive Secretary, a member may be linked to a Committee meeting by telephone or video conference, in which case their presence shall count toward the quorum. Failure by a member to participate actively in the work of the Committee, including regular attendance at ACHDNC meetings, may result in a request by the ACHDNC DFO/Executive Secretary to the Secretary, HHS to replace the affected member.

2. ACHDNC Related Contacts

ACHDNC members may be solicited to participate in consultations or surveys on screening issues that are addressed by the ACHDNC. ACHDNC members should not participate in such consultations or surveys if they are requested to participate because of their ACHDNC membership status.

The Standards of Conduct for Employees of the Executive Branch (Title 5, Code of Federal Regulations, Section 2635.807) prohibit receiving compensation for speaking, teaching, or writing on matters related to an ACHDNC member's official duties outside Committee or subcommittee meetings. ACHDNC members are prohibited from receiving compensation for any speech or publication in which the purpose is to report on the member's work on the ACHDNC.

3. Media Interaction

The ACHDNC Chair is the usual spokesperson for the Committee. Committee members and organizational representatives may be approached by the media for an interview. Members and representatives are free to give interviews and express their opinions, or the views of their employer, professional organization, etc., but should have HRSA approval to speak as an ACHDNC member or organizational representative on ACHDNC matters. Therefore, the Committee member should inform the Executive Secretary of such an interview to determine the appropriateness of the interview and the appropriate Committee member to participate in the interview. An organizational representative is free to represent their respective organization but may not represent the ACHDNC.

4. Committee Correspondence

Any correspondence (letter, fax, e-mail, solicitation of articles or commentary on ACHDNC matters, etc.) should be routed to the Executive Secretary for the ACHDNC who then determines who the most appropriate respondent is. No member or organizational representative should reply to Committee correspondence without consulting the Executive Secretary. The only exception to this rule is that all members are free to respond to questions about established points of fact (e.g., meeting dates, citations for ACHDNC recommendations, etc.).

5. Record Keeping and Reports

Meetings shall be conducted and records of the proceedings kept, as required by applicable law, regulation and the HHS General Administration Manual.

In the event a portion of a meeting is closed to the public, as determined by the Secretary, HHS, in accordance with the Government Sunshine Act (5 U.S.C. 552b(c)) and the Federal Advisory Committee Act, a report shall be prepared which shall contain, at a minimum, a list of the members and their business addresses, the Committee's function, dates and places of meetings, and a summary of Committee activities and recommendations made during the fiscal year. A copy of the report shall be provided to the Department Committee Management Officer.

Not later than 3 years after the date of enactment of the Newborn Screening Saves Lives Act of 2008, and each fiscal year thereafter, the Advisory Committee shall:

1. publish a report on peer-reviewed newborn screening guidelines, including follow-up and treatment, in the United States;
2. submit such report to the appropriate committees of Congress, the Secretary, the Interagency Coordinating Committee established under Section 1114 of the Newborn Screening Saves Lives Act of 2008, and the State departments of health; and
3. disseminate such report on as wide a basis as practicable, including through posting on the internet clearinghouse established under section 1112 of the Newborn Screening Saves Lives Act of 2008.

I. Selection of Topics

Potential topics for ACHDNC consideration can be suggested by anyone, but are most often proposed by the Committee chair in consultation with the DFO/Executive Secretary; HRSA; AHRQ, CDC, NIH and FDA program staff; ACHDNC members; scientific and medical professional organizations; lay advocacy groups; or manufacturers of technologies, tests or processes for screening newborns and children for heritable disorders.

Approximately 10 weeks prior to an upcoming meeting, a memorandum requesting potential agenda items is generally sent via postal mail or e-mail to the ACHDNC chair and HRSA, AHRQ, CDC, FDA and NIH and HRSA program staff. A list of topics based on action or follow-up items from the last meeting or previously suggested is included in the memorandum. The person suggesting an agenda item is asked to specify the topic to be on the agenda, issues of concern, and specific questions to be addressed by ACHDNC.

Agenda items are accepted for discussion by the DFO/Executive Secretary in consultation

with the Chair, and the Associate Administrator, MCHB, HRSA; and representatives from AHRQ, CDC, FDA and NIH. The ACHDNC DFO/Executive Secretary will prepare the agenda.

J. Process for Developing Recommendations

The Committee duties include (1) making evidence-based recommendations regarding disorders for which newborns and children should be screened (2) evaluating and updating the Committee's previously recommended uniform screening panel, (3) providing recommendations for the grants and other activities under the Heritable Disorders Program, and (4) providing recommendations, advice, or information on a variety of policies that affect the Secretary's ability to reduce the mortality or morbidity from heritable disorders in newborns and children. The ACHDNC process for developing recommendations is designed to be streamlined, consistent throughout the review process, transparent and evidenced based.

1. Technical Recommendations

The Committee's considers three broad areas when recommending disorders to screen infants and children: the condition (incidence, significance, etc); the screening test (analytical and clinical validity, etc); and the treatment (efficacy, effectiveness). The committee provides technical analysis as outlined in Section 1111(b) (3 and 4) of the Public Health Service Act (42 U.S.C. 300b-10 as amended in the Newborn Screening Saves Lives Act of 2008).

- Step 1: Submission of a completed nomination form (Appendix A) to the Executive Secretary for an administrative review prior to evaluation by the ACHDNC.
- Step 2: Administrative review by the DFO/Executive Secretary to determine the completeness of the form. If the form is complete, the nomination form is sent to the internal review workgroup of the ACHDNC.
- Step 3: Internal review by the Nomination and Prioritization Workgroup. If the nominated disorder is found to have sufficient evidence for each of the three components identified above (condition, test, and treatment); the nominated condition will be assigned to the external workgroup for an evidence-based review.
- Step 4: External Review Workgroup completes a systematic evidence review (SER) report and submits it to the Committee for further evaluation and recommendation.
- Step 5: The Committee reviews the SER report using the questions outlined in the analytic framework of the Process for the Evaluation of the External Review of Evidence on Conditions Nominated for Universal Newborn Screening (Appendix B). Additional factors may also be weighed, such as expert opinions and ethical, legal and public health issues.
- Step 6: The Committee will make a specific recommendation regarding the outcome of the nomination. The Decision Protocol (Attachment C) will be used to decide one of the following recommendations: addition to the current core panel of screened conditions; a requirement for more data prior to making a recommendation; or rejection.
- Step 7: The Committee presents its recommendations to the Secretary of HHS. The ACHDNC recommendations should be accompanied by:
 - Summary of evidence and strength of recommendation(s)
 - Recommendation(s) of other Groups
 - Discussion of rationale for ACHDNC recommendation(s), that will explicitly state the basis upon which the recommendations were made, i.e., a sufficient body of evidence based on results of controlled trials, observational studies, case series,

expert opinion, focus groups, cost-effectiveness analysis, policy analyses, ethical analysis, and other inputs.

- Recommended subsequent surveillance, research, education, and program evaluation activities (if applicable)

When relevant, recommendations will be developed in formal consultation with other national advisory committees. The committee will update the recommended uniform screening panel, as appropriate, using the decision-matrix (Appendix C) as outlined in Section 1111(b) (4) of the PHS Act (42 U.S.C. 300b-10 as amended in the Newborn Screening Saves Lives Act of 2008).

2. ACHDNC Recommendations for the Heritable Disorders Program

The Committee is authorized (Section 1111 (b) (1,2 & 5) of the PHS Act, 42 U.S.C. 300b-10, as amended in the Newborn Screening Saves Lives Act of 2008) to provide the following in relation to the grants and other activities performed by the Heritable Disorders Program (HDP):

- provide advice and recommendations to the Secretary concerning HDP grants and projects
- provide technical information to the Secretary for the development of policies and priorities for the administration of HDP grants
- consider ways to ensure that all States attain the capacity to screen for the conditions of the recommended uniform screening panel and include in such consideration the results of grant funding of the HDP.

3. Policy Analysis

Many of the issues addressed by the Committee are not technical but policy in nature. In such cases, a simple but formal policy analysis should be considered and may be requested and/or performed by the ACHDNC. Section 1111 (b) (6) of the Public Health Service (PHS) Act, 42 U.S.C. 300b-10, as amended in the Newborn Screening Saves Lives Act of 2008) provides a list of potential issues.

K. Publication of Recommendations

ACHDNC recommendations are published on the Committee web site. Occasionally, ACHDNC recommendations are also reprinted in other publications.

L. Implementation and Evaluation of the Recommendations

Implementation and evaluation of the impact of the recommendations is the responsibility of the relevant HHS program, and not the ACHDNC. However, HHS programs will develop an implementation and evaluation plan for each set of recommendations and periodically report information relevant to the implementation and evaluation activities to the ACHDNC, and others who may be involved in implementing the recommendation (e.g., State public health agencies, organizations and institutions, health care payers, private practitioners, etc.).

Attachment A: Nomination Form

NEWBORN SCREENING UNIFORM PANEL							
NOMINATION FORM FOR PROPOSED CONDITION							
Name of Proponent		<i>(Organization, if relevant)</i>			Date		
Condition							
Type of Disorder							
Screening Method							
Treatment strategy							
CONDITION	Comment	Gene		Locus		OMIM or other names for disorder	
Incidence	(Determined by what method(s): pilot screening or clinical identification?)						
Timing of clinical onset	(Relevance of the timing of newborn screening to onset of clinical manifestations)						
Severity of disease	(Morbidity, disability, mortality, what spectrum of severity)						
TEST	Comment						
Screening test(s) to be used	(High volume method, platform)						
Modality of screening	(Dried blood spot, physical or physiologic assessment, other)						
Clinical validation	(Location, duration, size, preliminary results of past/ongoing pilot study for clinical validation)						
Laboratory performance metrics	(Sensitivity, specificity, detection rate, positive predictive value, false positive rate)						
Confirmatory testing	(Reliability, availability)						
Risks	(False positives, carrier detection, invasiveness of method, other. Detection or suggestion of other disorders)						

NOMINATION OF CONDITION (page 2)

TREATMENT	Comment
Modality	(Drug(s), diet, replacement therapy, transplant, other)
Urgency	(How soon after birth treatment needs to be initiated to be effective)
Efficacy (Benefits)	(Extent of prevention of mortality, morbidity, disability. Treatment limitations, such as difficulty with acceptance or compliance.)
Availability	(Any limits of availability)
Risks	(Potential medical or other ill effects from treatment)

1		<p align="center">Submit Nominations to: Michele A. Lloyd-Puryear, M.D., Ph.D. Chief, Genetics Services Branch Division of Services for Children with Special Health Needs Maternal and Child Health Bureau 5600 Fishers Lane, Room 19-A-19 Rockville, MD 20857 301-443-8604 –fax 301-443-1080 - phone</p>						
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8		<p align="center">Submission Check list</p> <table border="1"> <tr> <td></td> <td>Cover letter by proponent</td> </tr> <tr> <td></td> <td>Nomination form</td> </tr> <tr> <td></td> <td>Copy of references listed on this form</td> </tr> </table> <p align="center">Contact information (proponent)</p>		Cover letter by proponent		Nomination form		Copy of references listed on this form
	Cover letter by proponent							
	Nomination form							
	Copy of references listed on this form							
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10		13						
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**REFERENCES
(continued)**

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Attachment B: Authorizing Legislation

TITLE XXVI—SCREENING FOR HERITABLE DISORDERS

SEC. 2601. PROGRAM TO IMPROVE THE ABILITY OF STATES TO PROVIDE NEWBORN AND CHILD SCREENING FOR HERITABLE DISORDERS.

Part A of title XI of the Public Health Service Act, as amended by section 2301 of this Act, is amended by adding at the end the following:

“SEC. 1109. IMPROVED NEWBORN AND CHILD SCREENING FOR HERITABLE DISORDERS.

“(a) IN GENERAL.—The Secretary shall award grants to eligible entities to enhance, improve or expand the ability of State and local public health agencies to provide screening, counseling or health care services to newborns and children having or at risk for heritable disorders.

“(b) USE OF FUNDS.—Amounts provided under a grant awarded under subsection (a) shall be used to—

“(1) establish, expand, or improve systems or programs to provide screening, counseling, testing or specialty services for newborns and children at risk for heritable disorders;

“(2) establish, expand, or improve programs or services to reduce mortality or morbidity from heritable disorders;

“(3) establish, expand, or improve systems or programs to provide information and counseling on available therapies for newborns and children with heritable disorders;

“(4) improve the access of medically underserved populations to screening, counseling, testing and specialty services for newborns and children having or at risk for heritable disorders; or

“(5) conduct such other activities as may be necessary to enable newborns and children having or at risk for heritable disorders to receive screening, counseling, testing or specialty services, regardless of income, race, color, religion, sex, national origin, age, or disability.

“(c) ELIGIBLE ENTITIES.—To be eligible to receive a grant under subsection (a) an entity shall—

“(1) be a State or political subdivision of a State, or a consortium of two or more States or political subdivisions of States; and

“(2) prepare and submit to the Secretary an application that includes—

“(A) a plan to use amounts awarded under the grant to meet specific health status goals and objectives relative to heritable disorders, including attention to needs of medically underserved populations;

“(B) a plan for the collection of outcome data or other methods of evaluating the degree to which amounts awarded under this grant will be used to achieve the goals and objectives identified under subparagraph (A);

“(C) a plan for monitoring and ensuring the quality of services provided under the grant;

“(D) an assurance that amounts awarded under the grant will be used only to implement the approved plan for the State;

“(E) an assurance that the provision of services under the plan is coordinated with services provided under programs implemented in the State under title V, XVIII, XIX, XX, or XXI of the Social Security Act (subject to Federal regulations applicable to such programs) so that the coverage of services under such titles is not substantially diminished by the use of granted funds; and

“(F) such other information determined by the Secretary to be necessary.

“(d) LIMITATION.—An eligible entity may not use amounts received under this section to—

“(1) provide cash payments to or on behalf of affected individuals;

“(2) provide inpatient services;

“(3) purchase land or make capital improvements to property; or

“(4) provide for proprietary research or training.

“(e) VOLUNTARY PARTICIPATION.—The participation by any individual in any program or portion thereof established or operated with funds received under this section shall be wholly voluntary and shall not be a prerequisite to eligibility for or receipt of any other service or assistance from, or to participation in, another Federal or State program.

“(f) SUPPLEMENT NOT SUPPLANT.—Funds appropriated under this section shall be used to supplement and not supplant other Federal, State, and local public funds provided for activities of the type described in this section.

“(g) PUBLICATION.—

“(1) IN GENERAL.—An application submitted under subsection (c)(2) shall be made public by the State in such a manner as to facilitate comment from any person, including through hearings and other methods used to facilitate comments from the public.

“(2) COMMENTS.—Comments received by the State after the publication described in paragraph (1) shall be addressed in the application submitted under subsection (c)(2).

“(h) TECHNICAL ASSISTANCE.—The Secretary shall provide to entities receiving grants under subsection (a) such technical assistance as may be necessary to ensure the quality of programs conducted under this section.

“(i) AUTHORIZATION OF APPROPRIATIONS.—There are authorized to be appropriated to carry out this section such sums as may be necessary for each of the fiscal years 2001 through 2005.

“SEC. 1110. EVALUATING THE EFFECTIVENESS OF NEWBORN AND CHILD SCREENING PROGRAMS.

“(a) IN GENERAL.—The Secretary shall award grants to eligible entities to provide for the conduct of demonstration programs to evaluate the effectiveness of screening, counseling or health care services in reducing the morbidity and mortality caused by heritable disorders in newborns and children.

“(b) DEMONSTRATION PROGRAMS.—A demonstration program conducted under a grant under this section shall be designed to evaluate and assess, within the jurisdiction of the entity receiving such grant—

“(1) the effectiveness of screening, counseling, testing or specialty services for newborns and children at risk for heritable disorders in reducing the morbidity and mortality associated with such disorders;

“(2) the effectiveness of screening, counseling, testing or specialty services in accurately and reliably diagnosing heritable disorders in newborns and children; or

“(3) the availability of screening, counseling, testing or specialty services for newborns and children at risk for heritable disorders.

“(c) ELIGIBLE ENTITIES.—To be eligible to receive a grant under subsection (a) an entity shall be a State or political subdivision of a State, or a consortium of two or more States or political subdivisions of States.

“SEC. 1111. ADVISORY COMMITTEE ON HERITABLE DISORDERS IN NEWBORNS AND CHILDREN.

“(a) ESTABLISHMENT.—The Secretary shall establish an advisory committee to be known as the ‘Advisory Committee on Heritable Disorders in Newborns and Children’ (referred to in this section as the ‘Advisory Committee’).

“(b) DUTIES.—The Advisory Committee shall—

“(1) provide advice and recommendations to the Secretary concerning grants and projects awarded or funded under section 1109;

“(2) provide technical information to the Secretary for the development of policies and priorities for the administration of grants under section 1109; and

“(3) provide such recommendations, advice or information as may be necessary to enhance, expand or improve the ability of the Secretary to reduce the mortality or morbidity from heritable disorders.

“(c) MEMBERSHIP.—

“(1) IN GENERAL.—The Secretary shall appoint not to exceed 15 members to the Advisory Committee. In appointing such members, the Secretary shall ensure that the total membership of the Advisory Committee is an odd number.

“(2) REQUIRED MEMBERS.—The Secretary shall appoint to the Advisory Committee under paragraph (1)—

“(A) the Administrator of the Health Resources and Services Administration;

“(B) the Director of the Centers for Disease Control and Prevention;

“(C) the Director of the National Institutes of Health;

“(D) the Director of the Agency for Healthcare Research and Quality;

“(E) medical, technical, or scientific professionals with special expertise in heritable disorders, or in providing screening, counseling, testing or specialty services for newborns and children at risk for heritable disorders;

“(F) members of the public having special expertise about or concern with heritable disorders; and

“(G) representatives from such Federal agencies, public health constituencies, and medical professional societies as determined to be necessary by the Secretary, to fulfill the duties of the Advisory Committee, as established under subsection (b).”

**One Hundred Tenth Congress
of the
United States of America**

AT THE SECOND SESSION

Begun and held at the City of Washington on Thursday,
the third day of January, two thousand and eight

An Act

To amend the Public Health Service Act to establish grant programs to provide for education and outreach on newborn screening and coordinated followup care once newborn screening has been conducted, to reauthorize programs under part A of title XI of such Act, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the “Newborn Screening Saves Lives Act of 2007”.

SEC. 2. IMPROVED NEWBORN AND CHILD SCREENING FOR HERITABLE DISORDER.

Section 1109 of the Public Health Service Act (42 U.S.C. 300b–8) is amended—

(1) by striking subsections (a), (b), and (c) and inserting the following:

“(a) **AUTHORIZATION OF GRANT PROGRAM.**—From amounts appropriated under subsection (j), the Secretary, acting through the Administrator of the Health Resources and Services Administration (referred to in this section as the ‘Administrator’) and in consultation with the Advisory Committee on Heritable Disorders in Newborns and Children (referred to in this section as the ‘Advisory Committee’), shall award grants to eligible entities to enable such entities—

“(1) to enhance, improve or expand the ability of State and local public health agencies to provide screening, counseling, or health care services to newborns and children having

or at risk for heritable disorders;

“(2) to assist in providing health care professionals and newborn screening laboratory personnel with education in newborn screening and training in relevant and new technologies in newborn screening and congenital, genetic, and metabolic disorders;

“(3) to develop and deliver educational programs (at appropriate literacy levels) about newborn screening counseling, testing, follow-up, treatment, and specialty services to parents, families, and patient advocacy and support groups; and

“(4) to establish, maintain, and operate a system to assess and coordinate treatment relating to congenital, genetic, and metabolic disorders.

“(b) **ELIGIBLE ENTITY.**—In this section, the term ‘eligible entity’ means—

“(1) a State or a political subdivision of a State;

“(2) a consortium of 2 or more States or political subdivisions of States;

“(3) a territory;

“(4) a health facility or program operated by or pursuant to a contract with or grant from

the Indian Health Service; or

“(5) any other entity with appropriate expertise in newborn screening, as determined by the Secretary.

“(c) APPROVAL FACTORS.—An application submitted for a grant under subsection (a)(1) shall not be approved by the Secretary unless the application contains assurances that the eligible entity has adopted and implemented, is in the process of adopting and implementing, or will use amounts received under such grant to adopt and implement the guidelines and recommendations of the Advisory Committee that are adopted by the Secretary and in effect at the time the grant is awarded or renewed under this section, which shall include the screening of each newborn for the heritable disorders recommended by the Advisory Committee and adopted by the Secretary.”;

(2) by redesignating subsections (d) through (i) as subsections (e) through (j), respectively;

(3) by inserting after subsection (c), the following:

“(d) COORDINATION.—The Secretary shall take all necessary steps to coordinate programs funded with grants received under this section and to coordinate with existing newborn screening activities.”; and

(4) by striking subsection (j) (as so redesignated) and inserting the following:

“(j) AUTHORIZATION OF APPROPRIATIONS.—There is authorized to be appropriated—

“(1) to provide grants for the purpose of carrying activities under section (a)(1), \$15,000,000 for fiscal year 2008; \$15,187,500 for fiscal year 2009, \$15,375,000 for fiscal year 2010, \$15,562,500 for fiscal year 2011, and \$15,750,000 for fiscal year 2012; and

“(2) to provide grant for the purpose of carrying out activities under paragraphs (2), (3), and (4) of subsection (a), \$15,000,000 for fiscal year 2008, \$15,187,500 for fiscal year 2009, \$15,375,000 for fiscal year 2010, \$15,562,500 for fiscal year 2011, and \$15,750,000 for fiscal year 2012.”.

SEC. 3. EVALUATING THE EFFECTIVENESS OF NEWBORN AND CHILD SCREENING PROGRAMS.

Section 1110 of the Public Health Service Act (42 U.S.C. 300b–9) is amended by adding at the end the following:

“(d) AUTHORIZATION OF APPROPRIATIONS.—There are authorized to be appropriated to carry out this section \$5,000,000 for fiscal year 2008, \$5,062,500 for fiscal year 2009, \$5,125,000 for fiscal year 2010, \$5,187,500 for fiscal year 2011, and \$5,250,000 for fiscal year 2012.”.

SEC. 4. ADVISORY COMMITTEE ON HERITABLE DISORDERS IN NEWBORNS AND CHILDREN.

Section 1111 of the Public Health Service Act (42 U.S.C. 300b–10) is amended—

(1) in subsection (b)—

(A) by redesignating paragraph (3) as paragraph (6);

(B) in paragraph (2), by striking “and” after the semicolon;

(C) by inserting after paragraph (2) the following:

“(3) make systematic evidence-based and peer-reviewed recommendations that include the heritable disorders that have the potential to significantly impact public health for

which all newborns should be screened, including secondary conditions that may be identified as a result of the laboratory methods used for screening;

“(4) develop a model decision-matrix for newborn screening expansion, including an evaluation of the potential public health impact of such expansion, and periodically update the recommended uniform screening panel, as appropriate, based on such decision-matrix;

“(5) consider ways to ensure that all States attain the capacity to screen for the conditions described in paragraph (3), and include in such consideration the results of grant funding under section 1109; and”;

(D) in paragraph (6) (as so redesignated by subparagraph (A)), by striking the period at the end and inserting “, which may include recommendations, advice, or information dealing with—

“(A) follow-up activities, including those necessary to achieve rapid diagnosis in the short-term, and those that ascertain long-term case management outcomes and appropriate access to related services;

“(B) implementation, monitoring, and evaluation of newborn screening activities, including diagnosis, screening, follow-up, and treatment activities;

“(C) diagnostic and other technology used in screening;

“(D) the availability and reporting of testing for conditions for which there is no existing treatment;

“(E) conditions not included in the recommended uniform screening panel that are treatable with Food and Drug Administration-approved products or other safe and effective treatments, as determined by scientific evidence and peer review;

“(F) minimum standards and related policies and procedures used by State newborn screening programs, such as language and terminology used by State newborn screening programs to include standardization of case definitions and names of disorders for which newborn screening tests are performed;

“(G) quality assurance, oversight, and evaluation of State newborn screening programs, including ensuring that tests and technologies used by each State meet established

standards for detecting and reporting positive screening results;

“(H) public and provider awareness and education;

“(I) the cost and effectiveness of newborn screening and medical evaluation systems and intervention programs conducted by State-based programs;

“(J) identification of the causes of, public health impacts of, and risk factors for heritable disorders; and

“(K) coordination of surveillance activities, including standardized data collection and reporting, harmonization of laboratory definitions for heritable disorders and testing

results, and confirmatory testing and verification of positive results, in order to assess and enhance monitoring of newborn diseases.”; and

(2) in subsection (c) (2)—

(A) by redesignating subparagraphs (E), (F) and (G) as subparagraphs (F), (H), and (I);

(B) by inserting after subparagraph (D) the following:

“(E) the Commissioner of the Food and Drug Administration;”;

(C) by inserting after subparagraph (F), as so redesignated, the following:

“(G) individuals with expertise in ethics and infectious diseases who

have worked and published material in the area of newborn screening;”;
and

(3) by adding at the end the following:

“(d) DECISION ON RECOMMENDATIONS.—

“(1) IN GENERAL.—Not later than 180 days after the Advisory Committee issues a recommendation pursuant to this section, the Secretary shall adopt or reject such recommendation.

“(2) PENDING RECOMMENDATIONS.—The Secretary shall adopt or reject any recommendation issued by the Advisory Committee that is pending on the date of enactment of the Newborn Screening Saves Lives Act of 2007 by not later than 180 days after the date of enactment of such Act.

“(3) DETERMINATIONS TO BE MADE PUBLIC.—The Secretary shall publicize any determination on adopting or rejecting a recommendation of the Advisory Committee pursuant to this subsection, including the justification for the determination.

“(e) ANNUAL REPORT.—Not later than 3 years after the date of enactment of the Newborn Screening Saves Lives Act of 2007, and each fiscal year thereafter, the Advisory Committee shall—

“(1) publish a report on peer-reviewed newborn screening guidelines, including follow-up and treatment, in the United States;

“(2) submit such report to the appropriate committees of Congress, the Secretary, the Interagency Coordinating Committee established under Section 1114, and the State departments of health; and

“(3) disseminate such report on as wide a basis as practicable, including through posting on the internet clearinghouse established under section 1112.

“(f) CONTINUATION OF OPERATION OF COMMITTEE.—Notwithstanding section 14 of the Federal Advisory Committee Act (5 U.S.C. App.), the Advisory Committee shall continue to operate during the 5-year period beginning on the date of enactment of the Newborn Screening Saves Lives Act of 2007.

“(g) AUTHORIZATION OF APPROPRIATIONS.—There are authorized to be appropriated to carry out this section, \$1,000,000 for fiscal year 2008, \$1,012,500 for fiscal year 2009, \$1,025,000 for fiscal year 2010, \$1,037,500 for fiscal year 2011, and \$1,050,000 for fiscal year 2012.”.

SEC. 5. INFORMATION CLEARINGHOUSE.

Part A of title XI of the Public Health Service Act (42 U.S.C. 300b–1 et seq.) is amended by adding at the end the following:

‘SEC. 1112. CLEARINGHOUSE OF NEWBORN SCREENING INFORMATION.

“(a) IN GENERAL.—The Secretary, acting through the Administrator of the Health Resources and Services Administration (referred to in this part as the ‘Administrator’), in consultation with the Director of the Centers for Disease Control and Prevention and the Director of the National Institutes of Health, shall establish and maintain a central clearinghouse of current educational and family support and services information, materials, resources, research, and data on newborn screening to—

“(1) enable parents and family members of newborns, health professionals, industry representatives, and other members of the public to increase their awareness, knowledge, and understanding of newborn screening;

“(2) increase awareness, knowledge, and understanding of newborn diseases and screening services for expectant individuals and families; and

“(3) maintain current data on quality indicators to measure performance of newborn screening, such as false-positive rates and other quality indicators as determined by the Advisory Committee under section 1111.

“(b) INTERNET AVAILABILITY.—The Secretary, acting through the Administrator, shall ensure that the clearinghouse described under subsection (a)—

“(1) is available on the Internet;

“(2) includes an interactive forum;

“(3) is updated on a regular basis, but not less than quarterly; and

“(4) provides—

“(A) links to Government-sponsored, non-profit, and other Internet websites of laboratories that have demonstrated expertise in newborn screening that supply research-based information on newborn screening tests currently available throughout the United States;

“(B) information about newborn conditions and screening services available in each State from laboratories certified under subpart 2 of part F of title III, including

information about supplemental screening that is available but not required, in the State where the infant is born;

“(C) current research on both treatable and not-yet treatable conditions for which newborn screening tests are available;

“(D) the availability of Federal funding for newborn and child screening for heritable disorders including grants authorized under the Newborn Screening Saves Lives Act of 2007; and

“(E) other relevant information as determined appropriate by the Secretary.

“(c) NONDUPLICATION.—In developing the clearinghouse under this section, the Secretary shall ensure that such clearinghouse minimizes duplication and supplements, not supplants, existing information sharing efforts.

“(d) AUTHORIZATION OF APPROPRIATIONS.—There are authorized to be appropriated to carry out this section, \$2,500,000 for fiscal year 2008, \$2,531,250 for fiscal year 2009, \$2,562,500 for fiscal year 2010, \$2,593,750 for fiscal year 2011, and \$2,625,000 for fiscal year 2012.”

SEC. 6. LABORATORY QUALITY AND SURVEILLANCE.

Part A of title XI of the Public Health Service Act (42 U.S.C. 300b–1 et seq.), as amended by section 5, is further amended by adding at the end the following:

“SEC. 1113. LABORATORY QUALITY.

“(a) IN GENERAL.—The Secretary, acting through the Director of the Centers for Disease Control and Prevention and in consultation with the Advisory Committee on Heritable Disorders in Newborns and Children established under section 1111, shall provide for—

“(1) quality assurance for laboratories involved in screening newborns and children for heritable disorders, including quality assurance for newborn-screening tests, performance evaluation services, and technical assistance and technology transfer to newborn screening laboratories to ensure analytic validity and utility of screening tests; and

“(2) appropriate quality control and other performance test materials to evaluate the performance of new screening tools.

“(b) AUTHORIZATION OF APPROPRIATIONS.—For the purpose of carrying out this section, there are authorized to be appropriated \$5,000,000 for fiscal year 2008, \$5,062,500 for fiscal year 2009, \$5,125,000 for fiscal year 2010, \$5,187,500 for fiscal year 2011, and \$5,250,000 for fiscal year 2012.

“SEC. 1114. INTERAGENCY COORDINATING COMMITTEE ON NEWBORN AND CHILD SCREENING.

“(a) PURPOSE.—It is the purpose of this section to—

“(1) assess existing activities and infrastructure, including activities on birth defects and developmental disabilities authorized under section 317C, in order to make recommendations for programs to collect, analyze, and make available data on the heritable disorders recommended by the Advisory Committee on Heritable Disorders in Newborns and Children under section 1111, including data on the incidence and prevalence of, as well as poor health outcomes resulting from, such disorders; and

“(2) make recommendations for the establishment of regional centers for the conduct of applied epidemiological research on effective interventions to promote the prevention of poor health outcomes resulting from such disorders as well as providing information and education to the public on such effective interventions.

“(b) ESTABLISHMENT.—The Secretary shall establish an Interagency Coordinating Committee on Newborn and Child Screening (referred to in this section as the ‘Interagency Coordinating Committee’) to carry out the purpose of this section.

“(c) COMPOSITION.—The Interagency Coordinating Committee shall be composed of the Director of the Centers for Disease Control and Prevention, the Administrator, the Director of the Agency for Healthcare Research and Quality, and the Director of the National Institutes of Health, or their designees.

“(d) ACTIVITIES.—The Interagency Coordinating Committee shall—

“(1) report to the Secretary and the appropriate committees of Congress on its recommendations related to the purpose described in subsection (a); and

“(2) carry out other activities determined appropriate by the Secretary.

“(e) AUTHORIZATION OF APPROPRIATIONS.—For the purpose of carrying out this section, there are authorized to be appropriated \$1,000,000 for fiscal year 2008, \$1,012,500 for fiscal year 2009, \$1,025,000 for fiscal year 2010, \$1,037,500 for fiscal year 2011, and \$1,050,000 for fiscal year 2012.”.

SEC. 7. CONTINGENCY PLANNING.

Part A of title XI of the Public Health Service Act (42 U.S.C. 300b–1 et seq.), as amended by section 6, is further amended by adding at the end the following:

“SEC. 1115. NATIONAL CONTINGENCY PLAN FOR NEWBORN SCREENING.

“(a) IN GENERAL.—Not later than 180 days after the date of enactment of this section, the Secretary, acting through the Director of the Centers for Disease Control and Prevention and in consultation with the Administrator and State departments of health (or related agencies), shall develop a national contingency plan for newborn screening for use by a State, region, or consortia of States in the event of a public health emergency.

“(b) CONTENTS.—The contingency plan developed under subsection (a) shall include a plan for—

- “(1) the collection and transport of specimens;
- “(2) the shipment of specimens to State newborn screening laboratories;
- “(3) the processing of specimens;
- “(4) the reporting of screening results to physicians and families;
- “(5) the diagnostic confirmation of positive screening results;
- “(6) ensuring the availability of treatment and management resources;
- “(7) educating families about newborn screening; and
- “(8) carrying out other activities determined appropriate by the Secretary.

“SEC. 1116. HUNTER KELLY RESEARCH PROGRAM.

“(a) NEWBORN SCREENING ACTIVITIES.—

“(1) IN GENERAL.—The Secretary, in conjunction with the Director of the National Institutes of Health and taking into consideration the recommendations of the Advisory Committee, may continue carrying out, coordinating, and expanding research in newborn screening (to be known as ‘Hunter Kelly Newborn Screening Research Program’) including—

- “(A) identifying, developing, and testing the most promising new screening technologies, in order to improve already existing screening tests, increase the specificity of newborn screening, and expand the number of conditions for which screening tests are available;
- “(B) experimental treatments and disease management strategies for additional newborn conditions, and other genetic, metabolic, hormonal and or functional conditions that can be detected through newborn screening for which treatment is not yet available; and
- “(C) other activities that would improve newborn screening, as identified by the Director.

“(2) ADDITIONAL NEWBORN CONDITION.—For purposes of this subsection, the term ‘additional newborn condition’ means any condition that is not one of the core conditions recommended by the Advisory Committee and adopted by the Secretary.

“(b) FUNDING.—In carrying out the research program under this section, the Secretary and the Director shall ensure that entities receiving funding through the program will provide assurances, as practicable, that such entities will work in consultation with the appropriate State departments of health, and, as practicable, focus their research on screening technology not currently performed in the States in which the entities are located, and the conditions on the uniform screening panel (or the standard test existing on the uniform screening panel).

“(c) REPORTS.—The Director is encouraged to include information about the activities carried out under this section in the biennial report required under section 403 of the National Institutes of Health Reform Act of 2006. If such information is included, the Director shall make such information available to be included on the Internet Clearinghouse established under section 1112.

“(d) NONDUPLICATION.—In carrying out programs under this section, the Secretary shall minimize duplication and supplement, not supplant, existing efforts of the type carried out

under this section.

“(e) PEER REVIEW.—Nothing in this section shall be construed to interfere with the scientific peer-review process at the National Institutes of Health.”.

Speaker of the House of Representatives.

*Vice President of the United States and
President of the Senate.*

H. R. 5919

To make technical corrections regarding the Newborn Screening Saves Lives
Act of 2007.

IN THE HOUSE OF REPRESENTATIVES

APRIL 29, 2008

Ms. ROYBAL-ALLARD introduced the following bill; which was referred to the
Committee on Energy and Commerce

A BILL

To make technical corrections regarding the Newborn
Screening Saves Lives Act of 2007.

*Be it enacted by the Senate and House of Representatives of the United States of America in
Congress assembled,*

SECTION 1. TECHNICAL CORRECTION TO NEWBORN SCREENING SAVES LIVES ACT.

(a) AMENDMENTS TO THE PUBLIC HEALTH SERVICE ACT.—

(1) **IMPROVED SCREENING.**—Section 1109 of the Public Health Service Act (42 U.S.C. 300b–8(j)), as added by section 2 of the Newborn Screening Saves Lives Act of 2007, is amended by striking subsection (j) and inserting the following:

“(j) **AUTHORIZATION OF APPROPRIATIONS.**—There are authorized to be appropriated—

“(1) to provide grants for the purpose of carrying out activities under subsection (a)(1), \$15,000,000 for fiscal year 2009; \$15,187,500 for fiscal year 2010, \$15,375,000 for fiscal year 2011, \$15,562,500 for fiscal year 2012, and \$15,750,000 for fiscal year 2013; and “

(2) to provide grants for the purpose of carrying out activities under paragraphs (2), (3), and (4) of subsection (a), \$15,000,000 for fiscal year 2009, \$15,187,500 for fiscal year 2010, \$15,375,000 for fiscal year 2011, \$15,562,500 for fiscal year 2012, and \$15,750,000 for fiscal year 2013.”.

(2) **EVALUATING THE EFFECTIVENESS.**—Section 1110(d) of the Public Health Service Act (42 U.S.C. 300b–9(d)), as added by section 3 of the Newborn Screening Saves Lives Act of 2007, is amended by striking “2008” and all that follows and inserting “2009, \$5,062,500 for fiscal year 2010, \$5,125,000 for fiscal year 2011, \$5,187,500 for fiscal year 2012, and \$5,250,000 for fiscal year 2013.”.

(3) **ADVISORY COMMITTEE.**—Section 1111 of the Public Health Service Act (42 U.S.C. 300b–11), as amended by section 4 of the Newborn Screening Saves Lives Act of 2007, is amended—

- (A) in subsection (d) (2), by striking “2007” and inserting “2008”;
- (B) in subsection (e), by striking “2007” and inserting “2008”;
- (C) in subsection (f), by striking “2007” and inserting “2008”;
- (D) in subsection (g), by striking “2008” and all that follows and inserting “2009, \$1,012,500 for fiscal year 2010, \$1,025,000 for fiscal year 2011, \$1,037,500 for fiscal year 2012, and \$1,050,000 for fiscal year 2013.”.

(4) **CLEARINGHOUSE.**—Section 1112 of the Public Health Service Act (as added by section 5 of the Newborn Screening Saves Lives Act of 2007) is amended—

- (A) in subsection (b) (4) (D), by striking “2007” and inserting “2008”; and
- (B) in subsection (d), by striking “2008” and all that follows and inserting “2009, \$2,531,250 for fiscal year 2010, \$2,562,500 for fiscal year 2011, \$2,593,750 for fiscal year 2012, and \$2,625,000 for fiscal year 2013.”.

(5) **LABORATORY QUALITY.**—Section 1113(b) of the Public Health Service Act (as added by section 6 of the Newborn Screening Saves Lives Act of 2007) is amended by striking “2008” and all that follows and inserting “2009, \$5,062,500 for fiscal year 2010, \$5,125,000 for fiscal year 2011, \$5,187,500 for fiscal year 2012, and \$5,250,000 for fiscal year 2013.”.

(6) **INTERAGENCY COORDINATING COMMITTEE.**—Section 1114(e) of the Public Health Service Act (as added by section 6 of the Newborn Screening Saves Lives Act of 2007) is amended by striking “2008” and all that follows and inserting “2009, \$1,012,500 for fiscal year 2010, \$1,025,000 for fiscal year 2011, \$1,037,500 for fiscal year 2012, and \$1,050,000 for fiscal year 2013.”.

(7) **HUNTER KELLY RESEARCH PROGRAM.**—Section 1116(a) (1) (B) of the Public Health Service Act (as added by section 7 of the Newborn Screening Saves Lives Act of 2007) is amended by striking “and or” and inserting “, or”.

(b) **OTHER TECHNICAL AMENDMENTS.**—The Newborn Screening Saves Lives Act of 2007 is amended—

- (1) in section 1, by striking “2007” and inserting “2008”; and
- (2) in section 4(2) (A), by inserting “, respectively” before the semicolon.

Attachment C: Committee Condition Nomination, Review and Decision Process

Process for the Evaluation of the External Review of Evidence on Conditions Nominated for Screening Newborns and Children

Purpose

The Advisory Committee on Heritable Disorders in Newborns and Children (the Advisory Committee) has, among its charges, the responsibility of making evidence-based recommendations regarding important health conditions for which newborns and children should be screened as well as evaluating and updating the Advisory Committee's previously recommended uniform newborn screening panel. The Advisory Committee on Heritable Disorders in Newborns and Children (Committee) was established under Section 1111 of the Public Health Service (PHS) Act, 42 U.S.C. 300b-10, as amended in the Newborn Screening Saves Lives Act of 2008 (Act). The Committee is governed by the provisions of the Federal Advisory Committee Act, as amended (5 U.S.C App.), which sets forth standards for the formation and use of advisory committees.

This document outlines the process for the Advisory Committee evaluation of the Advisory Committee's External Review Workgroup (ERW) evidence review reports, and its process for making subsequent recommendation(s) to the Secretary, United States Department of Health and Human Services (DHHS) regarding screening newborns or children – i.e., inclusion of the condition in the uniform screening panel for newborns or children with specific heritable conditions.

The process outlined in this document builds upon a broad array of methodologies for system evidence reviews (SERs) including approaches put forth by the World Health Organization (1) the National Academies of Science (2) the Council of Regional Genetic Networks (3) the American Academy of Pediatrics Newborn Screening Task Force (4), the ACCE (5), the United States Preventive Services Task Force (6), the Evaluation of Genomic Applications in Practice and Prevention (7) workgroup and the American College of Medical Genetics Newborn Screening Expert Panel (8).

The Advisory Committee has set the following steps to guide its consideration of a condition for screening or the use of a particular technology in screening:

1. A condition is nominated for consideration via a structured nomination process (9), sent to the Executive Secretary for the Advisory Committee via the process outlined on www.hrsa.gov/heritabledisorderscommittee/nominate.htm. The Executive Secretary is empowered to return incomplete nomination forms and packages to the nominators for further information.
2. On receipt of a completed Nomination Package from the Executive Secretary, the Advisory Committee evaluates and votes on whether a nominated condition should move forward for a full evidence review. The Advisory Committee receives advice on this determination from a formal internal workgroup – the Nomination and Prioritization Workgroup - that assesses, based on the nomination form for the condition and its own expertise, whether there is likely to be sufficient information on each of the three major components of a review: the aspects of the condition (incidence, prevalence, significance), the screening test, and treatment.
3. If the Advisory Committee agrees by majority vote that there is sufficient information available for an evidence review, the nominated condition and related nomination form is assigned to the Advisory Committee's External Review Workgroup (ERW) for a SER.

4. The ERW completes the SER and submits a written report to the Advisory Committee for further evaluation and recommendation.
5. The Advisory Committee uses the process outlined in this document to make one of the following recommendations to the Secretary DHHS:
 - inclusion of the condition in the uniform screening panel for newborns or children with heritable conditions;
 - identifying the need for more research before a decision can be made; or
 - recommending that a condition not be included in the uniform screening panel at this time.
6. The Advisory Committee Chair sends a letter of recommendation to the Secretary, DHHS.¹

The purpose of this document is to specify the Advisory Committee’s decision making process in greater detail (Step # 5 above). The document first addresses important considerations regarding the typical bodies of evidence in screening newborns and children for heritable disorders. It then lays out the analytic framework and related key questions that the Advisory Committee will use to evaluate the SER. A section on “weighing the evidence” addresses study design and criteria for evaluating study quality and adequacy of evidence. A final section addresses translating evidence into Advisory Committee recommendations to the Secretary, including the decision matrix that the Advisory Committee has agreed to use. Four appendixes provide more detail on defining analytic validity (Appendix A), ranking the quality of data sources (Appendix B), assessing study quality (Appendix C), and Advisory Committee decision elements (Appendix D).

Important Considerations Regarding Typical Bodies of Evidence for Evaluating Screening for Newborns and Children for Heritable Disorders

In general, the Advisory Committee’s approach requires development of an SER responsive to a set of key questions informed by its own analytic framework. While this approach is similar to those used in other evidence-based recommendation processes, the Advisory Committee recognizes that allowances likely will need to be made for evaluations involving rare disorders. The rapid pace of development in genomics and screening technologies makes it increasingly feasible to identify disorders and the potential for disorders much earlier in life than previously, facilitating the provision of timely, effective treatment, thereby avoiding preventable child morbidity and mortality, as well as painful “diagnostic odysseys”. Compared to highly prevalent and relatively well characterized disorders (e.g., diabetes and certain forms of cancer), in many previously unknown heritable disorders the clinical significance of screening and diagnostic test results, phenotype expression of detected genotypes, the full range of potentially effective medical or other management options, and the harms or other benefits that might be associated with testing and subsequent interventions may not be fully understood. The Advisory Committee recognizes that it is unlikely there will be peer-reviewed, published large scale, controlled trials using rigorous intervention research designs for evaluation of the rare, heritable conditions

¹ Not later than 180 days after the Advisory Committee issues a recommendation pursuant to Section 1111, the Secretary shall adopt or reject such recommendation, and publicize that determination. The Secretary shall adopt or reject any recommendation issued by the Advisory Committee that is pending on the date of enactment of the Newborn Screening Saves Lives Act of 2007 by not later than 180 days after the date of enactment of such Act. The Secretary shall publicize any determination on adopting or rejecting a recommendation of the Advisory Committee pursuant to this subsection, including the justification for the determination.

typically nominated for potential inclusion in a uniform screening panel of disorders. For many if not most disorders, it may be necessary to consider evidence from studies using less robust research designs, such as modest-sized open label clinical studies for evaluating treatment and population-based observational studies, as available, when evaluating conditions or testing technologies. Despite these limitations, the evidence should be adequate to make decisions with clearly described, consistent rationale. In recognition of the limitations of available approaches to SERs and the potential for unintended consequences and costs of implementing new technologies without a sufficient evidence base, the Advisory Committee is taking this opportunity to further develop rigorous review approaches relevant to evaluating evidence and making recommendations for screening of newborns and children with heritable disorders.

Evaluation of the External Review Workgroup report

For the Advisory Committee’s evaluation, three broad areas are considered: the condition (incidence, prevalence, significance); the screening test and diagnostic testing methodology - based on current best available technical approach(es) (clinical utility, analytical and clinical validity); and the treatment (clinical utility, efficacy or effectiveness). Applying the analytic framework in Figure 1 to the SER, the Advisory Committee will evaluate if the current evidence for each of the six key questions is adequate or inadequate. Based on the strength of the evidence and the predicted magnitude of net benefit (benefits minus harms), the Advisory Committee will make a specific recommendation regarding the outcome of the nomination: addition to the current core panel of screened conditions; a requirement for more data prior to making a recommendation; or rejection.

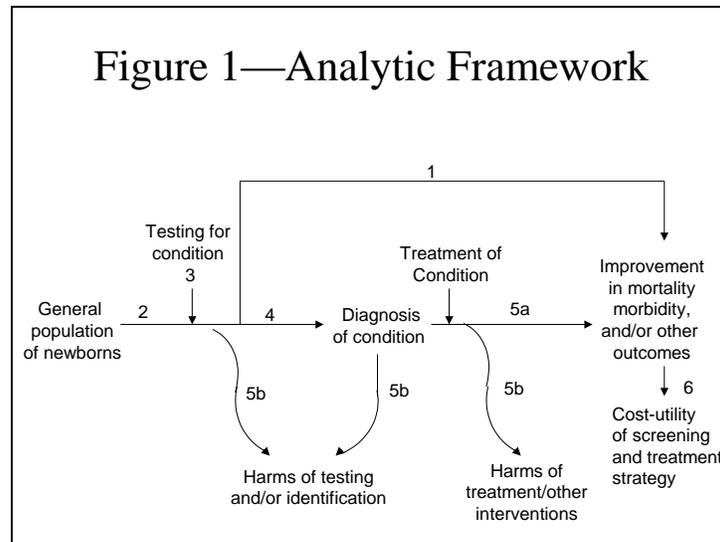


Figure 1: The Analytic Framework depicts the considerations of evidence for population-based screening of newborns for a specific important health condition (or set of conditions). Each number corresponds to a key question which, in total, describes the structured analysis for considering the existing data (modification of figure in references 12, 13).

Key question 1: This is the overarching question for the evidence review: Is there direct evidence that screening for the condition at birth leads to improved outcomes for the infant or child to be screened, or for the child's family?

Outcomes encompass the impact(s) of screening, diagnosis or lack of diagnosis, the prognosis, therapeutic choice or lack of therapy, patient outcomes, and familial and societal issues. Positive patient outcomes are typically measured as reductions in morbidity or mortality, and may extend to aspects such as improved quality of life and patient or family satisfaction with health and related services for the condition.

If adequate direct evidence is available to make a recommendation, there is no need to address the remaining key questions in the analytic framework.

Key question 2: Is there a case definition that can be uniformly and reliably applied? What are the clinical history and the spectrum of disease of the condition, including the impact of recognition and treatment?

Sufficient importance can be judged by considering both incidence of the condition and the severity of its health impact, such that a condition of lower severity can be important due to a high incidence, and a rare condition can be important due to serious health consequences. Understanding the spectrum of disease is essential in considering whether there are cases of the condition for which treatment is not effective or otherwise unwarranted or if the condition is readily clinically identified in a newborn or child without screening.

Key question 3: Is there a screening test or screening test algorithm for the condition with sufficient analytic validity?

Analytic validity refers to the technical accuracy of the laboratory test in measuring the intended analyte(s), as distinguished from clinical validity, which is the test's ability to predict the development of clinical disease. This aspect of evaluation focuses on the laboratory component. Analytic validity is an assessment of the sensitivity and specificity of the testing protocol for detecting a target disorder or set of disorders. Analytic validity includes pre-analytic, analytic, and post-analytic issues [see Appendix A], as well as standardization between different laboratories performing the test. The four specific elements of analytic validity include analytic sensitivity (or the analytic detection rate), analytic specificity, laboratory quality control, and assay robustness. Analytic sensitivity defines how effectively the test identifies specific analytes that are present in a sample. Analytic specificity defines how effectively the test correctly classifies samples that do not have specific analytes. Quality control assesses the procedures for ensuring that results fall within specified limits. Robustness measures how resistant the assay is to changes in pre-analytic and analytic variables.

The Advisory Committee's goal is that testing programs across the country would be able to implement the use of a testing platform with the same level of analytic validity. Laboratory newborn screening suggests that laboratory methodology could achieve a detection rate between 1:2,000 and 1:3,000, a false positive rate (FPR) <0.3% and a positive predictive value (PPV) >20%.

Key question 4: Has the clinical validity of the screening test or screening algorithm, in combination with the diagnostic test or test algorithm, been determined and is that validity adequate?

The clinical validity of a genetic test defines its ability to detect or predict the associated disorder (phenotype). There are two parts to the question of clinical validity:

1. Is the evidence sufficient to conclude that we know what the clinical validity is? This involves only a consideration of the strength and quality (taken together as adequacy) of the evidence in the SER to determine that we know the sensitivity and specificity of the screening and diagnostic testing or testing algorithm, i.e. its ability to positively predict the disorder.
2. Is this level of clinical validity sufficient to justify testing?

This question gauges the ability of the screening test (or test algorithm), when used to identify individuals who merit diagnostic testing, to detect a reasonable number of affected individuals who would be expected to manifest clinical disease, the tradeoff of risks of false positives, and the benefits of early detection of true positives. These issues relate to both performance of the screening and diagnostic tests and the incidence/prevalence of the condition. Consideration must be given to the potential for individuals to test positive but not develop clinical disease: those who screen positive and whose disease is confirmed by diagnostic testing. Issues of trade-offs between false positives, false negatives, and identification of non-clinical conditions also all impact clinical *utility*.

It is possible that evidence on clinical validity will be adequate, while evidence on analytic validity is not available or is otherwise inadequate. It may be acceptable for the Advisory Committee to make a positive recommendation to add the condition to the core set, though issues of dissemination and implementation will need to be carefully considered.

Key question 5: What is the clinical utility of the screening test or screening algorithm?

5a: What are the benefits associated with use of the screening test?

5b: What are the harms associated with screening, diagnosis and treatment?

The clinical utility of a genetic test defines the elements of both *testing* and *treatment* that need to be considered when evaluating the benefits and harms or risks associated with its introduction into routine practice. In considering benefits, the question of clinical utility involves the ability of testing for the condition to translate to improvements in important health outcomes, primarily decreased morbidity and mortality. Broader benefits to the individual infant, such as non-clinical interventions or benefits to family and community, such as avoiding a diagnostic odyssey or informing non-medical decision-making, may also be considered.

The consideration of harms or risks includes evaluating the potential for risks of physical harm associated with testing, identification and/or treatment as well as those harms or risks that are non-physical, such as the possibility for labeling, anxiety, adverse impacts on parent and family relationships, and other ethical, legal and social implications. Risk of physical harm is an aspect inherent to all medical intervention and evaluation requires an implicit assignment of an estimate of the potential morbidity or even mortality to support decisions regarding net benefit of testing and treatment.

Questions to evaluate clinical utility for *testing* include: Does the screening test result, in combination with the diagnostic testing, inform clinical decision making? Can the diagnosis be made in an accurate and timely manner? Does the screening lead to the prevention or amelioration of adverse health outcomes associated with the disorder (assumes the adoption of an accompanying efficacious treatment conditioned on test results)? Have the risks and benefits associated with the

introduction of testing for this condition been identified (again, assuming the adoption of an accompanying efficacious treatment conditioned on test results)? Are quality assurance assessment procedures in place for controlling pre-analytic, analytic, and post-analytic factors that could influence the risks and benefits of testing? Have pilot trials assessed the performance of testing under real-world conditions? Are there practical limits to the use or availability of the screening or diagnostic tests, such as patent or licensing protections or limiting capacity for diagnostics?

When considering *treatment*, the question of clinical utility involves evaluating whether there are treatments available that improve important health outcomes. Health outcomes may encompass the impact(s) of diagnosis or lack of diagnosis, the prognosis, therapeutic choice or lack of therapy, the patient outcome, and familial and societal issues. These outcomes are not of equal weight or value. Assigning value involves balancing the tradeoffs between different favorable and unfavorable outcomes. Other questions regarding treatment include: Does treatment of the condition detected through screening improve important health outcomes when compared with waiting until clinical detection? Are the treatments for affected children standardized, widely available, and if appropriate, FDA approved? Are there subsets of affected children more likely to benefit from treatment that can be identified through testing or clinical findings? It is important to note that treatment may include a broad list of interventions including counseling and support services, beyond the narrow definition of medical therapy.

Both risks and benefits are often incompletely addressed in medical research, yet their consideration is key to enabling the Advisory Committee to balance the potential benefits and harms/risks when making a recommendation regarding screening for a condition.

Key question 6: How cost effective is the screening, diagnosis and treatment for this disorder compared to usual clinical case detection and treatment?

There is little published empiric research on the cost-effectiveness of most health care services, and thus studies involving primary data collection on comprehensive costs or cost effectiveness related to newborn or child screening and treatment would not be expected. Nonetheless, consideration should include available data on the incremental costs for screening, diagnosis and treatment for a disorder, compared to costs for not screening. The approaches used by Carroll and Downs (9) will serve to guide the Advisory Committee's analysis of the impact of cost of screening, diagnosis and treatment for a particular condition.

Weighing the Evidence

Study design

A hierarchical list of study designs that will be used to provide a quality ranking of data sources on treatment of identified conditions is included in Appendix B, while considering the potential limitations in the quality of some of the data sources, as described above ("Important Considerations"). Study design hierarchy is different for questions of analytic validity of screening tests; here the best information comes from collaborative studies using a single large, carefully selected panel of well-characterized control samples that are blindly tested and reported, with the results independently analyzed. Data from proficiency testing schemes can provide information about all three phases of analytic validity (*i.e.*, analytic, pre- and post-analytic) and inter-laboratory variability.

Criteria for evaluating study quality

The assessment of the quality of data includes evaluating the number of reports, the total number of positive and negative controls studied, and the range of methodologies represented (Appendix C). The consistency of findings will be assessed formally (*e.g.*, by testing for homogeneity when possible), or by less formal methods (*e.g.*, providing a central estimate and range of values) when sufficient data are lacking. One or more internally valid studies do not necessarily provide sufficient information to justify routine clinical usage. Support for the screening for a condition or use of a test in routine clinical practice generally requires studies that provide estimates of analytic validity that are generalizable to use in diverse “real world” settings. Also, existing data may support the reliable performance of one methodology, but no data may be available to assess the performance of one or more other methodologies. A list of criteria to assess study quality is in Appendix C.

Evaluating adequacy of evidence

The adequacy of the evidence to answer the key questions can be summarized and classified *across* the questions as adequate or inadequate (using explicit criteria). This is also referred to as assessing the strength of the linkages in the chain of evidence. Adequate evidence would require studies of fair or better quality of at least clinical utility to support a recommendation. Insufficient evidence would include no evidence, studies of poor quality, or studies with conflicting results.

The evidence is examined overall and a decision is made regarding whether the evidence is graded as *Adequate* or *Inadequate* to answer the key question.

- When the quality of evidence is *Adequate*, the observed estimate or effect is likely to be real, rather than explained by flawed study methodology, and the Advisory Committee concludes the results are unlikely to be strongly affected by the results of future studies.
- When the quality of evidence is *Inadequate*, the observed results are more likely to be the result of limitations and/or flaws in study methodology rather than an accurate assessment, and subsequent information is more likely to change the estimate or effect enough to change the conclusion.
- Availability of only marginal quality studies always results in *Inadequate* quality.

Magnitude and Certainty of Net Benefit

Essential factors for the development of a recommendation include the relative importance of the outcomes considered; the health benefits associated testing for the condition and subsequent interventions; if the actual or estimated health benefits are not available from the literature, then the maximum potential benefits; the harms associated with testing for the condition such as adverse clinical outcomes, increase in risk, unintended ethical, legal, and/or social issues that result from testing and subsequent interventions; if the actual or estimated harms are not available from the literature, then the maximum potential harms; and the efficacy and effectiveness of testing for the condition and follow-up compared to current practice, which might even include no specific medical intervention. Benefits and harms may include psychosocial, familial and social outcomes. Simple decision models or outcomes tables might be helpful in assessing the magnitudes of benefits and harms, and in estimating the net effect.

Consistent with the processes of other evidence-based recommendation groups, the magnitude of net benefit (benefit minus harm) can be classified as at least moderate, small, or zero/net harm. For the purposes of the Advisory Committee in making recommendations, moderate or greater net benefit will be considered “significant” and will support a recommendation to add the condition, and zero/harmful net

benefit will support a recommendation to not add the condition. Those conditions where the magnitude of net benefit is classified as small will be discussed on a case-by-case basis and classified as either significant or not significant. A recommendation to add a condition where testing is expected to provide only small net benefit should be supported by a high degree of certainty based on the evidence (see certainty of net benefit below).

Based on the summaries of the evidence for each key question and the evidence chain, the certainty of the conclusions regarding the net benefit can be classified as sufficient or low. A conclusion to either recommend adding or not adding the condition with sufficient certainty has an acceptable risk or level of comfort of “being wrong” and thus a low susceptibility to being overturned or otherwise altered by additional research. Insufficient certainty should not lead to a recommendation for or against adding the condition, but should lead to a recommendation for further research. (Appendix D)

Translating Evidence into Advisory Committee Recommendations

The process is designed to be streamlined, transparent, evidence-based and consistent throughout the review process and across different conditions under consideration. For its technical analyses, the Advisory Committee’s purview explicitly includes children as well as newborns and therefore is relevant to both the screening in the neonatal and pediatric clinical settings. After the evidence-based review is completed, the Advisory Committee will review the report and reached a formal recommendation based on the quality and strength of the data as summarized in the evidence review. Additional factors may also be weighed, such as expert opinions and ethical, legal and public health issues. When relevant, the Advisory Committee will also consult with other federal Advisory Committees when developing their recommendations.

The Advisory Committee recommendations should be accompanied by:

- Summary of evidence and strength of recommendation(s);
- Recommendation(s) of other professional groups;
- Discussion of rationale for Advisory Committee recommendation(s), that will explicitly state the basis upon which the recommendations were made, i.e., a sufficient body of evidence based on results of controlled trials, observational studies, case series, expert opinion, focus groups, cost-effectiveness analysis, policy analyses, ethical analysis, and other inputs; and
- Recommended subsequent surveillance, research, education, and program evaluation activities, if applicable.

The Advisory Committee’s recommendations are intended to provide transparent, authoritative advice. These may also be used to promote specific research to fill in gaps in the evidence for specific conditions. Three elements are considered in making recommendations:

1. The magnitude of net benefit (are the benefits of screening, diagnosis and treatment minus the harms significant?)
2. Overall adequacy of evidence (does the evidence overall meet the standards for having adequate quality?), and
3. Certainty of net benefit/harm (is the Committee sufficiently certain that the research supports a conclusion that benefits exceed harms or not?) (Appendix D).

In addition, there are six critical appraisal questions that should be used to determine adequacy of the evidence for each key question. For adequate evidence to support a conclusion there must be evidence to support most if not all of these questions satisfactorily.

1. Do the studies have the appropriate research design to answer the key question?
2. To what extent are the studies of high quality (internal validity)?

3. To what extent are the studies generalizable to the US population (external validity)?
4. How many studies and how large have been done to answer the key question (precision of the evidence)?
5. How consistent are the studies?
6. Are there additional factors supporting conclusions?

Recommendations will be based on the level of certainty that testing will result in significant net health benefit, based on the evaluation of the evidence. The following matrix (Figure 1) serves to outline the recommendation category.

Table 1. Decision Matrix for Advisory Committee Recommendations

CATEGORY	RECOMMENDATION	LEVEL OF CERTAINTY	MAGNITUDE OF NET BENEFIT
1.	Recommend adding the condition to the core panel	Sufficient	Significant
2.	Recommend not adding the condition to the core panel	Sufficient	Zero or net harm
3.	Recommend not adding the condition, but instead recommend additional studies	Insufficient, but the potential for net benefit is compelling enough to recommend additional studies to evaluate	Potentially significant, and supported by contextual considerations
4.	Recommend not adding the condition now	Insufficient, and additional evidence is needed to make a conclusion about net benefit	Potentially significant or unknown

Category 1: The Committee has sufficient certainty of significant net benefit to recommend adding the condition to the core panel

Category 2: The Committee has sufficient certainty of no net benefit, or of net harm, to recommend not adding the condition to the core panel

Category 3: The evidence is insufficient to make a recommendation.

- However, there is compelling potential for net benefit and the Committee wants to make a strong recommendation for additional studies, such as pilot studies, to fill in the evidence gaps

Category 4: The evidence is insufficient to make a recommendation.

- There is insufficient evidence of potential net benefit to lead the Committee to want to make a strong recommendation regarding pilot studies

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Appendix A: Defining Analytic Validity

Pre-analytic phase: such as sample stability and reagent performance.

Analytic phase: evaluating accuracy (including method comparison), precision (both inter- and intra-assay), recovery, linearity, carry-over (if applicable), detection limits, signal suppression (if applicable, especially for MS/MS), intensity criteria (signal/noise), age and gender matched reference values (if applicable), disease range, and cutoff level defining clinical significance (required for 2nd tier test).

Post-analytic phase: include evaluation of interpretive guidelines, used to define a case, the spectrum of differential diagnoses, and the algorithm for short term follow-up/confirmatory testing (biochemical, in vitro, and/or molecular).

Appendix B: Ranking the Quality of Data Sources

Hierarchy of study designs/data sources, based on generally accepted principles of evidence review

Level 1 – usually yields good quality evidence

- Collaborative study using a large panel of well characterized samples
- Summary data from well-designed external proficiency testing schemes or inter-laboratory comparison programs
- Well-designed longitudinal cohort studies
- Meta-analysis of randomized controlled trials
- Randomized open label clinical studies

Level 2 – usually yields fair quality evidence

- Other data from proficiency testing schemes
- Well-designed peer-reviewed studies (e.g., method comparisons, validation studies) or case-control or cohort studies
- Expert panel reviewed FDA summaries
- A single randomized controlled trial
- Non-randomized open label clinical studies

Level 3 – depending on flaws, may yield fair or poor quality evidence

- Less systematic peer-reviewed studies, case-control studies

Level 4 – usually yields poor quality evidence

- Unpublished and/or non-peer reviewed research, clinical laboratory or manufacturer data
- Studies on performance of the same basic methodology, but used to test for a different target
- Case series

Level 5 – usually yields poor quality evidence

- Consensus guidelines
- Expert Opinion

Appendix C: Assessing Study Quality

1. Clear description of test or disorder/phenotype and outcomes of interest
2. Adequate description of study design and methodology
 - For test evaluation: Specific methods evaluated; Number of positive samples and negative controls tested
 - For clinical validity: clear description of clinical outcomes
 - Was data collection retrospective or prospective
 - Were subjects randomized?
 - Were intervention and evaluation of outcomes blinded?
3. Interventions are clearly identified, scientifically sound and consistently provided.
4. Adequate descriptions of the basis for the 'right answer'
 - Comparison to a 'gold standard' referent test
 - Consensus (*e.g.*, external proficiency testing)
 - Characterized control materials (*e.g.*, NIST*, sequenced)
5. Avoidance of biases
 - Blinded testing and interpretation
 - Specimens represent routinely analyzed clinical specimens in all aspects (*e.g.*, collection, transport, processing)
 - Reporting of test failures and uninterpretable or indeterminate results
6. Analysis of data
 - Is the information provided sufficient to rate the quality of the studies?
 - Are the data relevant to each outcome identified?
 - Is the analysis or modeling explicit and understandable?
 - Are analytic methods pre-specified, adequately described, and appropriate for the study design?
 - Were losses to follow-up and resulting potential for bias accounted for?
 - Is there assessment of other sources of bias and confounding?
 - Are there point estimates of impact with 95% CI?
 - Is the analysis adequate for the proposed use?

Appendix D: Advisory Committee Decision Elements

Certainty of net benefit

There are likely to be conditions where the evidence is inadequate to reach a conclusion and make a recommendation based on at least fair evidence of clinical utility and significant net benefit, but contextual issues support a recommendation to add the condition with a commitment to fill in the gaps in evidence as experience with the test is gained. We recognize that these recommendations do not meet the strict criteria of evidence-based as generally accepted, but are “evidence-informed” or “evidence-supported”. Contextual issues might include things such as known benefits associated with testing (and intervention) for similar conditions, high incidence that would translate to potential substantial net benefit, availability of promising but yet unproven new therapies, or indirect evidence of perhaps lower value health outcomes but with evidence of low potential harm. These conditions will not be recommended at the time of review. Instead, the Advisory Committee will encourage the undertaking - and funding - of one or more specific studies to address key knowledge gaps and/or evaluate specific aspects of case definition, screening and/or treatment for which some uncertainty persists. For example, one or more pilot studies in the U.S. may need to be performed and evaluated prior to the Advisory Committee making any decision about inclusion or exclusion in newborn screening. Conditions for which specific data are needed should be re-evaluated at a time when sufficient new data exist that may be available to fill in the gaps in the evidence chain. The Advisory Committee would expect that these studies would be undertaken in a timely manner. However, the time required to satisfy these knowledge gaps will depend on the incidence of the condition in the populations tested, such as for pilot studies, and/or the practical, technical or other barriers in the targeted research.

Similarly, population-based pilot studies should be developed and implemented in order to answer specific evidence gaps. These pilots must be applicable to heterogeneous U.S. populations. The decision whether to recommend a test provisionally or to refer for pilot studies should be made with careful considerations of the potential harms associated with the premature acceptance of unproven clinical strategies, weighed against the potential but health benefits and potential harms of waiting for more compelling evidence.