Secretary's Advisory Committee on Heritable Disorders in Newborns and Children

May 13, 2009

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Genetic Alliance

Secretary's Advisory Committee on Heritable Disorders in Newborns and Children

Genetic Alliance Webinar
March 18, 2009

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Chair, Secretary's Advisory Committee
On Heritable Disorders in Newborns and Children

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Authorizing Legislation

- **Title XXVI of the Children's Health Act of 2000 (The same act that established the National Children's Study) enacts three sections of the Public Health Service (PHS) Act:**
  - **two grant programs under Sections 1109 and 1110, and**
  - **Established the Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children under Section 1111.**
  - **Committee first met on June 7-8, 2004**
  - **Although Committee charge is broad, to date committee has focused efforts on newborn screening**
  - **The Committee was reauthorized in 2008 and renamed the Advisory Committee on Heritable Disorders in Newborns and Children**

Advisory Committee on Heritable Disorders in Newborns and Children

2. **Advises on a grant program associated with its legislation:**

   "Provide technical information to the Secretary for the development of policies and priorities for the administration of grants under Section 1109 of the PHS Act"; and

2. **Gives technical advice on heritable disorders:**

   "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 in newborns and children from heritable disorders." and the "**appropriate application of universal newborn screening tests, technologies, policies, guidelines and programs** for effectively reducing morbidity and mortality in newborns and children having or at risk for heritable disorders**."**

Advisory Committee on Heritable Disorders in Newborns and Children

- **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;**

- **Members of the public having special expertise about or concern with heritable disorders; and**

- **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**

What is Happening to Drive Such Interest and Expansion in Newborn Screening?

- Newborn screening has always been technologically driven, beginning with the discovery of the ability to screen for phenylalanine elevations using the dried blood spot and the bacterial inhibition assay
- Newborn screening is a public health measure, and as such is operated by the states, which has resulted in enormous variability from state to state to both the numbers and types of conditions for which screening is done
- The development of MS/MS has been the single major force in our expanded ability to detect serious conditions in the newborn infant
- In addition to NBS expansion being driven by developing technology, the extraordinary efforts from advocacy groups has caused a dramatic increase in the numbers of conditions for which screening is performed
- This rapid expansion has created even larger variations among the states in their screening programs

Proportion of US Births Screened for Different Numbers of Conditions (2000-2006)

From AAP and NNSGRC

Year	≤5	5-10	11-20	21-30	≥30
2000	35%	65%	0%	0%	0%
2002	30%	66%	0%	2%	3%
2004	18%	35%	9%	17%	20%
2006	0%	20%	14%	3%	63%

Uniform Screening Panel (2005)

- **29 primary conditions**
  - **20 detected by MS/MS (AA, FAO, OA)**
  - **3 Hb-pathies**
  - **6 others (BIOT, CAH, CF, CH, GAL, HEAR)**
- **25 secondary targets**
  - **22 detected by MS/MS**

Advisory Committee for Heritable Disorders in Newborns and Children

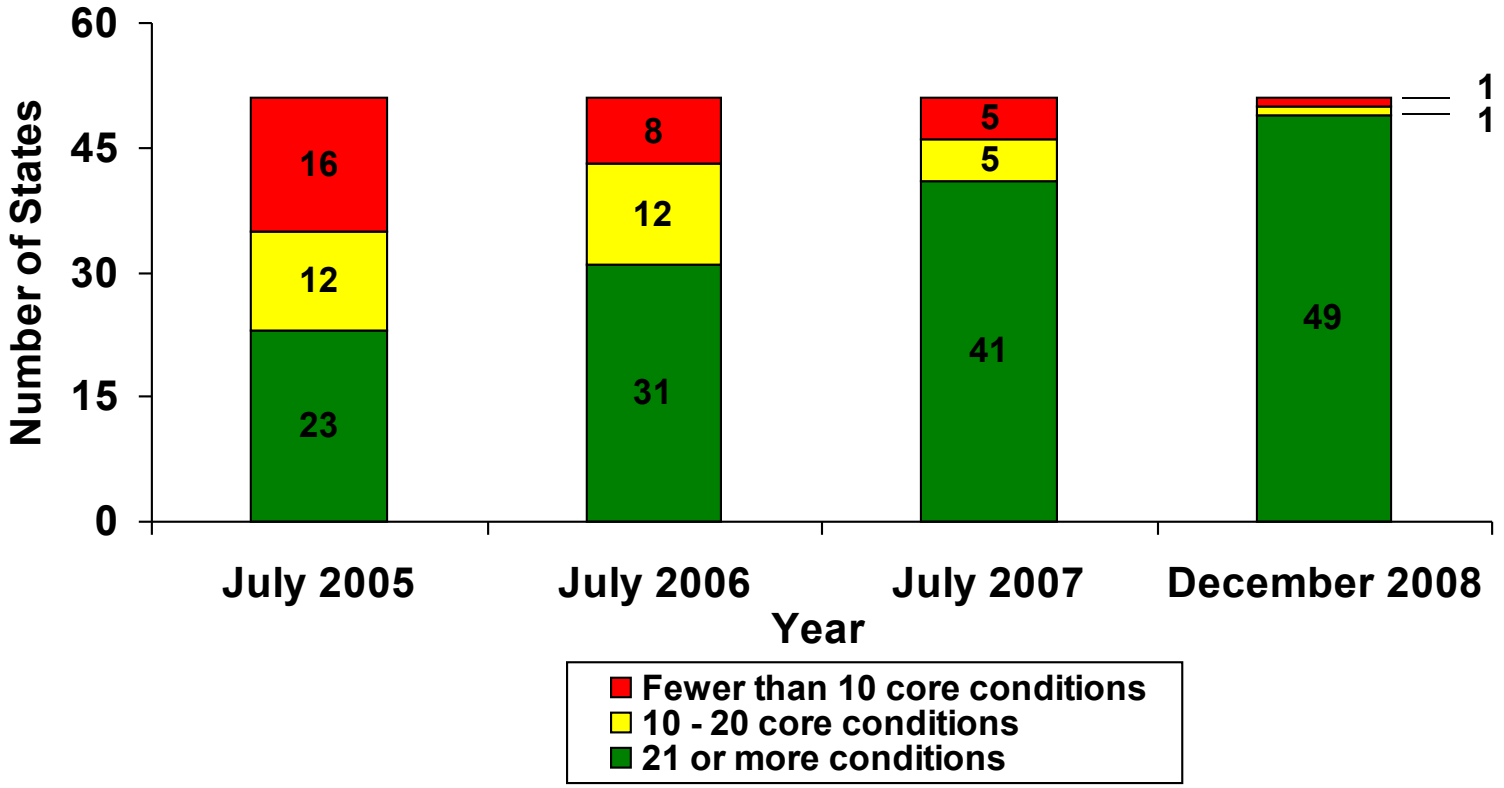
- **The Committee spent a great deal of time reviewing and discussing the HRSA-ACMG Report: Newborn Screening: Toward a Uniform Screening Panel and System**

- **After this extensive review, the Committee unanimously accepted this report and sent a letter to the Secretary of HHS recommending adoption and implementation of this report.**

Advisory Committee on Heritable Disorders in Newborns and Children

- The Committee since its first meeting in June of 2004 has met for 17 sessions
- Extensive discussion and work has been focused on all issues surrounding newborn screening
- The Committee has considered many things surrounding newborn screening and long-term follow up, and has recently sent a letter to the Secretary of HHS recommending solutions to the major problem of medical foods for rare genetic disorders
- The single major focus has been on establishing operating principals, and establishing the plan for
  - Nominating new conditions
  - Establishing the evidence review group for rare screened disorders and the mechanism by which the Committee would hand recommendations of this group

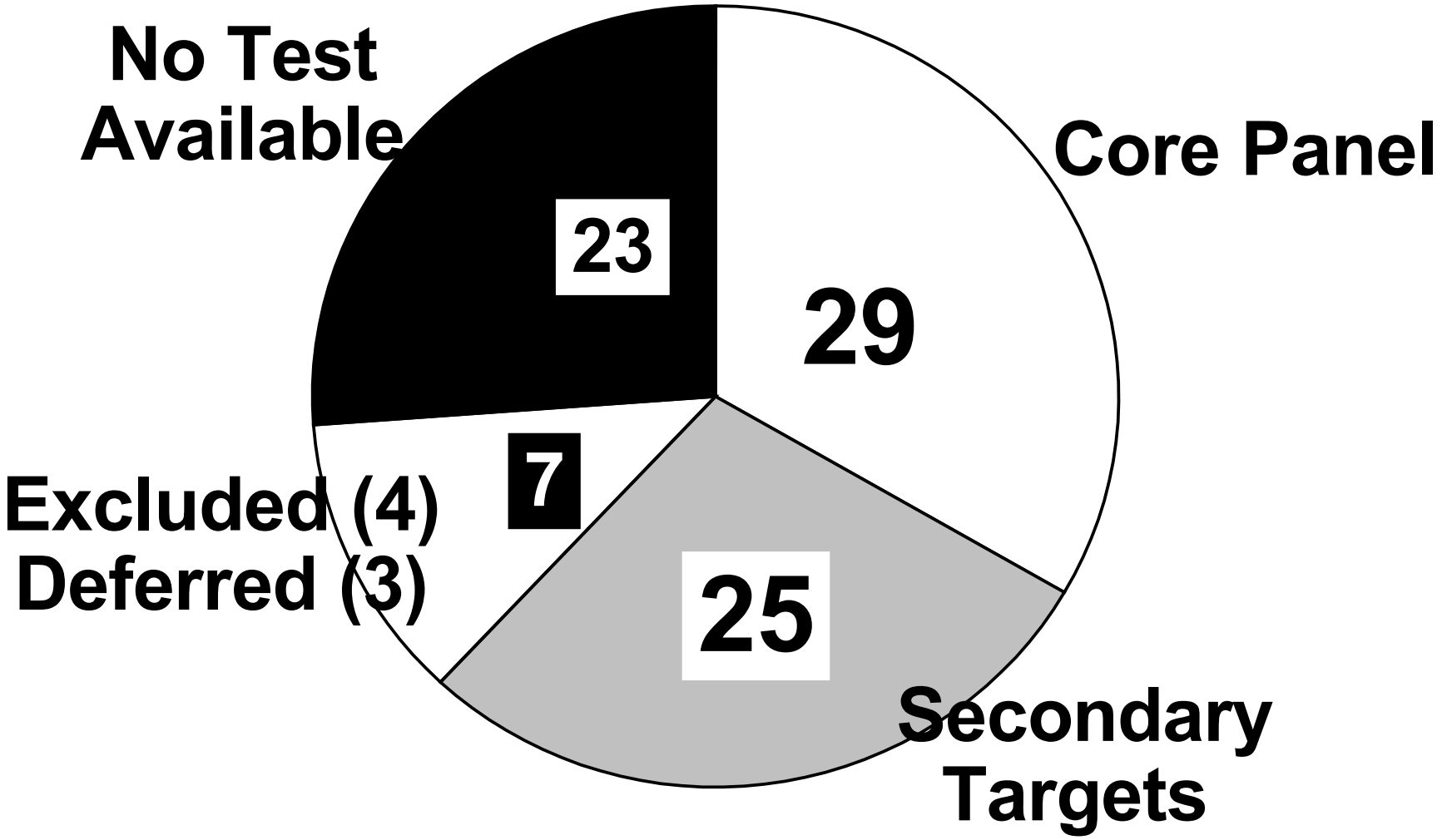
Newborn Screening Tests



Source: March of Dimes. Data reported from NNSGRC.

Challenges and Opportunities for Newborn Screening

- **Enormous expansion of potential targets, and how to prioritize**
- **Multiple technologies, comparability, quality**
- **Poor understanding of clinical significance of screening results, including long term outcomes**
- **Need to integrate findings from multiple risk factors**
- **Scalability and affordability**
- **Variability and complexity of policies**
- **Striking lack of published, peer-reviewed articles on conditions included in newborn screening, and their long-term outcomes**
- **If the test used provides a relatively low positive predictive value, the large numbers of false positives can produce serious issues for the families involved, but increase the work of follow-up enormously**


No Test Available
23
Core Panel
29
Excluded (4)
Deferred (3)
7
25
Secondary Targets

Nomination Process - concepts

- **Broad access to the process**
- **Considered review**
- **Streamlined process**
- **Transparency**
- **Consistent criteria throughout nomination process**
- **Structured Evidence-Based Review through ACHDGDNC external workgroup (Dr. Perrin)**
- **3 main areas for consideration:**

  <u>Condition, Test, Treatment</u>

Nomination Form (ftp://ftp.hrsa.gov/mchb/genetics/NominationForm.doc

NEWBORN SCREENING UNIFORM PANEL NOMINATION FORM FOR PROPOSED CONDITION			
Name of Proponent	*(Organization, if relevant)*	Date	
Condition			
Type of Disorder			
Screening Method			
Treatment strategy			

CONDITION	Comment

Gene		Locus		OMIM or other names for disorder	

*Note: Please reference each statement, listing references below (p.2)

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 adherence.)
Availability	(Any limits of availability)
Risks	(Potential medical or other ill effects from treatment)

KEY REFERENCES (Specific citations – limit to 15)	
1	
2	
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Submission Check list	
	Cover letter by proponent
	Nomination form
	Copy of references listed on this form
	Formal conflict of interest statement by proponent

Submit Nominations to:

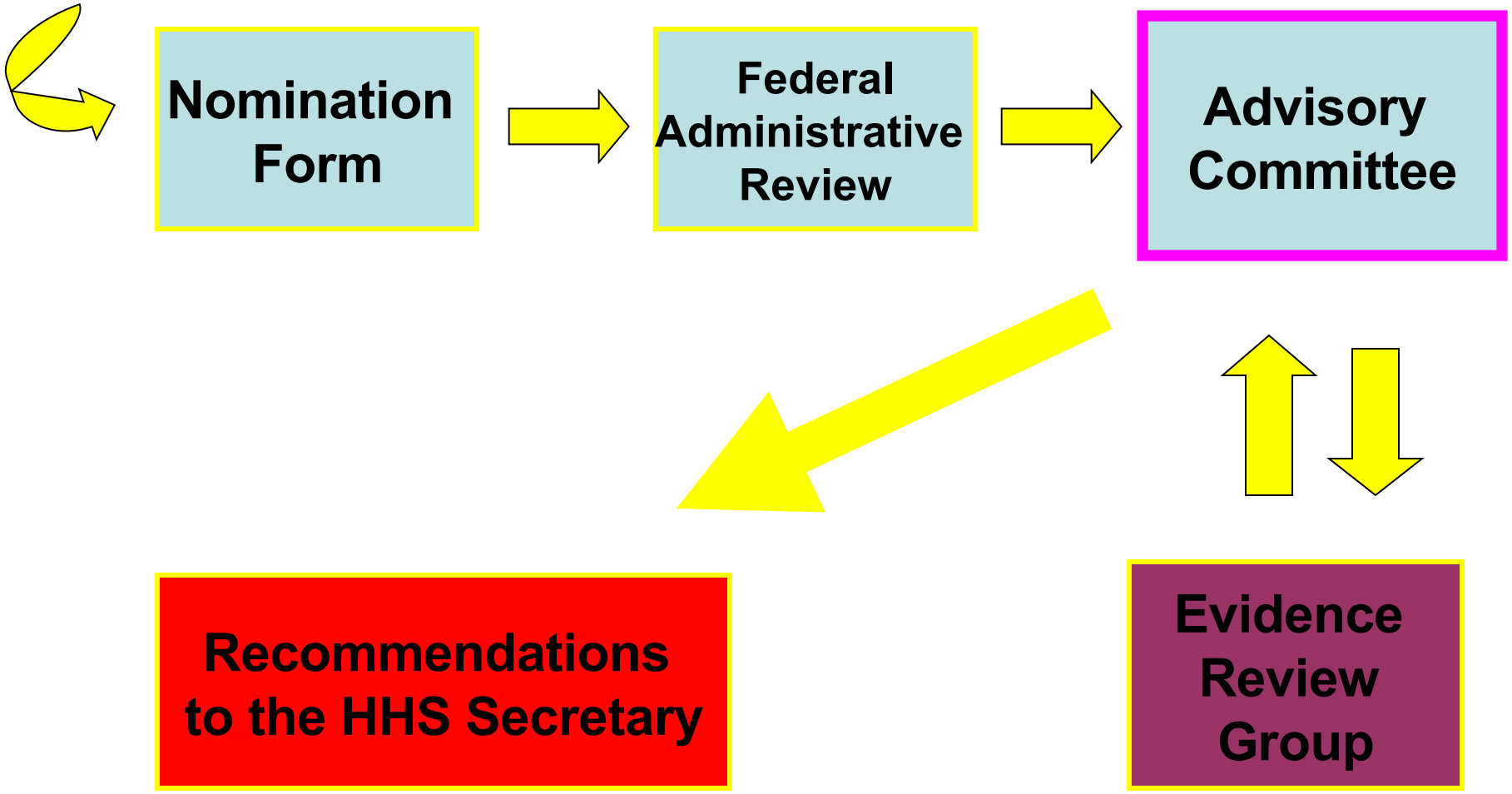
Michele A. Lloyd-Puryear, M.D., Ph.D.
Chief, Genetics Services Branch
Division of Services for Children with Special Health Needs
Maternal and Child Health Bureau
5600 Fishers Lane, Room 18-A-19
Rockville, MD 20857
301-443-8604 –fax 301-443-1080 - phone

Contact information (proponent)

ACHDNC Review and Decision Process

- Condition is nominated for review
- After brief HRSA review to ensure that the application is complete, the Advisory Committee receives advice on this nomination from a formal internal workgroup that assesses, based on the nomination package 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.
- Advisory Committee evaluates and votes on whether a nominated condition should move forward for a full evidence review.
- The Decision Criteria and Process to be used in reviewing all nominations was presented by this workgroup at the February 26-27, 2009 meeting, approved and adopted by the Committee

Paradigm for Committee Consideration for Adding Disorders to the NBS Panel



Issues in Evidence Review

- **Rare conditions**
  - **Lack of randomized trials in many cases**
  - **Limited information on costs and benefits across all potential outcomes (i.e., true and false positives and negatives)**

- **Access to evidence**
  - **Published evidence**
  - **Investigator findings (unpublished)**
  - **FDA trials database**
  - **Proprietary data**

  - **From Perrin**

Evidence Review Main Questions I

- **Questions for Review**
  - **Natural history, including variations in phenotype**
  - **Prevalence, including genotype, phenotype and phenotypic variations**
  - **Impact and severity**
  - **Methods of screening and diagnosis (in screen positive individuals)**
    - **Screening test utilities (sensitivity, specificity, predictive values)**
    - **Feasibility and acceptability of screening**

From Perrin

Evidence Review Main Questions II

- **Benefits of treatment**
  - **in screen positive individuals**
  - **In otherwise diagnoses individuals**

- **Harms or risks of**
  - **Screening**
  - **Diagnosis**
  - **Treatment**

- **Costs (screening, diagnosis, treatment, late treatment; failure to diagnose in newborn period)**

From Perrin

Evidence Review Model and Methods

- **Decision model and development of evidence questions**
- **Search methods (time frame and search engines used)**

From Perrin

Systematic Review and Additional Data Collection and Review

- **Study selection and data abstraction and review**
  - **Inclusion/exclusion criteria**
    - **Peer-reviewed published literature**
    - **English only**
    - **Gray literature – limited to pharmaceutical companies, unpublished studies (and related data)**
    - **Exclude case reports**
    - **Review consensus statements as guides, not for abstraction**

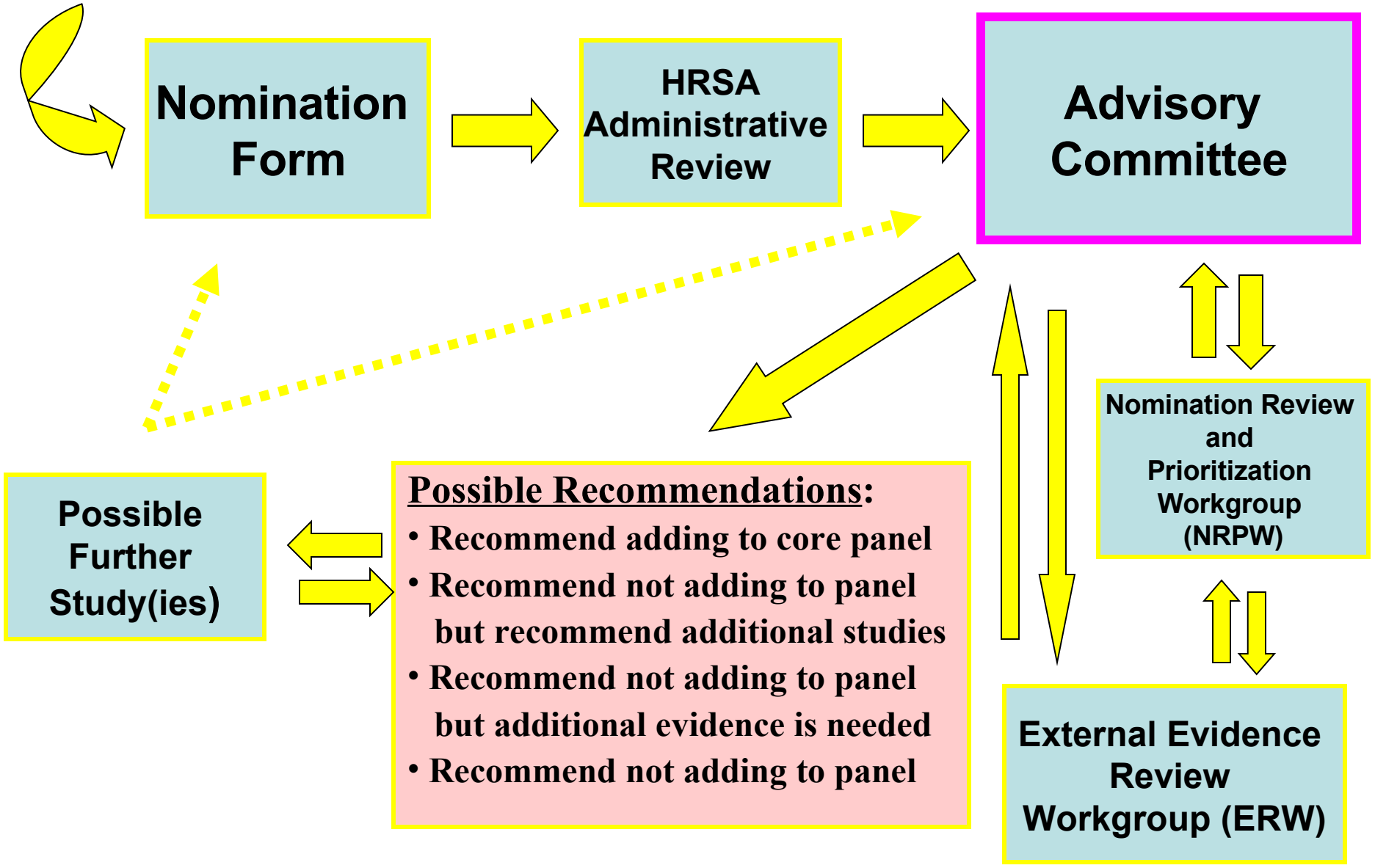
From Perrin

Systematic Review and Additional Data Collection and Review

- Data abstraction and quality assessment
  - Standard quality assessment methods
  - Analyses of (any) additional raw data from unpublished sources
    - Special issues of data format and constraints on use (data sharing agreement template in process)
- Focus groups of experts (investigators and families) re impact and severity estimates
- Data synthesis

From Perrin

ACHDNC Evidence Review Process: Overview



Conditions Nominated and Considered by Committee Using This Format

- **Fabry and Niemann-Pick Diseases were nominated and were deemed by the Committee not to be ready for an evidence review**
- **Pompe disease and Severe Combined Immune Deficiency have been completely reviewed (with formal evidence review): Recommended not adding to panel at this time, felt very promising and requested specific additional information, and then reconsider**
- **Spinal Muscular Atrophy (no formal evidence review) not recommended for addition at this time, requested specific additional information prior to evidence review**
- **Krabbe Disease is currently undergoing formal evidence review; will be discussed at the next Advisory Meeting**

ACHDNC Update: February 2009 meeting

Moderator: Jeffrey R. Botkin, M.D., M.P.H.

- Provided overview of Regulation and Oversight of Research with Children

Edward Bartlett, Ph.D.

Discussed the following:

- Regulatory options for multi-center research
- Meetings on alternative IRB review models
- Proposal to hold IRBs directly accountable

Alan Fleischman, M.D.

- Translational Research in the Context of Newborn Screening—How Can We Make it Work?
- Provided overview of CA and MA models of obtaining informed consent for newborn screening research

ACHDNC Update: February 2009 meeting

RESIDUAL BLOOD SPOTS: POLICIES AND USES

William Hannon, Ph.D. National Newborn Screening and Genetics Resource Center

- **Storage, Retention, and Use of Residual Dried Blood Spots (DBS)**
  - **Storage of residual DBS by screening labs**
  - **Retention times for residual DBSs**
  - **Use of residual DBSs and the restrictions**
  - **Policies impacting DBS use**

Jeffrey R. Botkin, M.D., M.P.H. University of Utah School of Medicine

- **Ethical and Regulatory Considerations in Research using Residual Specimens**

Public Law 110-204
Newborn Screening Saves Lives Act of 2008

- **This statute amends the Public Health Service Act to facilitate the creation of Federal guidelines on newborn screening**
  - **To assist State newborn screening programs in meeting federal guidelines**
  - **To establish grant programs to provide for education and outreach on newborn screening and follow-up care once newborn screening has been conducted**
  - **To reauthorize programs under Part A of Title XI of the Act**

Public Law 110-204
Newborn Screening Saves Lives Act of 2008

- **The Act reauthorizes and expands the role of the Advisory Committee on Heritable Disorders in Newborns and Children**

- **Establishes an Interagency Coordinating Committee on Newborn and Child Screening**

- **Creates an Internet-based information clearinghouse to provide information about newborn and child screening for heritable disorders**

Public Law 110-204
Newborn Screening Saves Lives Act of 2008

- **Bill requires the Secretary of HHS**
  - **To ensure the quality of laboratories involved in newborn screening activities**
  - **To develop a national contingency plan for newborn screening**

- **Gives the National Institutes of Health the authority to carry out research in newborn screening, including identifying new screening technologies and researching diseases management strategies for the conditions that can be detected through screening (NIH program to be known as the Hunter Kelly Newborn Screening Research Program)**

- **There are seven sections to the bill**

ACHDNC: Next steps

Directions the Committee is exploring:

- **The Committee is preparing a White paper reflecting possible approaches to long-term follow-up and other translational research activities-will focus heavily on Informed consent issues for multi-site studies**
  - **The draft will be discussed at the Committee's May meeting.**
- **Recommendations to HHS Secretary on policies for retaining Residual Blood Spots and obtaining informed consent for storage of the samples**