Developing a National Network for Pilot NBS Research

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NBS Research

- DACHDNC supports and embodies an evidence-based system
- But robust evidence review process requires robust evidence to review
- Screening programs outside a research paradigm do not consistently generate quality data on clinical outcomes

NBS Research

- Evidence necessary on:
  - Natural history of the condition
  - Range of clinical manifestations
  - Association between phenotypes and genotypes
  - Efficacy of early detection and intervention strategies
  - Adverse effects of detection and treatment alternatives
  - Cost effectiveness analyses

The Current "System"

- 4 million infants per year undergo newborn screening each year in the US
- Screening is considered sufficiently beneficial to warrant state mandates in most states
- NBS screening has become much more uniform state-to-state over the past decade
- Yet the research infrastructure to evaluate the efficacy and safety of new and existing screening modalities is entirely haphazard
  - We have no system to formally evaluate these critically important screening tests and systems

NBS Research

- The "test article" for a new condition for the RUSP is the NBS *system* that supports detection and early intervention
- Essential to conduct pilot studies of screening for a new condition on a population level to evaluate the efficacy and safety of NBS *system*
- All conditions proposed for inclusion on the RUSP should be evaluated through population-based pilot study prior to adoption to the RUSP

Barriers to NBS Research

- NBS is state health department based
  - State programs do not have research mission or budgets
  - Individual state populations too small for research on rare conditions
- System relies on research that is investigator initiated and dependent on collaborative state programs
  - Substantial variation in acceptable designs for state programs (parental consent models)
- Research projects are large, expensive, and raise ethical concerns
- Limited commercial incentives to attract commercial sponsors of research

History

- CF remains in the only condition on the RUSP that was evaluated prior to national implementation through a randomized, controlled trial
- Policy decisions often made from studies with a small number of cases and outcomes assessed through comparisons with historical controls

A Research Agenda for NBS

- **Phase I**: Evaluate clinical response to treatment/prevention
- **Phase II**: Assess benefits of population screening
- **Phase III**: Economic analysis of screening protocol
- **Phase IV**: Post implementation monitoring and evaluation

Phase II

- Research Methods
  - Randomized controlled trial of screening versus clinical diagnosis with outcome tracking
    - Parallel sample analysis with withholding/blinding of results (Wisconsin CF trial)
  - Concerns:
    - Large trials
    - Long follow-up period may be necessary
    - Ethical issues
    - Ascertainment in un-screened group

Phase II

- Cohort analysis
  - Comparison of screening in one or more states versus clinical diagnosis in comparable states.
    - Retrospective analysis of stored specimens in similar population w/outcome tracking
  - Less valuable than RCT but potentially fewer ethical concerns

Phase II

- Historical Controls
  - Comparison of clinical outcomes from detection through NBS with outcomes documented in historical controls
- Biases/Concerns
  - Bias common in historical controls due to case ascertainment differences and changes in medical care over time

SMA Study Example

- Natural history is reasonably well understood for SMA subtypes
- Preliminary evidence that early intervention can delay muscle weakness and respiratory failure
  - Promising pharmaceutical agents under evaluation
- SACHDNC recommended a pilot study of NBS for SMA prior to making any recommendations
- NICHD funded study (Swoboda, PI) to evaluate feasibility of NBS. An existing clinical research study available for identified infants

SMA Study Example

- Study planned to add SMA pilot screening to NBS panels in Colorado and Utah over a 3 year period (N= ~400,000 infants screened)
- Anticipated the identification of ~40 affected infants
- Formal support obtained in the grant application from NBS programs in Colorado and Utah
- Initial aim of the study was to determine public attitudes on what decision-making role was appropriate for parents for pilot screening for SMA
  - Public was strongly supportive of an opt-out model assuming parents were adequately informed of the study

SMA Study Example

- Once the study was funded and underway…
  - Colorado health department withdrew support for the study
  - Utah NBS program maintained support but DOH IRB approved the study with a requirement for full informed consent
- Study is currently going forward with IRB approval at individual hospitals in CO and UT without involvement of the health departments
  - Concerns about adequate recruitment to achieve study goals

Proposal

- A multi-state network to support population-based Phase II through Phase IV research
  - A network of states familiar with and supportive of NBS research
  - DOH IRB's that are familiar with the issues
  - State infrastructure to be supported by federal funds to be awarded through a competitive mechanism
  - Established organization to coordinate projects (NBSTRN)

Advantages

- Generation of higher quality data than available through haphazard adoption of screening in clinical programs
- Recruitment of large populations through a network will enable more rapid conclusions on effective/ineffective approaches
- State pilots can be varied in selected ways to provide comparisons on elements of the NBS system (e.g., test platforms)
- The network can be responsive to recommendations of organizations like the DACHDNC for pilot studies
- National peer review system for federal funding will increase the quality of the research protocols

Disadvantages/Challenges

- Establishing uniform approaches to pilot studies between multiple state programs will require extensive collaboration
- Network participation may burden NBS programs in participating states
- Families in participating network states would become research subjects on behalf of families in non-participating states
- A network of a limited number of states may mean that investigators with disease expertise are remote from participating states
- Conducting research through a network may delay adoption of screening modalities that are clearly beneficial