Newborn Screening Policy Development in the United States

The Changing Scene and The Way Forward in the Genomic Era

Association of Public Health Laboratories
2013 Annual Meeting
Raleigh, North Carolina

June 2-5, 2013
The Classic Wilson and Jungner Screening Criteria-45 Years Later
Revisiting Wilson and Jungner in the Genomic Age: A review of Screening Criteria Over the Past 40 years

Almost 40 years ago, WHO commissioned a report on screening from James Maxwell Glover Wilson, then Principal Medical Officer at the Ministry of Health in London, England, and Gunner Jungner, then Chief of the Clinical Chemistry Department of Sahlgren's Hospital in Gothenburg, Sweden. The report, published in 1968, was entitled: Principles and practice of screening for disease and it has since become a public health classic.
James Maxwell Glover Wilson and Gunner Jungner Never Expected That Their Original Criteria Would Remain Unchanged

The criteria of Wilson and Jungner are still upheld today as “classics” and the “gold standard of screening assessment” having stood well the test of time. However the authors (Quoted Below) never expected their criteria to remain unchanged over time, but rather hoped that their publication would provoke further reflection and debate in this complex area.


“If anywhere we have appeared dogmatic, we hope that this may serve to stimulate discussion, since, in the end, real development depends on an exchange of views”

Wilson and Jungner, Principles and Practice of Screening for Disease, World Health Organization, 1968
Revisiting Wilson and Jungner in the genomic age: a Review of Screening Criteria over the past 40 years

Box 2. Synthesis of emerging screening criteria proposed over the past 40 years

- The screening programme should respond to a recognized need.
- The objectives of screening should be defined at the outset.
- There should be a defined target population.
- There should be scientific evidence of screening programme effectiveness.
- The programme should integrate education, testing, clinical services and programme management.
- There should be quality assurance, with mechanisms to minimize potential risks of screening.
- The programme should ensure informed choice, confidentiality and respect for autonomy.
- The programme should promote equity and access to screening for the entire target population.
- Programme evaluation should be planned from the outset.
- The overall benefits of screening should outweigh the harm.
The Most Extensive Review to Date Relating to Standardization of Newborn Screening was Carried out by the American College of Medical Genetics, under a grant from HRSA, from 2002-2006

- Expert group originally convened in December 2002
  - >70 physicians, scientists, consumers, state laboratorians, lawyers, ethicists, and others
  - Results reviewed by an independent newborn screening external review group
  - Newborn Screening: Toward a Uniform Screening Panel and System (report published in 2006)
Selection Criteria of Uniform Panel

- Incidence of conditions
- Identifiable at birth
- Burden of disease
- Mortality prevention

- Availability of treatment
- Cost of treatment
- Efficacy of treatment
- Benefits of early intervention
- Benefits of early identification
- Acute management
- Simplicity of therapy

- Availability of test
- Test characteristics
- Diagnostic confirmation
Title XXVI of the Children’s Health Act of 2000 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 in Newborns and Children (Section 1111)
- Committee first met on June 7-8, 2004
- Although Committee charge includes testing newborns and children, to date, committee has focused efforts on newborn screening
### Nomination Form (ftp://ftp.hrsa.gov/mchb/genetics/NominationForm.doc)

#### NEWBORN SCREENING UNIFORM PANEL

**Nomination Form for Proposed Condition**

<table>
<thead>
<tr>
<th>Name of Proponent</th>
<th>Organization</th>
<th>Relevant</th>
<th>Date</th>
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<tbody>
<tr>
<td><strong>Condition</strong></td>
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<tr>
<td>Type of Disorder</td>
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<tr>
<td>Screening Method</td>
<td></td>
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<tr>
<td>Treatment strategy</td>
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#### CONDITION

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<thead>
<tr>
<th>Gene</th>
<th>Locus</th>
<th>OMIM or other names for disorder</th>
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*Note: Please reference each statement, listing references below (p. 2)*

1. **Incidence**
   - (Determined by what methods: pilot screening or clinical identification?)

2. **Timing of clinical onset**
   - (Relevance of screening)

3. **Severity of disease**
   - (Morbidity, disability)

#### TEST

<table>
<thead>
<tr>
<th>Screening test(s) to be used</th>
<th>Comment</th>
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<tbody>
<tr>
<td>(High volume method, platform)</td>
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<table>
<thead>
<tr>
<th>Modality of screening</th>
<th>Comment</th>
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<tbody>
<tr>
<td>(Dried blood spot, physical or physiologic assessment, other)</td>
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<thead>
<tr>
<th>Clinical validation</th>
<th>Comment</th>
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<tbody>
<tr>
<td>(Location, duration, validity)</td>
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<tr>
<th>Laboratory performance metrics</th>
<th>Comment</th>
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<tbody>
<tr>
<td>(Sensitivity, specificity, availability)</td>
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<tr>
<th>Confirmatory testing</th>
<th>Comment</th>
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<tr>
<td>(Reliability, availability)</td>
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<tr>
<th>Risks</th>
<th>Comment</th>
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<tbody>
<tr>
<td>(False positives, carrier detection, invasiveness of method, other. Detection or suggestion of other disorders)</td>
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#### Treatment

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<thead>
<tr>
<th>Modality</th>
<th>Comment</th>
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<tr>
<td>(Drug(s), diet, replacement therapy, transplant, other)</td>
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<tr>
<th>Urgency</th>
<th>Comment</th>
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<tr>
<td>(How soon after birth treatment needs to be initiated to be effective)</td>
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<tr>
<th>Efficacy (Benefits)</th>
<th>Comment</th>
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<tr>
<td>(Extent of percent of acceptance or benefit such as difficulty with</td>
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<tr>
<th>Availability</th>
<th>Comment</th>
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<tr>
<td>(Any limit on)</td>
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<tr>
<th>Risks</th>
<th>Comment</th>
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<tr>
<td>(Potential medical or other ill effects from treatment)</td>
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#### References

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<th>Key References (Specific citations – limit to 15)</th>
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<td>15</td>
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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-Pryear, 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)
Outcome of Nominated Conditions

- **Fabry, Niemann-Pick and SMA** not subjected to formal evidence review and not approved for addition

- **Pompe, and Krabbe** formal evidence review and not approved for addition

- **Hemoglobin H and Hyperbilirubinemia** were subjected to formal evidence reviews and not approved for addition

- **SCID** formal evidence review and approved for addition. Very successful pilot studies have been completed

- **Critical Congenital Cyanotic Heart Disease** formal evidence review and approved for addition-specified additional activities

- **Pompe Disease** was resubmitted, underwent a new evidence review and has been approved for addition to the recommended uniform panel
Pompe Disease Approved for Addition to the Recommended Uniform Panel on May 17, 2013

On May 17, 2013 - in a long awaited meeting in Washington DC (USA), the Secretary’s Discretionary Advisory Committee for Heritable Disorders in Newborns and Children (DACHDNC), recommended the addition of Pompe Disease to the recommended uniform newborn screening panel (RUSP). The letter to the Secretary will highlight the need for states currently implementing Pompe screening to coordinate activities and help establish a framework for state-based screening. The committee considered both the significant benefit to screening for infantile as well as the need for more studies about the optimal management of those with late onset.

Screening is based on measuring enzyme activity and genotyping is used to diagnose the condition as well as identify carriers, predicts infantile versus late onset disease. Treatment for Pompe Disease is enzyme replacement therapy.

The state Missouri began screening for Pompe Disease on January 15, 2013. In the first four months of this screening, 1 classic infantile baby was found while 7 others needed further examination.
CARDIOMEGALIA
GLYCOCENICA

ACADEMISCH PROEFSCHRIFT TER VERKRIJGING
VAN DEN GRAAD VAN DOCTOR IN DE GENEES-
KUNDE AAN DE UNIVERSITEIT VAN AMSTER-
DAM, OP GEZAG VAN DEN RECTOR-MAGNIFICUS,
DR. W. P. C. ZEEMAN, HOOGLEERAAR IN DE FA-
CULTEIT DER GENEESKUNDE, IN HET OPENBAAR
TE VERDEIGEN IN DE AULA DER UNIVERSITEIT,
OP VRIJDAG 15 MEI 1936, DES
NAMIDDAGS TE 4½ UUR,

DOOR

JOANNES CASSIANUS POMPE
GEBOREN TE UTRECHT
De vergrooting deze microfoto's is 175:1.
INFANTILE ONSET GSD-II (POMPE DISEASE)

• Deposition of glycogen in heart, liver and skeletal muscle, within lysosomes
• Generalized Weakness
• Muscle Wasting
• Feeding Difficulties
• Failure to Thrive
• Macroglossia
• Hepatomegaly
• Progressive Respiratory Distress
• Progressive Hypertrophic Cardiomyopathy
Pompe Disease

Glycogen Accumulation
Condition Review of Newborn Screening for Pompe Disease

- Key findings from the systematic evidence review
- Projected population-level benefit based on findings from the systematic evidence review and decision analysis
- Summary of current capacity of state newborn screening programs to offer comprehensive screening for Pompe disease
Classification of Pompe Disease

**Infantile: Most severe**

- **Onset ≤12 months of age**
  - *Infantile Onset with Cardiomyopathy* ("Classic Form") – progressive hypotonia and cardiomyopathy; without treatment, death usually within the first year of life
  - *Infantile Onset without Cardiomyopathy* ("Nonclassic Form") – typically no cardiomyopathy; longer survival, but without treatment, death in early childhood

**Late-onset: Variable Presentation**

- **Clinical onset >12 months of age**
- **Most seek care for symptom onset in adulthood (>18 years)**
- **Diagnosis ~8-10 years later, and death ~27 years later**
- **May have mild weakness in childhood that can go unrecognized**
- **Slowly progressive myopathy**
- **Variable long-term outcomes without treatment (e.g., wheelchair dependence; ventilator assistance; respiratory failure)**
Newborn Screening

- GAA enzyme activity measured in dried-blood spots
- Current methods:
  - Fluorometric assay
  - Tandem mass spectrometry (MS/MS)
  - Digital microfluidics
- All available screening tests effectively measure enzyme activity
- No data about whether any particular screening test would operate better in a high-throughput setting
Pompe Disease MS/MS Enzyme Assay Data

Internal Standard

Product

Internal Standard

Paper Blank

Healthy Adult

Pompe Patient
Activity ($\mu$mol/h/L blood)

<table>
<thead>
<tr>
<th>n =</th>
<th>Patients</th>
<th>Carries</th>
<th>Adults</th>
<th>Infants</th>
</tr>
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<tbody>
<tr>
<td>5</td>
<td>5</td>
<td>48</td>
<td>32</td>
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</table>
Enzyme Replacement Therapy (ERT)

Treatment: Replace alglucosidase alfa (GAA) deficiency

<table>
<thead>
<tr>
<th>FDA Approval</th>
<th>Pompe Disease Form (Indication)</th>
<th>Drug</th>
<th>Wholesale Acquisition Cost per 50mg vial</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>Infantile-onset (ERT start ≤3.5 years)</td>
<td>Myozyme</td>
<td>$975</td>
</tr>
<tr>
<td>2010</td>
<td>Late-onset (≥ 8 years)</td>
<td>Lumizyme</td>
<td>$725</td>
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- *Not curative*
- *Infusion typically every two weeks with central line*
- *Typical dose is 20 mg/kg infused over 2 hours*
- *Adverse Effects: Infusion Associated Reactions, Antibody Formation*
Taiwan Newborn Screening Program

- **Fluorescence assay** – 473,738 samples
  - 9 cases of infantile-onset Pompe disease
  - 26 cases of “later-onset” Pompe disease
  - Algorithm has changed over time
  - Using two-tiered approach all cases of infantile-onset Pompe disease and 24/26 cases of “later-onset” disease would be identified

<table>
<thead>
<tr>
<th>Estimated Results: All Pompe Disease Forms</th>
</tr>
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<tbody>
<tr>
<td>Overall Incidence</td>
</tr>
<tr>
<td>Overall Positive Rate</td>
</tr>
<tr>
<td>Overall Positive Predictive Value</td>
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Effectiveness of ERT

• Compared to historical controls, ERT at 52 weeks (first infusion by 6 months of age)
  – Reduced the risk of death by 95%
  – Reduced the risk of death or invasive ventilation by 87%
• Overall survival at 36 months: 72%
• Overall ventilator-free survival at 36 months: 49%
• CRIM- status associated with worse outcomes
• Lower survival if ERT begun after 6 months of age
Pt 103- 8 years after ERT

Goes to kindergarten
Pre-symptomatic Detection of Late-Onset Pompe Disease

- No trials of pre-symptomatic ERT for late-onset disease
- Treatment decisions based on presence of weakness or muscle damage (e.g., elevated CK). MRI can also show muscle damage.
- Recommendations for follow-up not standardized
- Potential harms of early identification include treatment with ERT, central line placement, economic cost of lifelong treatment, and psychosocial harm.
- There is evidence from an RCT of ERT for symptomatic individuals (mean age in the 40s) that ERT can improve respiratory status and motor function.
Some Personal Thoughts About Newborn Screening for Pompe Disease

• The evidence review supports the addition of Pompe Disease to the Recommended Uniform Screening Panel
• There are FDA approved drugs which are life-saving
• The State Laboratories, as presented to the Advisory Committee, have a variety of needs that have to be addressed before the screening can cover the nation
• As with SCID, there must be an extremely well-planned, very large “pilot” screening program which can address rigorously a number of questions such as the timing of treatment for the late onset disease
• It is clearly of great value to detect the later onset disease in the newborn so that early treatment, before muscle destruction occurs, can be planned
• These “pilot” studies should be coordinated by the NIH-funded Newborn Screening Translational Network (NBSTRN)
The Role of Genomic Technology in Newborn Screening:

Initial Stimulus

- Secretary’s Advisory Committee on Heritable Disorders in Newborns and Children, early 2010 suggested topic
- NICHD, NHGRI, and ORDR held workshop, late 2010
- Chaired by Drs. David Valle and Piero Rinaldo
- Proposed an NIH research agenda to inform application of genomics to NBS & child health

An Important Distinction when Considering the Application of Genomic Sequencing to Newborn Infants

• **Newborn screening vs. screening of newborns**
  
  – Newborn Screening is our current practice of a strictly focused screening for a limited number of specific disorders
  
  – Screening of Newborns suggests a broad, potentially comprehensive screen using genomic technologies
  
  – Health services, education, and ethics of these are distinct
Some Key Aspects of NIH Recent RFA relating to the Potential Value of Next Generation Sequencing in Newborn Screening

Collect a Comprehensive Genomic Data Set from Infants with known NBS Results

For disorders currently screened, how can genomic sequences replicate or augment known newborn screening results

What knowledge about conditions not currently screened for could genomic sequences of newborns promote

What additional clinical information could be learned from genomic sequences relevant to the clinical care of newborns

Some Key Aspects of NIH Recent RFA relating to the Potential Value of Next Generation Sequencing in Newborn Screening

Each Applicant Must Have Research Components:

To acquire and analyze genomic datasets to in order to expand the scale of data available in the newborn period

Clinical research that will advance the understanding of specific disorders identifiable with newborn screening through promising new DNA-based analysis

Research related to ethical, legal and social implications of the possible implementation of genomic sequencing of newborns

We Screen Newborns, Don’t We?: Realizing the Promise of Public Health Genomics

- These authors point out how very successful newborn screening has been by having a public health program screen all newborns for rare disorders which when identified in the newborn period have dramatic therapeutic benefits.
- They point out, correctly, that the cost of sequencing has declined so dramatically that one could consider testing adult populations for rare conditions with potentially dramatic treatments. For example:
  - Roughly 0.2% of the individuals in the US harbor one of the four Lynch Syndrome associated deleterious mutations
  - Persons harboring any one of these four genes are at >80% risk for developing colon cancer
  - These authors point out that there is a great opportunity to combine genomics and public health to consider population screening for some rare adult disorders which might have dramatic benefits.
  - The authors are careful to outline the many issues that must be resolved in such a plan.

Evans, JP. Et al. We screen newborns, don’t we?: Realizing the promise of public health genomics. Genetics in Medicine 15:332, 2013