NEWBORN SCREENING FOR FABRY DISEASE

Dietrich Matern, MD, PhD
Biochemical Genetics Lab
Mayo Clinic
Disclosure of Interests

Relevant financial relationship(s)
Consultant, Mayo Clinic

Research Support
National Institute of Child Health and Development (NICHD)
Newborn Screening Translational Research Network (NBSTRN)
Legacy of Angels Foundation
Hunter’s Hope Foundation
GlaxoSmithKline

Off-label usage(s)
None
Why NBS for LSDs?

- LSDs are historically devastating conditions but now increasingly treatable.
- Prognosis better when treatment started early (NBS!).
- Dried blood spot (DBS) based assays now available.
<table>
<thead>
<tr>
<th>Method</th>
<th>multiplex</th>
<th>Platform</th>
<th>Complexity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzyme Assay (Chamoles et al)</td>
<td>no</td>
<td>Fluorometry</td>
<td>low</td>
</tr>
<tr>
<td>Multiplex Enzyme Assay (Gelb/Scott)</td>
<td>yes</td>
<td>MS/MS</td>
<td>high</td>
</tr>
<tr>
<td>Multiplex Immune-Quantification Assay</td>
<td>yes</td>
<td>Luminex</td>
<td>low</td>
</tr>
<tr>
<td>(Hopwood et al)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digital Microfluidics (Baebies, Inc.)</td>
<td>yes</td>
<td>“Fluorometry-on-a-chip”</td>
<td>low</td>
</tr>
</tbody>
</table>
executive summary

The Maternal and Child Health Bureau commissioned the American College of Medical Genetics to outline a process for the standardization of outcomes and guidelines for state newborn screening programs and to define responsibilities for collecting and evaluating outcome data, including a recommended uniform panel of conditions to include in state newborn screening programs. The expert panel identified 29 conditions for which screening should be mandated. An additional 25 conditions were identified because they are part of the differential diagnosis of a condition in the core panel, they are clinically significant and revealed with screening technology but lack an efficacious treatment, or they represent incidental findings for which there is potential clinical significance. The process of identification is described, and recommendations are provided. *Genet Med* 2006;8(5, Supplement): 1S–11S.
ACMG Panel: final score

29 Primary Targets
25 Secondary Targets

Fig. 1. Scoring by test availability (separates out those conditions that have an acceptable, validated, population-based screening test from those that do not).
ACMG Panel: final score

**Primary Targets**

- 29

**Secondary Targets**

- 25

**Not Yet Appropriate**

- 500

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Fig. 1. Scoring by test availability (separates out those conditions that have an acceptable, validated, population-based screening test from those that do not).
### Recommended Uniform Screening Panel

Printer-Friendly Recommended Uniform Screening Panel (PDF - 50 KB)

**Recommended Uniform Screening Panel**

<table>
<thead>
<tr>
<th>ACMG Code</th>
<th>Core Condition</th>
<th>Metabolic Disorder</th>
<th>Endocrine Disorder</th>
<th>Hemoglobin Disorder</th>
<th>Other Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROP</td>
<td>Propionic acidemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MUT</td>
<td>Methylmalonic acidemia (methylmalonyl-CoA mutase)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cbl</td>
<td>Methylmalonic acidemia (cobalamin)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Core 2 Conditions**

(as of March 2015)
Why NBS for LSDs

- LSDs are historically devastating conditions but now increasingly treatable
- Prognosis better when treatment started early (NBS!)
- Dried blood spot (DBS) based assays now available
- Pressure from advocacy groups
HRSA’s ACHDNC

Advisory Committee on Heritable Disorders in Newborns and Children

- 09/2007: SCID
- 10/2007: Pompe disease
- 12/2007: Niemann-Pick A/B disease
- 12/2007: Fabry disease
- 01/2008: Krabbe disease
- 06/2008: Spinal muscular atrophy
- 04/2009: Hemoglobin H disease
- 07/2008: Hyperbilirubinemia/Kernicterus
- 10/2009: Critical Congenital Heart Disease
- 01/2011: 22q11 deletion syndrome
- 02/2012: Pompe disease
- 02/2012: MPS I
- 02/2012: X-Adrenoleukodystrophy
- 09/2013: X-Adrenoleukodystrophy
HRSA’s ACHDNC

09/2007: SCID
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Advisory Committee on Heritable Disorders in Newborns and Children

- 09/2007: SCID → added to RUSP: 02/2010
- 10/2007: Pompe disease
- 12/2007: Niemann-Pick A/B disease
- 12/2007: Fabry disease
- 01/2008: Krabbe disease
- 06/2008: Spinal muscular atrophy
- 04/2009: Hemoglobin H disease
- 07/2008: Hyperbilirubinemia/Kernicterus
- 10/2009: CCHD → added to RUSP: 09/2011
- 01/2011: 22q11 deletion syndrome
- 02/2012: Pompe disease → added to RUSP: 03/2015
- 02/2012: MPS I
- 02/2012: X-Adrenoleukodystrophy
- 09/2013: X-Adrenoleukodystrophy
<table>
<thead>
<tr>
<th>Nomination Date</th>
<th>Proponents</th>
<th>ACHDNC vote to send to ERG*</th>
<th>ERG* Final Report</th>
<th>ACHDNC vote to add to RUSP</th>
<th>Secretary approval to add to RUSP</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/2007</td>
<td>Dr. Maryam Banikazemi, NYU</td>
<td>Not approved (8/2008)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*(External) Evidence Review Group
Fabry Disease

- α-galactosidase A (GLA) def.
- X-linked, but most females will become symptomatic
- Accumulation of glycosphingolipids > Disruption of cellular metabolic processes > cell death > inflammation > progressive organ dysfunction
- Not life-threatening in childhood
- Classic vs. later onset cardiac and renal variants

Table 2 Summary of reported clinical manifestations in Fabry patients (newborn–4 years)

<table>
<thead>
<tr>
<th>Fabry-related signs and symptoms</th>
<th>Earliest report of symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Storage of globotriaosylceramide found in organs on biopsy</td>
<td>Prenatal</td>
</tr>
<tr>
<td>Corneal whorls/verticillata</td>
<td>Prenatal/newborn</td>
</tr>
<tr>
<td>Gastrointestinal problems, including nausea, vomiting, diarrhea, constipation, and abdominal pain</td>
<td>1.0 year</td>
</tr>
<tr>
<td>Slow growth in boys (mean height/weight &lt;50th percentile)</td>
<td>2.0 years</td>
</tr>
<tr>
<td>Intermittent acroparesthesia/neuropathic pain triggered by stress, heat, fatigue, or exercise</td>
<td>2.0 years</td>
</tr>
<tr>
<td>Hypohidrosis or anhidrosis</td>
<td>2.5 years</td>
</tr>
<tr>
<td>Fabry crises of agonizing neuropathic pain typically begin in the hands and feet and may radiate proximally</td>
<td>2.5 years</td>
</tr>
<tr>
<td>Heat, cold, and/or exercise intolerance</td>
<td>3.5 years</td>
</tr>
<tr>
<td>Retinal vascular tortuosity</td>
<td>4.0 years</td>
</tr>
<tr>
<td>Tinnitus/vertigo</td>
<td>4.0 years</td>
</tr>
<tr>
<td>Low glomerular filtration rate</td>
<td>4.0 years</td>
</tr>
<tr>
<td>T-wave inversion on electrocardiogram</td>
<td>4.0 years</td>
</tr>
<tr>
<td>Trivial cardiac valve disease</td>
<td>4.0 years</td>
</tr>
<tr>
<td>Angiokeratoma</td>
<td>4.4 years</td>
</tr>
</tbody>
</table>

Diagnosis of Fabry Disease

- Clinical and/or (maternal) family history
- Non-specific symptoms >> late or missed diagnoses
- Routine labs: not informative!
- Specialty labs:
  - GLA enzyme assay in DBS or WBC (unreliable for female carriers)
  - Molecular genetic analysis of GLA (esp. females)
  - Urine globotriaosylceramide (Gb3) (informative in newborns?)
  - Plasma lyso-Gb3 (informative in newborns?)
- Newborn screening
  - Currently done in Taiwan, MO and IL by GLA activity assay
  - Several other pilot projects completed/underway (WA, Austria, Hungary, Mayo)
- Treatment:
  - Enzyme replacement therapy (Fabrazyme, Replagal)
  - Chaperone, substrate reduction, and gene therapy trials ongoing
Family studies revealed undiagnosed Fabry disease in affected individuals. In this population, the incidence of α-Gal A deficiency was 1 in ~3,100, with an 11:1 ratio of patients with the later-onset:classic phenotypes.

These results suggest that the later-onset phenotype of Fabry disease is underdiagnosed among males with cardiac, cerebrovascular, and/or renal disease.
## Newborn Screening for Fabry Disease


<table>
<thead>
<tr>
<th>Country/state</th>
<th>Taiwan</th>
<th>Taiwan</th>
<th>Austria</th>
<th>Hungary</th>
<th>WA</th>
<th>MO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Condition</strong></td>
<td>Fabry</td>
<td>Fabry</td>
<td>Fabry</td>
<td>Fabry</td>
<td>Fabry</td>
<td>Fabry</td>
</tr>
<tr>
<td><strong>Method</strong></td>
<td>Fluorometry</td>
<td>Fluorometry</td>
<td>MS/MS</td>
<td>MS/MS</td>
<td>MS/MS</td>
<td>MS/MS</td>
</tr>
<tr>
<td><strong># of NBS samples</strong></td>
<td>110,027</td>
<td>171,977</td>
<td>191,767</td>
<td>34,736</td>
<td>40,024</td>
<td>108,905</td>
</tr>
<tr>
<td><strong>TP</strong></td>
<td>42 (m); 3 (f)</td>
<td>73 (m); 2 (f)</td>
<td>64</td>
<td>31</td>
<td>6 (m); 3 (f)</td>
<td>7 (m); 3 (f)</td>
</tr>
<tr>
<td><strong>FPR</strong></td>
<td>1.83% (m); 0.97% (f)</td>
<td>0.63% (m); 0.40% (f)</td>
<td>17%</td>
<td>9%</td>
<td>0.08%</td>
<td>0.001% (m); 0.0006% (f)</td>
</tr>
<tr>
<td><strong>PPV</strong></td>
<td>3.84% (m); 0.58% (f)</td>
<td>11% (m); 0.62% (f)</td>
<td>32%</td>
<td>54%</td>
<td>6 (m); 3 (f)</td>
<td>54%</td>
</tr>
<tr>
<td><strong>Frequency: 1 in</strong></td>
<td>1368 (m)</td>
<td>1237 (m)</td>
<td>2996</td>
<td>13,341</td>
<td>7800 (m)</td>
<td>2913 (m + f)</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>Clinical</td>
<td>Clinical</td>
<td>Clinical</td>
<td>Mol. genetics</td>
<td>Mol. genetics</td>
<td>Mol. genetics</td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td>1 (m) and 42 (m) late onset</td>
<td>86% (m) late onset</td>
<td>9 (m), 53 late (m), and 3 (f)</td>
<td>2 Uncertain significance</td>
<td>Mutations suggest late onset</td>
<td>2 Uncertain</td>
</tr>
<tr>
<td><strong>Second tier test</strong></td>
<td>No</td>
<td>Yes (beta-galactosidase/alpha-galactosidase ratio)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>References</strong></td>
<td>75</td>
<td>9</td>
<td>74</td>
<td>38</td>
<td>39</td>
<td>75</td>
</tr>
</tbody>
</table>

DMF, digital microfluidics; f, female; FP, false-positive cases; FPR, false-positive rate; m, male; MS/MS, flow-injection tandem mass spectrometry; PPV, positive predictive value; TP, true positive cases.

*False-positive cases (FP) are based on the first DBS sample and include carriers with sequence variants considered non-disease-causing by the relevant programs.

*Study used de-identified samples.
## Minnesota NBS Performance

209,432 babies screened in 2008, 2009 and 2010

<table>
<thead>
<tr>
<th>Condition</th>
<th>FPR</th>
<th>PPV</th>
<th>Detection Rate</th>
<th>Unnecessary evaluations/month (100,000 births/yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoacidopathies</td>
<td>0.02%</td>
<td>45%</td>
<td>1 : 5,660</td>
<td>2</td>
</tr>
<tr>
<td>FAO disorders</td>
<td>0.04%</td>
<td>36%</td>
<td>1 : 5,108</td>
<td>3</td>
</tr>
<tr>
<td>Organic acidemias</td>
<td>0.03%</td>
<td>49%</td>
<td>1 : 3,952</td>
<td>2</td>
</tr>
<tr>
<td>Biotinidase def.</td>
<td>0.09%</td>
<td>9%</td>
<td>1 : 11,635</td>
<td>7</td>
</tr>
<tr>
<td>CAH (with 2nd tier)</td>
<td>0.11%</td>
<td>8%</td>
<td>1 : 11,023</td>
<td>9</td>
</tr>
<tr>
<td>Cong. Hypothyroid.</td>
<td>0.21%</td>
<td>27%</td>
<td>1 : 1,232</td>
<td>18</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>0.34%</td>
<td>5%</td>
<td>1 : 5,511</td>
<td>28</td>
</tr>
<tr>
<td>Galactosemia</td>
<td>0.06%</td>
<td>22%</td>
<td>1 : 6,545</td>
<td>5</td>
</tr>
<tr>
<td>Hemoglobinopathies</td>
<td>0.02%</td>
<td>67%</td>
<td>1 : 2,685</td>
<td>2</td>
</tr>
</tbody>
</table>
Fabry Disease

The Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) received your nomination form and all accompanying materials (nomination package) for Fabry Disease on January 7, 2008. The ACHDNC reviewed the nomination package and reported the results of that review on August 7, 2008. Based on a review of the nomination form and accompanying materials, the decision was made not to send the nomination package forward to the ACHDNC’s evidence review group at this time.

Although Fabry Disease is technically detectable in a screening panel for lysosomal storage disorders, the Committee felt that there were several factors that limit its appropriateness for inclusion in the routine newborn screening panel at this time: a) variable and possible late onset (>10 years) of the disease; b) unclear if those at highest risk of serious symptoms can be discerned in newborns; c) the lack of published data of preventive treatment early in life; d) some risk of immunologic response to enzyme replacement therapy; and e) the need for a prospective study of screening and therapeutic intervention to demonstrate the benefit of newborn screening for Fabry Disease. The ACHDNC is available for further discussion of screening newborns for Fabry Disease. The next ACHDNC meeting is October 1-2, 2008. ACHDNC may be contacted at 301-443-1080 if you wish to make public comments at this meeting.

Thank you for your interest and support of newborn screening programs and the ACHDNC’s activities.

Sincerely yours,

/s/

R. Rodney Howell, M.D.
Chairperson

Rejected because of uncertainties about:

- variable/late onset of disease,
- sensitivity of screening test,
- effectiveness of and immunologic response to treatment, and
- lack of prospective NBS and treatment studies
NBS for LSDs in the USA 2015

Blinded study

Legislation has been passed ( ) or introduced ( )

Active screening

KDIGO
NBS for Fabry Disease in the USA 2015

Blinded study

Legislation has been passed ( ) or introduced ( )

Active screening

KDIGO
NBS for Fabry Disease

Some considerations:

- Cost of screening (1st tier, 2nd tier)
- Cost of follow up
- Differentiation between classic disease vs. milder variants vs. pseudodeficiency
- Cost of treatment
- Short/long term efficacy of treatment
- Acceptance by society vs. affected families
- No FDA approved NBS or confirmatory assay (not really a problem but an issue)
## Approaches to NBS for LSDs

<table>
<thead>
<tr>
<th>Method</th>
<th>multiplex</th>
<th>platform</th>
<th>ease of use</th>
<th>performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzyme Assay (Chamoles et al.)</td>
<td>no</td>
<td>Fluorometry</td>
<td>low</td>
<td>poor</td>
</tr>
<tr>
<td>Multiplex Enzyme Assay (Gelb/Scott)</td>
<td>yes</td>
<td>FIA-MS/MS</td>
<td>moderate</td>
<td>high (?)</td>
</tr>
<tr>
<td>Multiplex Immune-Quantification Assay (Hopwood et al)</td>
<td>yes</td>
<td>LC-MS/MS</td>
<td>high</td>
<td>moderate</td>
</tr>
<tr>
<td>Digital Microfluidics (Baebies, Inc.)</td>
<td>yes</td>
<td>Fluorometry</td>
<td>low</td>
<td>(?)</td>
</tr>
</tbody>
</table>

Which one should be used?
Mayo’s Comparative Effectiveness Study

Prospective analysis of 100,000 de-identified NBS samples from the California Department of Public Health (CDPH)

FIRST TIER ASSAYS (run in parallel)
- FIA-MS/MS
- Liquid Logic
- Luminex xMAP
<table>
<thead>
<tr>
<th>DISORDER</th>
<th>MS/MS</th>
<th>Immunocapture</th>
<th>Dig. Microfluidics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fabry disease</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Gaucher disease</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Krabbe disease</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>MLD</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>MPS I</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>MPS II</td>
<td></td>
<td>+</td>
<td>(+)</td>
</tr>
<tr>
<td>MPS IIIA</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>MPS IIIB</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>MPS VI</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Mucolipidosis II/III</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>MSD</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Niemann-Pick A/B</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Pompe Disease</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Wilson disease</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Aceruloplasminemia</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Menkes disease</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Friedreich Ataxia</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>X-Adrenoleukodystrophy</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Zellweger spectrum dis.</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Acyl-CoA oxidase def.</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Bifunctional protein def.</td>
<td></td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>
Design of Mayo Study

FIRST TIER ASSAYS (run in parallel)

- FIA-MS/MS
  - Enzyme activity/Analyte Concentration normal
  - Enzyme activity/Analyte Concentration abnormal

- Liquid Logic

- Luminex xMAP
  - Protein Concentration abnormal
  - Protein Concentration normal

SECOND TIER ASSAY

- Biochemical Assay
  - Abnormal
  - Normal

- Confirmatory testing by molecular genetic analysis

NORMAL

Presumptive Positive
Goal of Mayo Study

To identify an effective and efficient testing approach. NOT to determine which condition should be screened for!!!
What We Found

• The high-throughput assays we tested were well received by the technologists and sufficiently robust.

• All assays seem sensitive.

• No assay seems sufficiently specific on its own.

• 2nd tier testing:
  ▪ Genotyping improves specificity … but may not be cost effective (+ too many variants of uncertain significance)
  ▪ Only few other potentially helpful biomarkers (PSY, GPSY, LSM, lysoGb3, GAGS, LSM)

• Somewhat surprising prevalence findings (means what?).
What could help NBS for Fabry Disease?

- Do not use a simple cut off, but consider ‘disease’ AND ‘normal’ ranges
- Do not use GLA as the only screening marker
- Measure other enzymes simultaneously as internal controls
- Measure other enzymes simultaneously and use enzyme activity ratios as additional markers
NBS Data Project

LABORATORY QUALITY IMPROVEMENT OF NEWBORN SCREENING
GLA Activity

MS/MS

Controls

Fabry (female)

False Positive

Fabry (male)
NBS for Fabry Disease

MS/MS

**Fabry (male)**

**Fabry (female)**
GLA Activity

Digital Microfluidics

GLA–DMF DBS – Alpha Galactosidase activity by DMF in DBS

Adjustment: No Adjustment
NBS for Fabry Disease

Digital Microfluidics

![Graph showing multiple comparisons between GAA/GLA, GBA/GLA, and GLA for Fabry (male) and Fabry (female) groups. The x-axis represents different genetic markers, and the y-axis shows the multiple of reference median. The graph illustrates the variability and distribution of these markers across the different groups.]
GLA Activity

Immunocapture

GLA-EU DBS - Alpha Galactosidase concentration by Luminex in DBS

Adjustment: No Adjustment

Controls  Fabry (female)  False Positive  Fabry (male)
NBS for Fabry Disease

Immunocapture

<table>
<thead>
<tr>
<th>Multiple of Reference Median</th>
<th>GAA/GLA</th>
<th>GBA/GLA</th>
<th>GLA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>GAA/GLA</td>
<td>GBA/GLA</td>
<td>GLA</td>
</tr>
<tr>
<td>10</td>
<td>GBA/GLA</td>
<td>GAA/GLA</td>
<td>GLA</td>
</tr>
</tbody>
</table>

Fabry (male)

Fabry (female)
What else could help NBS for Fabry Disease?

- Do not use a simple cut off, but consider ‘disease’ AND ‘normal’ ranges
- Do not use GLA as the only screening marker
- Measure other enzymes simultaneously as internal controls
- Measure other enzymes simultaneously and use enzyme activity ratios as additional markers
- Find another marker, even as a 2\textsuperscript{nd} tier test, to increase specificity
Closing Thoughts

If we want Newborn Screening for LSDs, incl. Fabry disease

- Need better definitions of what we want to identify through Newborn Screening:
  - Conditions affecting the baby only?
  - Conditions affecting the baby only early in life (classic phenotypes)
- Need to agree if identification of unknowing family members (mother, uncles) is an appropriate reason for Newborn Screening.

Would “Child Screening” be more appropriate for late onset conditions?

What is the impact of increasing prenatal/-conception genetic screening?
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Devin Oglesbee, PhD
Dimitar Gavrilov, MD, PhD
Grazia Isaya, MD, PhD
Kimiyo Raymond, MD
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Screening Criteria

1968 - WHO (Wilson & Jungner)

- Treatable illness
- Detectable in newborn period
- Presymptomatic initiation of treatment is beneficial
- Available resources for diagnosis/treatment/follow-up
- Availability of a simple method for sample collection
- Evidence of substantial public benefit & acceptance
- Suitable and simple test methods
- Acceptable costs

2006 - ACMG Criteria

- Clinical characteristics (e.g., incidence, burden of disease if not treated, phenotype in the newborn);
- Analytical characteristics of the screening test (e.g., availability, features of the platform);
- Diagnosis, treatment and management of the condition in both acute and chronic forms (includes the availability of health professionals experienced in diagnosis, treatment, and management).