Newborn Screening for Lysosomal Storage Disorders, Friedreich Ataxia, Wilson Disease and X-Adrenoleukodystrophy.

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Rochester, MN, USA
Disclosure Summary

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Mayo Clinic

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National Institute of Child Health and Development (NICHD)
Newborn Screening Translational Research Network (NBSTRN)
Legacy of Angels Foundation

Off-label usage(s)
None
Outline

• Why NBS for LSDs, Friedreich Ataxia, Wilson disease and X-ALD

• NBS for LSDs:
  How is it done & How is it going?

• Mayo’s Comparative Effectiveness Study
Why NBS for More Conditions

- Historically devastating conditions but now increasingly treatable
- Prognosis better when treatment started early
- Dried blood spot (DBS) based assays now available
- Pressure from advocacy groups
Outline

• Why NBS for LSDs, Friedreich Ataxia, Wilson disease and X-ALD

• NBS for LSDs: How is it done & How is it going?

• Mayo’s Comparative Effectiveness Study
<table>
<thead>
<tr>
<th>LSDs:</th>
<th>Method</th>
<th>Multiplex</th>
<th>Platform</th>
<th>Complexity</th>
<th>Performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSDs</td>
<td>Enzyme Assay (Chamoles et al.)</td>
<td>no</td>
<td>Fluorometry</td>
<td>low</td>
<td>poor</td>
</tr>
<tr>
<td>LSDs</td>
<td>Multiplex Enzyme Assay (Gelb/Scott)</td>
<td>yes</td>
<td>(LC-)MS/MS</td>
<td>high</td>
<td>?</td>
</tr>
<tr>
<td>LSDs</td>
<td>Multiplex Immune-Quantification Assay (Hopwood et al)</td>
<td>yes</td>
<td>Luminex</td>
<td>low</td>
<td>?</td>
</tr>
<tr>
<td>LSDs</td>
<td>Digital Microfluidics (Adv. Liquid Logic)</td>
<td>yes</td>
<td>“Lab-on-a-chip”</td>
<td>low</td>
<td>?</td>
</tr>
</tbody>
</table>

Which one should be used?
Statewide NBS for Krabbe disease since 2006 (>1.5 Mill. babies screened)

Results:
- 4 EOKD cases
- 33 ‘high/moderate risk’ cases
- 231 false positive cases

Expensive approach (MS/MS for 1 condition + DNA testing + f/u cost)
NBS for LSDs in the USA 2013

- 5 LSDs
- Soon
- Not yet
- Krabbe
- No plans yet
## False Positive Rates

<table>
<thead>
<tr>
<th>Program</th>
<th>NY # screened</th>
<th>WA</th>
<th>IL</th>
<th>Taiwan*</th>
<th>Austria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(technology)</td>
<td>109,000</td>
<td>8,012</td>
<td>(ca. 90%)</td>
<td>34,736</td>
</tr>
<tr>
<td>Fabry</td>
<td>&gt;1 Mill. (MS/MS)</td>
<td>0.01%</td>
<td>0.05%</td>
<td>0.87%</td>
<td>0.055%</td>
</tr>
<tr>
<td>Gaucher</td>
<td>-</td>
<td>-</td>
<td>0.25%</td>
<td>-</td>
<td>0.006%</td>
</tr>
<tr>
<td>Krabbe</td>
<td>0.015%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MPS I</td>
<td>-</td>
<td>0.01%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>NP A/B</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.003%</td>
</tr>
<tr>
<td>Pompe</td>
<td>-</td>
<td>0.01%</td>
<td>0.025%</td>
<td>0.83%</td>
<td>0.006%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>0.015%</td>
<td>0.03%</td>
<td>0.325%</td>
<td>0.86%</td>
<td>0.07%</td>
</tr>
</tbody>
</table>

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 2\textsuperscript{nd} 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>
If LSD were added in MN

<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>Current MN Program (54 conditions)</td>
<td>0.90%</td>
<td>21%</td>
<td>1 : 431</td>
<td>75</td>
</tr>
</tbody>
</table>
If LSD were added in MN

<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>Current MN Program (54 conditions)</td>
<td>0.90%</td>
<td>21%</td>
<td>1 : 431</td>
<td>75</td>
</tr>
<tr>
<td>+ one of the following approaches of NBS for LSDs:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Austria (4 LSDs)*</td>
<td>0.07%</td>
<td>40%</td>
<td>1 : 2,315</td>
<td>6</td>
</tr>
<tr>
<td>Taiwan (Pompe &amp; Fabry)</td>
<td>0.86%</td>
<td>3%</td>
<td>1 : 3,426</td>
<td>71</td>
</tr>
<tr>
<td>IL (3 LSDs)#</td>
<td>0.33%</td>
<td>26%</td>
<td>1 : 890</td>
<td>27</td>
</tr>
<tr>
<td>WA (3 LSDs)^</td>
<td>0.03%</td>
<td>33%</td>
<td>1 : 7,800</td>
<td>2</td>
</tr>
<tr>
<td><strong>TOTAL (56-58 conditions)</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>81 - 146</strong></td>
</tr>
</tbody>
</table>


#Burton et al. WORLD Symposium, 2012 (Pompe, Fabry, Gaucher)

Outline

• Why NBS for LSDs, Friedreich Ataxia, Wilson disease and X-ALD

• NBS for LSDs: How is it done & How is it going?

• Mayo’s Comparative Effectiveness Study
Mayo’s Comparative Effectiveness Study

• Implement all assays available for testing of DBS for up to 13 LSDs, Friedreich Ataxia, Wilson disease and X-ALD;

• Conduct a prospective NBS study of 100,000 blinded DBS with the goal to identify an effective and efficient testing approach;

• Evaluate approaches to rapidly confirm a presumptive diagnosis applying biochemical and molecular genetic analyses;

• Build a web site to gather data and provide analytical protocols, reference and disease ranges, and guides to result interpretation (http://www.clir-r4s.org/).*

*emulate the Region 4 Genetics Collaborative MS/MS Data Project
Prospective analysis of 100,000 de-identified NBS samples from the Design of Mayo Study
Design of Mayo Study

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

First Tier Assays (run in parallel)

- FIA-MS/MS
- Liquid Logic
- Luminex xMAP

Digital microfluidic cartridge
- Capable of rapidly and simultaneously performing 5 assays on 40 dried blood spot extracts along with 4 controls & 4 calibrators
- Minimal hands on time for reagent loading
- Disposable under standard biohazard procedures
- Reagents for each assay type are formulated at Advanced Liquid Logic under controlled manufacturing practices.
<table>
<thead>
<tr>
<th>DISORDER</th>
<th>MS/MS</th>
<th>Luminex</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 IIIB</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>MPS IIIA</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

Presumptive Positive
- Confirmatory testing by molecular genetic analysis

NORMAL

NORMAL
To identify an effective and efficient testing approach.
NOT to determine which condition should be screened for!!!
NBS Data Project
Clinical validation of cutoff target ranges in newborn screening of metabolic disorders by tandem mass spectrometry. A worldwide collaborative project

David M. S. McHugh1, Cynthia A. Cameron, PhD2, Joe E. Abdenur, MD3, Mahesan Abdurrahman, MD, PhD4, Ona Adar, PhD5, Shabana Ahmed Ali Naiani, BSc6, Henrik Dahlin, MSc, Jennisson J. Allen, RN, BSN, Ivalo Anttonen, MD, Shalina Archer, MSc7, Stacia Birke, MSc5, Reza Behdad, PhD5, Ioana Birnbaum, MSc8, Gang Ben9, MSc10, Stanislaw Berberich11, Robert Binard12, Francois Boomer, PhD13, Jim Bonham, MD14, Nancy N. Bren, MT15, Sandra C. Bryant, MT16, Michele Cusumano, ScD17, S. Graham Cuthbert18, Marta Cumplido, Ph.D.19, Carolina Cuccurullo, MSc20, Claudia D’Amico21, Noomi Caccy, MSc22, Oceania D’Apollito, PhD23, Tim Davis, BS24, Monique G. de Sain-Van der Velden, PhD25, Carmen Delgado-Peckern, PhD26, Iole Maria De Gaudio, PhD27, Cristina Maria Di Stefano, PhD28, Yanni Donos, PhD29, Melanie Drouin, BSc30, MD31, Stephen M. Dukas, MD32, Linus Eriksson, BSc33, Roger Eaton, PhD34, Barbara M. Ecker35, Fatima El Mougy, MD36, Sarah Erosh37, Mercedes Espada, PhD38, Catherine Evans, PhD39, Sandy Fawcett, RN40, Kristi F. Fjellal41, Lawrence Fisher42, Lefni Franz43, Diane M. Freytag, PhD44, Luciana R. Garcia45, Carla Garcia-Velasco46, BSc47, Dimitar Garin, MD48, Dimitar Gavgani, MD49, Rosamar Giugova50, MD51, Vitor Gomes52, MD53, Paulo Goncalves54, MD55, Claudia Gosselin, MD56, Marco Gouw57, MD58, Fei Gu59, MD60, Arthur F. Hagen, PhD61, Lanhua Han, MD62, W. Harry Hannah, Ph.D.63, Christa Hais64, Jan B. Haskell-Wright65, William Hoffman, BS66, Philip Hoggatt67, Victor V. Hool68, David M. Kowal, MD69, Korie Hughes70, Patricia R. Hunter71, Wai-Ling Huo72, June Hwang73, Isabel Burguera-Gonzalez74, Cindy A. Ingham, RN, REN75, Maria Ivanova, MD76, W. B. Jackson77, Catharine John, PhD78, John P. Johnson, MD79, Joe J. Jonas80, PhD81, Cecery Karp, MD82, David Kasper, PhD83, Brenda Klepper84, Dimitris Katsakounis, PhD85, Ioan Kehrer86, MD87, Delia Knoll88, MD89, Hironori Kobayashi, MD90, Ronald Konishi91, Victor Kothik, MD, PhD92, Rasoul Komapet93, Ph.D94, Dirk Koubek95, MD96, Emre Kroum97, MD98, Giancarlo La Marca99, MD100, Marco Lazzarotto, MD101, A. Marcia Lage102, PhD103, Simon Lee104, PhD105, K. M. Lee106, PhD107, Todd L. Lee108, PhD109, Jorge Lorenzo110, MD111, Dennis L. Lehotay, PhD112, Aida Lemos113, PhD114, Joyce Lepage115, Barbara Leslie116, Barry Lewis117, MD118, Carol Lim, BS119, Sharon Linard, MS120, Martin Lindner, MD121, Michele A. Lloyd-Puryear, MD122, Fred Lowry, MD123, Yannic L. Loukas, PhD124, Julie Luebke, BSc125, John F. Magnani, PhD126, Shavon Manuk127, NHS128, Sandrine Marie, PhD129, Siniia Marzec-Hadad130, Greg Marzuk131, Stephen J. Martin, MD132, Dietrich Mattner133, Stephanie K. Mayfield Gabel134, Philip Mayne, MD135, Tonya D. McCaffiter, MS136, MPH137, Mark McCann, BA138, Julie McCarr, MPH139, James J. McGill, MBBS140, Christine D. McHugh, PhD141, Panagiotis Moutoupis, MD142, Eleanor A. Mcdonough, RNC143, Dimitris Nikolaou, MD144, Bent Norgaard-Pedersen, PhD145, Devi Oglesby146, Marina Opatrny147, MD148, Daniela Obradovic149, Jelida Ochova, MPH150, Vagelis Papadopoulos151, MD152, Sherry Parlow Reyes, MD153, Hyung-Doo Park, MD154, Marie-Pascale Parry, MD155, Mario Partal, PhD156, Pallas Pasini, MD157, Kenneth A. Pearce158, MD159, balcony Peterson, MD160, William Peterson, MD161, James P. Pitt162, PhD163, Sherry Poh, MD164, Arnold Pollak, MD165, Cory Porter166, Philip A. Poston, PhD167, Wick P. Price, BSc168, Cecilia Quirino, BS169, Jose Ely Quiroz, MD170, Edward Randall171, PhD172, Kimiko Rayman173, John E. Reckle, PhD174, Alekzandra Resheva175, Charla Riccardi, BS176, Pietro Rizzuto, MD177, Jeff D. Rivera, PhD178, Alicia Roberts179, Hugo Rocha, MD180, Geraldine Roche, MD181, Sarah R. Rood, MD182, Scott Rood, PhD183, Ali Roudi184, MD185, Angela S. Roche, DSc186, Luisa Rojas, MD187, Rebecca Rojas, MD188, Joseph Rojas, MD189, Robyn Rojas, MD190, William Rojas, MD191, Mary A. Sceurman, PhD192, David E. Sessler193, Darren W. Siegel194, Scott M. Shore, PhD195, Graham Sinclair, PhD196, Greg Sivertsen, MD197, David Slocum, MD198, Charles Smith, MD199, Thomas D. Snodgrass, MD200, Rebecca Sobolewski, MD201, Kermit B. Sorensen, MD202, Karin Sorrell, MD203, John Stanley, MD204, Ashley Stasik, MD205, Alex Strickland, MD206, Emily S. Streeter, PhD207, Steve Struecker, MD208, Karen J. Stuever, MD209, Mark S. Suchy, MD210, Michael Szablewski, MD211, Veronica Tacher, MD212, Zarah Taylor213, MD214, Elinor T. Ching, MD215, Ferenc Tuly, MD216, Marco Vailati, MD217, Roberto Valderramos, MD218, Aric L. Van Den Heuvel, MD219, Francesca Vigano, MD220, J. Robert Thompson, MS221, B. Chris Verrier, FCPH222, Michael S. Waterson, Ph.D223, Dianne Webster, Ph.D224, Sheila West, MD225, Bruce Wicht, MD226, Kenneth Williams, MD227, Karen Wilson, MD228, Raghav Yajnik, MD229, Seiji Yamaguchi, MD230, Melissa Yazel, MD231, MB, UCSF, FC Path(SA) Chem232, and Wendy M. Zakowicz, BS233

http://www.clir-r4s.org/
NBS Data Project

Mayo Study (as of March 21st, 2013)

True positive cases (not NBS): 553
Is There a Highly Specific NBS Assay for Pompe Disease?
Is There a Highly Specific NBS Assay for Pompe Disease?

Luminex [concentration]

99th %ile
90th %ile
Median
10th %ile
1st %ile

ng/mL

normal
Cidrait Percentiles
FP
pseudo
carrier
TP
TP (NBS)

Disease Ranges
Is There a Highly Specific NBS Assay for Pompe Disease?

Advanced Liquid Logic [activity]
Samples tested: 53,290  53,290  45,116

GAA abnormal:
- Luminex: 143
- MS/MS 251
- Adv. Liquid Logic 191

GAA activity (2\textsuperscript{nd} Tier) 21 abnormal
Status of NBS Study for Pompe Disease

Samples tested: 53,290 53,290 45,116

GAA abnormal:
- Luminex: 143 (0.27%)
- MS/MS: 251 (0.47%)
- Adv. Liquid Logic: 191 (0.42%)

GAA activity (2nd Tier)
21 abnormal (0.04%)
Samples tested: 53,290  53,290  45,116

GAA abnormal:
- Luminex: 143 (0.27%)  
- MS/MS: 251 (0.47%)  
- Adv. Liquid Logic: 191 (0.42%)

GAA activity (2nd Tier)
- 21 abnormal (0.04%)

GAA genotyping
- 2 Affected (likely late onset)
- 4 Pseudo deficiency
- 3 Carrier
- 1 False positive
Samples tested: 53,290 53,290 45,116

GAA abnormal:
- Luminex: 143 (0.27%)
- MS/MS: 251 (0.47%)
- Adv. Liquid Logic: 191 (0.42%)

Developed as more study samples are sequenced and categorized (TP, FP, Carrier, Pseudo).
**Status of NBS Study for Krabbe Disease**

Samples tested:

53,290

(3 samples with 2 mutations)

False positive rates for analyte COMBINATIONS:

- GALC Concentration LOW
  - Poly: 64
  - Mono: 159
  - Both: 54
  - 0.12%

- Concentration & Activity LOW:
  - 16
  - 0.03%

- GALC Activity LOW
  - 56
  - 0.10%
Is There a Highly Specific NBS Assay for Krabbe Disease?

Psychosine (galactosylsphingosine) is a substrate for GALC

Accumulation leads to demyelination and neurodegeneration
Is There a Highly Specific NBS Assay for Krabbe Disease?

Psychosine [conc.]
(LC-MS/MS; 2\textsuperscript{nd} Tier)
What about the other Disorders?

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>Prevalence</th>
<th>FPR</th>
<th>PPV</th>
<th>Predicted Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fabry disease</td>
<td>1 : 1,100 boys</td>
<td>0.03%</td>
<td>60%</td>
<td>mostly mild</td>
</tr>
<tr>
<td>Gaucher disease</td>
<td>1 : 53,000</td>
<td>0.04%</td>
<td>4.6%</td>
<td>GD I</td>
</tr>
<tr>
<td>Krabbe disease</td>
<td>1 : 18,000</td>
<td>0.05%</td>
<td>9.6%</td>
<td>late onset</td>
</tr>
<tr>
<td>MLD</td>
<td>1 : 53,000</td>
<td>0.02%</td>
<td>8.3%</td>
<td></td>
</tr>
<tr>
<td>MPS I</td>
<td>1 : 26,500</td>
<td>0.04%</td>
<td>8.3%</td>
<td>MPS IS</td>
</tr>
<tr>
<td>MPS II</td>
<td>1 : 4,500 boys</td>
<td>0.01%</td>
<td>50%</td>
<td>all VUS</td>
</tr>
<tr>
<td>MPS IIIA</td>
<td>1 : 26,500</td>
<td>0.03%</td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td>MPS IIIB</td>
<td>&lt;1 : 53,000</td>
<td>0.02%</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>MPS VI</td>
<td>1 : 53,000</td>
<td>0.02%</td>
<td>7.1%</td>
<td></td>
</tr>
<tr>
<td>MSD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Niemann-Pick A/B</td>
<td>1 : 26,500</td>
<td>0.05%</td>
<td>7.1%</td>
<td>comp. hetero with VUS</td>
</tr>
<tr>
<td>Pompe Disease</td>
<td>1 : 26,500</td>
<td>0.02%</td>
<td>20%</td>
<td>late onset</td>
</tr>
<tr>
<td>Wilson disease</td>
<td>&lt;1 : 53,000</td>
<td>0.05%</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Friedreich Ataxia</td>
<td>&lt;1 : 53,000</td>
<td>0.01%</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>X-ALD</td>
<td>&lt;1 : 53,000</td>
<td>0.08%</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>1 : 1,200</strong></td>
<td><strong>0.46%</strong></td>
<td><strong>18%</strong></td>
<td></td>
</tr>
</tbody>
</table>

Very preliminary data
Mayo Clinic’s Biochemical Genetics Lab is evaluating 3 different multiplex assays in a prospective, comparative effectiveness study of 100,000 NBS samples (ends 9/2013).

53,290 NBS samples tested to date.

All assays seem sensitive.

No assay seems sufficiently specific (but combining assays helps to reduce false positive rate).

Genotyping improves specificity … but may not be cost effective (+ too many variants of uncertain significance).

Need biomarkers to improve specificity and for disease prediction.
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