An Update on R4S and CLIR

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The Advisory Committee on Heritable Disorders in Newborns and Children
May 11, 2017
Guidance from ACHDNC

• Provide a high level overview of R4S and CLIR
• Specific questions to address:
  – What are R4S and CLIR used for and what is the difference between the two systems?
  – Who can access R4S and CLIR and how are they accessed?
  – How can these tools be used in the context of setting cutoffs or establishing algorithms?
Outline

• Background of the two systems

• Comparison between R4S and CLIR
  – Differences
  – Access
  – Utilization
  – Examples of performance
About R4S

• Region 4 Stork (R4S) started as a regional laboratory quality improvement project of expanded newborn screening by tandem mass spectrometry (7 state programs)

• R4S was selected in 2004 as one of three priority projects of the Regional Genetics Collaborative Program funded by the Health Resources and Services Administration

• In May 2012 the R4S database became part of the Newborn Screening Translational Research Network, which is funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development

www.nbstrn.org
What Is R4S Used For?

• R4S is used **exclusively** for newborn screening by tandem mass spectrometry (MS/MS), limited to **FIRST SPECIMEN**
  – 258 sites in 68 countries
  – 1,227 users with an active password
  – 2016 average of daily user logins: 72
  – 2016 average of monthly user access: 335 (27%)
  – 2016 calculated tool scores 88 millions (17M cases)

• Other applications (SCID, BIOT, MS/MS[2]) **have not** reached a critical mass of users and data to be clinically relevant, due in part to fading engagement of content experts initially asked to serve as curators (“hunters”)

• R4S **is not** an ideal environment for pilot studies of new conditions (more rationale later)
About CLIR

https://clir.mayo.edu

CLIR 2 Releases

- 2.00 Jan 23, 2015
- 2.01 Jun 03, 2015
- 2.02 Sep 09, 2015
- 2.03 Apr 18, 2017
About CLIR

Collaborative Laboratory Integrated Reports (CLIR) is an interactive Web Tool created jointly by staff of the Biochemical Genetics Laboratory, Department of Laboratory Medicine and Pathology, and of the Department of Information Technology, Mayo Clinic. Key contributors and collaborators are located at Oslo University Hospital, Norway, and at the California Department of Public Health.

The clinical utility of CLIR is based on three major elements:

1. Replacement of traditional cutoff values with continuous adjustments for age and other covariates of reference ranges shown as seamless percentile charts. CLIR reference ranges are derived by retrospective analysis of "big data", tens and even hundreds of thousands of data points from a growing worldwide community of collaborators.

2. Creation of cumulative, covariate-adjusted disease ranges for all informative markers for target conditions, usually clustered by specialty and/or type of markers;

3. Post-analytical interpretive tools that integrate all relevant results into a single score. Tools are applicable either to the diagnosis and/or prognosis of a condition or to the differential diagnosis between pairs of conditions (for example benign variant vs. classic disease, responsive/not responsive to treatment).

A complete list of clinical applications can be provided upon request.

Please contact us (RSTCLIRsupport@mayo.edu) if you would like to participate in CLIR or have any questions.
What Does CLIR Do, Exactly?

• Replaces conventional reference ranges
  – With continuous, covariate-adjusted %iles

• Replaces analyte cutoff values
  – With a condition-specific degree of overlap

• Enhances the clinical utility of individual markers
  – With all possible permutation of ratios

• Replaces sequential algorithms ("AND")
  – With tool-based parallel algorithms ("OR")
<table>
<thead>
<tr>
<th>Feature</th>
<th>R4S</th>
<th>CLIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous covariate-adjusted percentiles</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Condition specific degree of overlap</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>All possible permutations of ratios</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Tool based parallel algorithms</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Consideration for cutoff values</td>
<td>yes</td>
<td>no</td>
</tr>
</tbody>
</table>
17-OH Progesterone Ref. Range Adjusted for Age, BW, and Sex

(N=1,672,266)

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What Is CLIR Used For?

• R4S is also used for newborn screening by tandem mass spectrometry (MS/MS), ANY SPECIMEN up to 1 yr of age
  – 57 sites in 34 countries (13 US states)
  – 275 users with an active password

• 100+ other applications (NBS, diagnostic labs, research), 39 of them have reached a critical mass of data to be clinically relevant
Serum Cholesterol Ref. Range
Adjusted for Age, BMI, and Sex

Data sample from NHANES - CDC (N=15,188)

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  – 275 users with an active password

• 100+ other applications (NBS, diagnostic labs, research), 39 of them have reached a critical mass of data to be clinically relevant

• CLIR is an ideal environment for pilot studies of new conditions under consideration for addition to RUSP
Main Differences between R4S and CLIR

- Code
- Comparison
- Data
- Team
- Tools
## Differences in **CODE**

<table>
<thead>
<tr>
<th>Feature</th>
<th>R4S</th>
<th>CLIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>IT infrastructure</td>
<td>NBSTRN</td>
<td>Mayo</td>
</tr>
<tr>
<td>.net version</td>
<td>3.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Integration of statistical package R</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>SQA documented testing scenarios</td>
<td>not done</td>
<td>2,854</td>
</tr>
<tr>
<td>* SQA recorded testing hours</td>
<td>not done</td>
<td>4,667</td>
</tr>
<tr>
<td>Last code update</td>
<td>08/01/2013</td>
<td>04/18/2017</td>
</tr>
<tr>
<td>Microsoft long term support</td>
<td>limited</td>
<td>extended</td>
</tr>
</tbody>
</table>

* SQA, System Quality Assurance of IT Department, Mayo Clinic
<table>
<thead>
<tr>
<th>Differences in <strong>COMPARISON</strong> Tools</th>
<th>R4S</th>
<th>CLIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual markers</td>
<td>c</td>
<td>yes-by</td>
</tr>
<tr>
<td>(conditions)</td>
<td>by group</td>
<td>selection</td>
</tr>
<tr>
<td>Reference percentiles</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>(adjusted values)</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Cutoff values</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Performance metrics</td>
<td>yes</td>
<td>not yet</td>
</tr>
<tr>
<td></td>
<td>cumulative</td>
<td>by marker</td>
</tr>
</tbody>
</table>
## Differences in DATA

<table>
<thead>
<tr>
<th></th>
<th>R4S</th>
<th>CLIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covariate adjustments</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Contribution of reference data</td>
<td>percentiles</td>
<td>raw data</td>
</tr>
<tr>
<td>Contribution of covariate data</td>
<td>no</td>
<td>raw data</td>
</tr>
<tr>
<td>Procedure to generate ratios</td>
<td>manual</td>
<td>automated</td>
</tr>
<tr>
<td>Quarantine of new data</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Centralized marker repository</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Process to upload data</td>
<td>manual</td>
<td>automated</td>
</tr>
<tr>
<td>Process to delete data</td>
<td>only by Mayo team level</td>
<td>At the site level</td>
</tr>
</tbody>
</table>
### Differences in **TEAM**

<table>
<thead>
<tr>
<th></th>
<th>R4S</th>
<th>CLIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayo team size</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>System manager (statistician)</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>External development collaborators</td>
<td>0</td>
<td>6</td>
</tr>
</tbody>
</table>

**Mayo IT personnel**
- Bob Currier (CA)
- Leifur Franzson (ISL)
- Tricia Hall (GA)

**Mayo IT personnel**
- Lars Mørkrid (Oslo)
- Joe Orsini (NY)
- Alex Rowe (Oslo)

**Mayo IT personnel**
- Joshua Brown
- Eduardo Camara
- John Kappler
- Gregg Marquardt
- David McHugh

**Mayo IT personnel**
- Bobby Miller
- Alanna Petersen
- Neil Schubauer
- Stephanie Stoway
- (system manager)
## Differences in **TOOLS**

<table>
<thead>
<tr>
<th>Feature</th>
<th>R4S</th>
<th>CLIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Productivity tool types</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>Usability enhancements</td>
<td>none</td>
<td>many!</td>
</tr>
<tr>
<td>Printable reports (PDF)</td>
<td>basic</td>
<td>customized</td>
</tr>
<tr>
<td>Customization of site-specific tools</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Configuration of site-specific panels</td>
<td>no</td>
<td>yes</td>
</tr>
</tbody>
</table>

![Buttons](image)
Access to R4S

• Process initiated by
  – Request send directly to Mayo team via email (~70%)
  – Registration process on NBSTRN website home page (~30%)

Request Access to NBSTRN Tools

Select NBSTRN Tool(s)

- R4S
- VRDBS
- LPDR
Access to R4S

• Process initiated by
  - Request send directly to Mayo team via email (~70%)

From:
Sent: Monday, May 08, 2017 3:16 PM
To: Rinaldo, Piero, M.D., Ph.D.
Subject: R4S Access request

Hello Dr Rinaldo,
I am hoping you can grant me access to your R4S program. I heard about it at XXXXX recent conference in XXXXX and know it would be a valuable tool in my role as newborn screen coordinator at XXXXX. I look forward to hearing from you. Thanks for your consideration,

XXXXXX
Eligibility (R4S)

- Actual or indirect (professional working in the same state) affiliation with a newborn screening program
- Residents and fellows in training
- Patient advocates
- Organizations (ACMG)
- Government (NIH, HRSA, CDC, FDA)
- Commercial entities (case by case)
6-Month Moving Average of R4S User Logins/Month

- US users
- International users

12/2015 vs. 12/2016

- 22% increase
- 9% decrease
CT, GA, KY, and MD are the only US states among the top 20 locations (countries) worldwide.
Access to CLIR

• Process initiated by
  – Request send directly to Mayo team via email (~5%)
  – Registration process on CLIR website log in page (~95%)
How to Request Access to CLIR

Email sent to RSTCLIRsupport@mayo.edu

Select Institution Type
- Academic Institution
- Business
- Government
- Hospital
- Non Profit Organization

Select Professional Field
- Biochemical Geneticist
- Clinical Chemist
- Development Technologist
- Fellow
- Genetic Counselor
- Laboratory Director
- Laboratory Technologist
- Pathologist
- Pediatrician
- Physician/Surgeon
- Researcher
- Resident
- Statistician
- Student
- Other - please explain in comment box

Send Request

RST CLIR Support

Inbox
Eligibility (CLIR)

• After initial vetting, any individual or entity willing to contribute sufficient anonymized data* UPFRONT (before access is granted)

• Access is given to all applications utilizing the submitted data (from the central repository)

• If data are deleted by user, access to the same application(s) is revoked, but not to others

• Surfers, lurkers, and the just curious are ….. not eligible

* de-identified data with demographic covariates have been deemed by the Mayo Clinic IRB to still constitute anonymized data
What is the Main Difference in Access/Participation/Utilization between R4S and CLIR?
Examples of Performance (R4S/CLIR Tools without cutoffs)

<table>
<thead>
<tr>
<th>Performance Example</th>
<th>R4S</th>
<th>CLIR</th>
<th>CLIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>NBS test</td>
<td>MS/MS</td>
<td>KMP</td>
<td>MPX</td>
</tr>
<tr>
<td>Conditions</td>
<td>RUSP</td>
<td>Krabbe MPS I Pompe</td>
<td>MPS I Pompe X-ALD</td>
</tr>
<tr>
<td>From (date)</td>
<td>1/1/2013</td>
<td>2/18/2016</td>
<td>11/18/2016</td>
</tr>
<tr>
<td>To (date)</td>
<td>12/31/2013</td>
<td>4/30/2017</td>
<td>4/30/2017</td>
</tr>
<tr>
<td>State</td>
<td>MN</td>
<td>KY</td>
<td>Mayo</td>
</tr>
<tr>
<td>Newborns tested</td>
<td>71,207</td>
<td>65,433</td>
<td>2,635</td>
</tr>
<tr>
<td>True positive cases</td>
<td>38</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>False positive case</td>
<td>17</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>False positive rate (FPR)</td>
<td>0.02%</td>
<td>0.00%</td>
<td>0.00%</td>
</tr>
</tbody>
</table>
Future Releases of CLIR

2017 CLIR Roadmap

Key:
- Development
- SQA Testing
- Implementation

Milestones:
- 2.03.00: N/A
- 2.04.00: N/A
- 2.05.00: N/A

- Code Begin: N/A
- Test Plan Begin: N/A
- Code Complete: N/A
- Test Complete: N/A
- Release Readiness: N/A
- Implementation: N/A

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