An Update on R4S and CLIR

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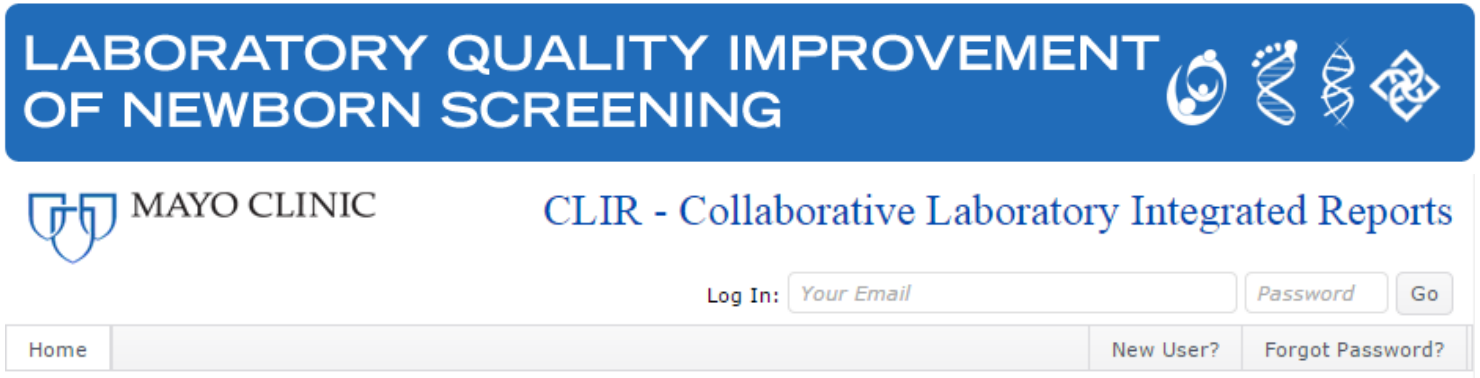


The Advisory Committee on Heritable Disorders in Newborns and Children

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

Region4
Genetics Collaborative

- 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

NBSTRN
Newborn Screening
Translational Research
Network

www.nbstrn.org

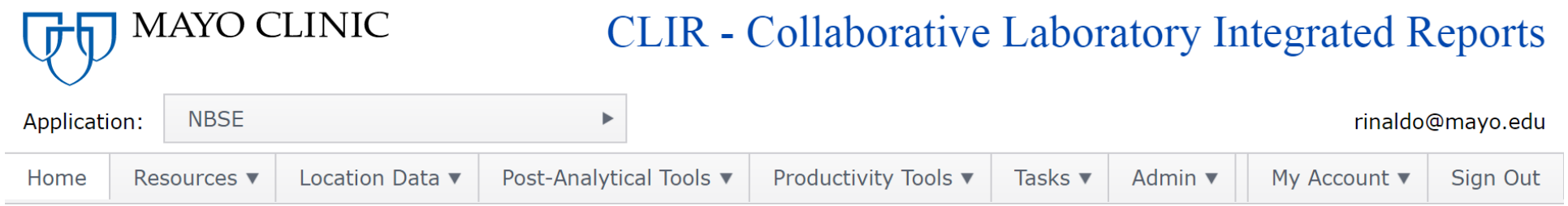
What Is R4S Used For?

- **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)**

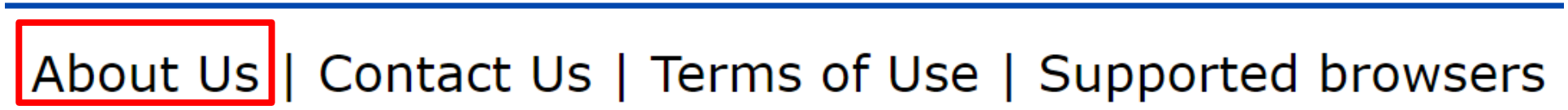
About CLIR



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**



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About CLIR

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.

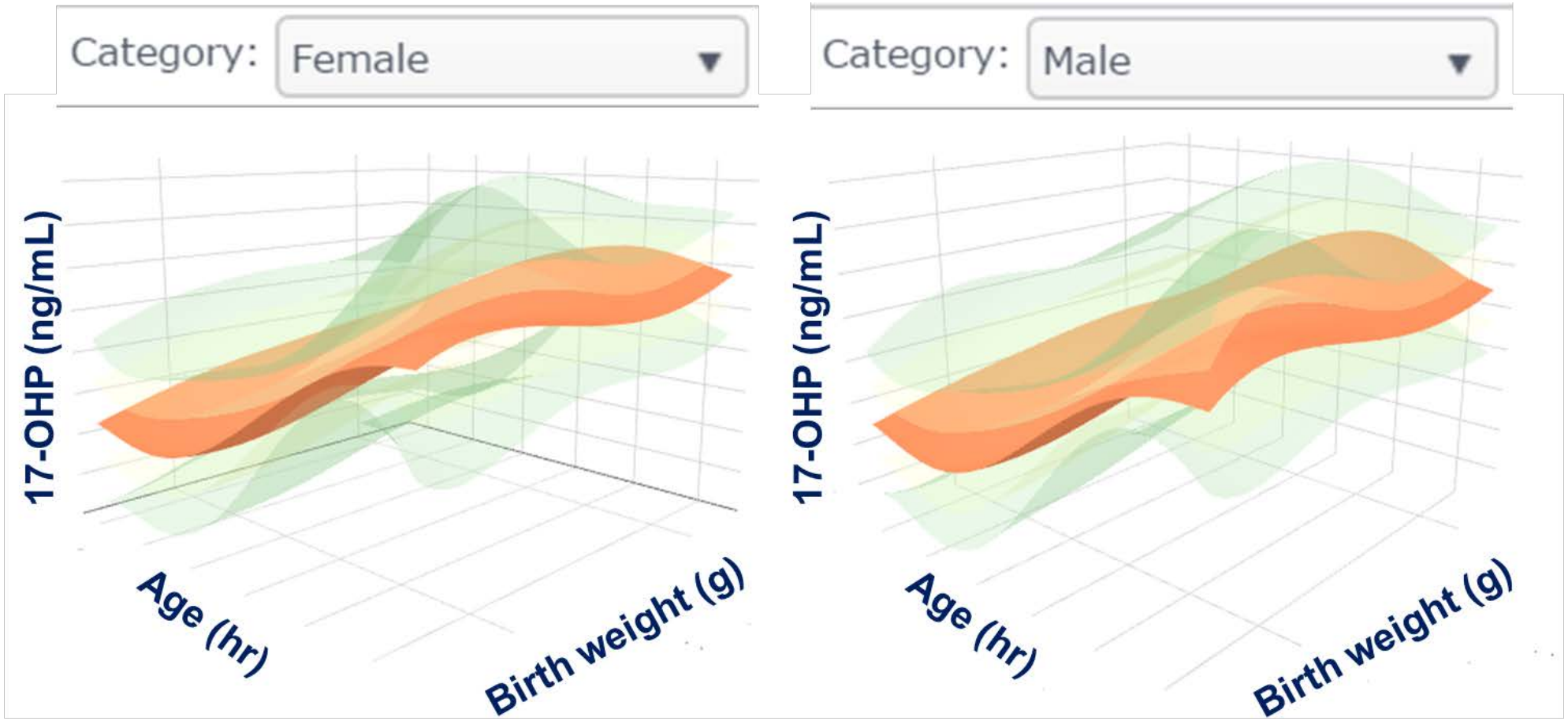
What Does CLIR Do, Exactly?

- 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”)

What are the Differences?

	R4S	CLIR
Continuous covariate-adjusted percentiles	no	yes
Condition specific degree of overlap	yes	yes
All possible permutations of ratios	yes	yes
Tool based parallel algorithms	yes	yes
Consideration for cutoff values	yes	no

17-OH Progesterone Ref. Range Adjusted for Age, BW, and Sex



(N=1,672,266)

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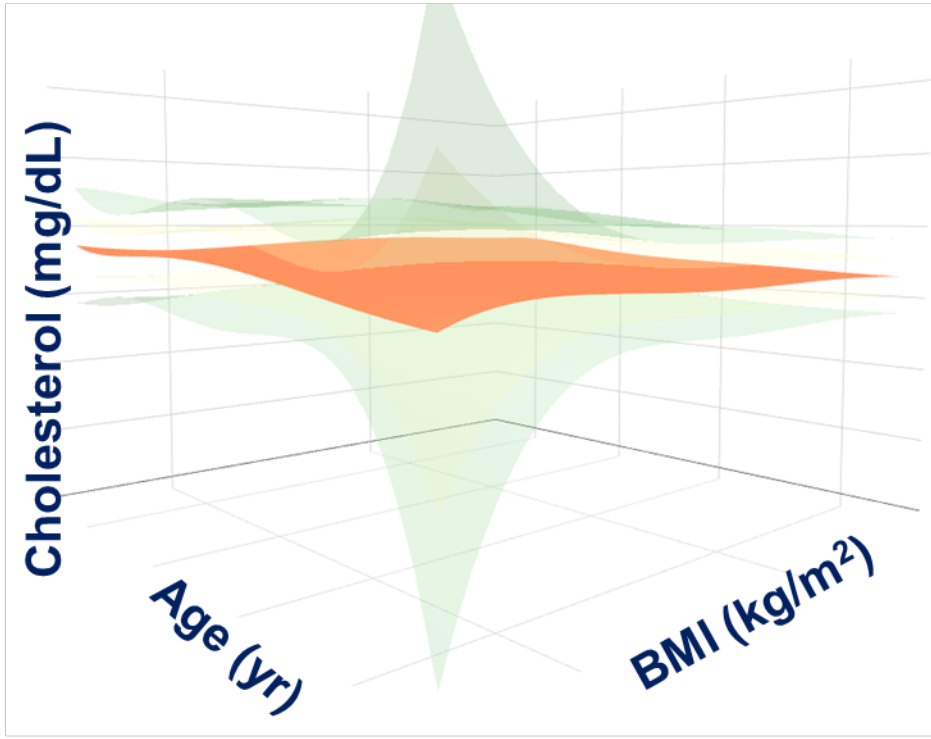
What Is CLIR Used For?

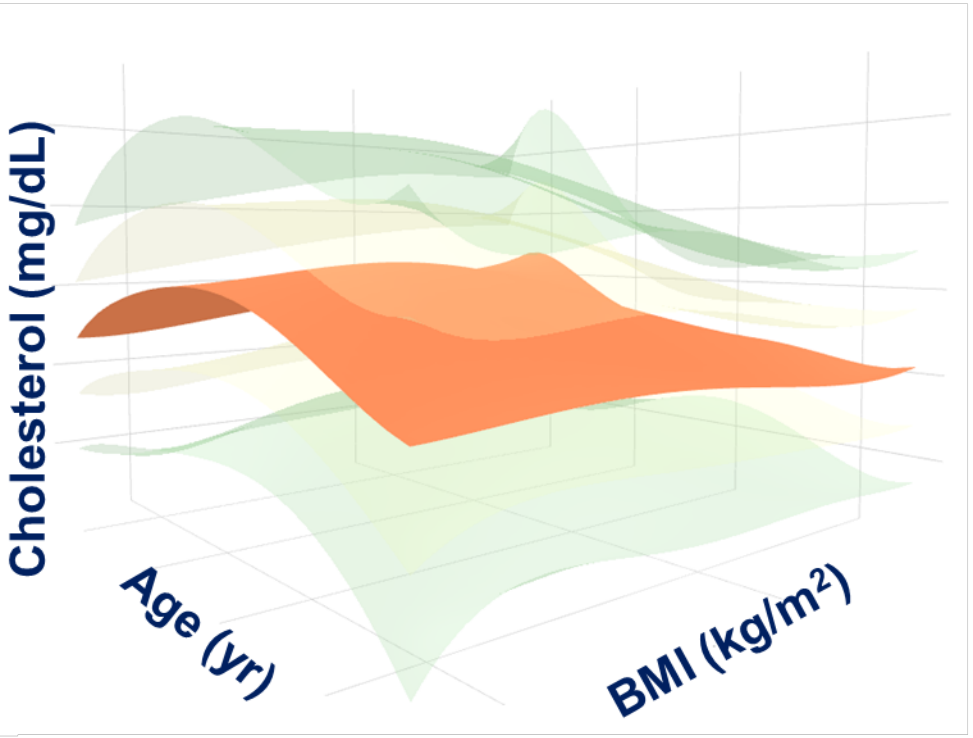
- R4S is also used for newborn screening by tandem mass spectrometry (MS/MS), ANY SPECIMEN up to 1 yr of age
  - 57 sites in 34 countries (13 US states)
  - 275 users with an active password
- 100+ other applications (NBS, diagnostic labs, research), 39 of them have reached a critical mass of data to be clinically relevant

Serum Cholesterol Ref. Range Adjusted for Age, BMI, and Sex

Category: Female



Category: Male



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

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- 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

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

* SQA, System Quality Assurance of IT Department, Mayo Clinic

Differences in COMPARISON Tools

	R4S	CLIR
Individual markers (conditions)	c by group	yes-by selection
Reference percentiles (adjusted values)	yes no	yes yes
Cutoff values	yes	no
Performance metrics	yes cumulative	not yet by marker

Differences in DATA

	R4S	CLIR
Covariate adjustments	no	yes
Contribution of reference data	percentiles	raw data
Contribution of covariate data	no	raw data
Procedure to generate ratios	manual	automated
Quarantine of new data	no	yes
Centralized marker repository	no	yes
Process to upload data	manual	automated
Process to delete data	only by Mayo team	At the site level

Differences in TEAM

	R4S	CLIR
Mayo team size	3	10
System manager (statistician)	no	yes
External development collaborators	0	6

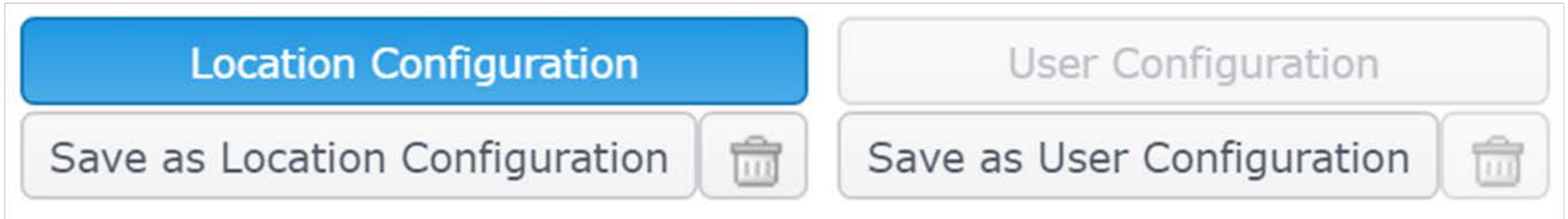
Bob Currier (CA)
Leifur Franzson (ISL)
Tricia Hall (GA)
Lars Mørkrid (Oslo)
Joe Orsini (NY)
Alex Rowe (Oslo)

Mayo IT personnel

Joshua Brown
Eduardo Camara
John Kappler
Gregg Marquardt
David McHugh
Bobby Miller
Alanna Petersen
Neil Schubauer
Stephanie Stoway (system manager)

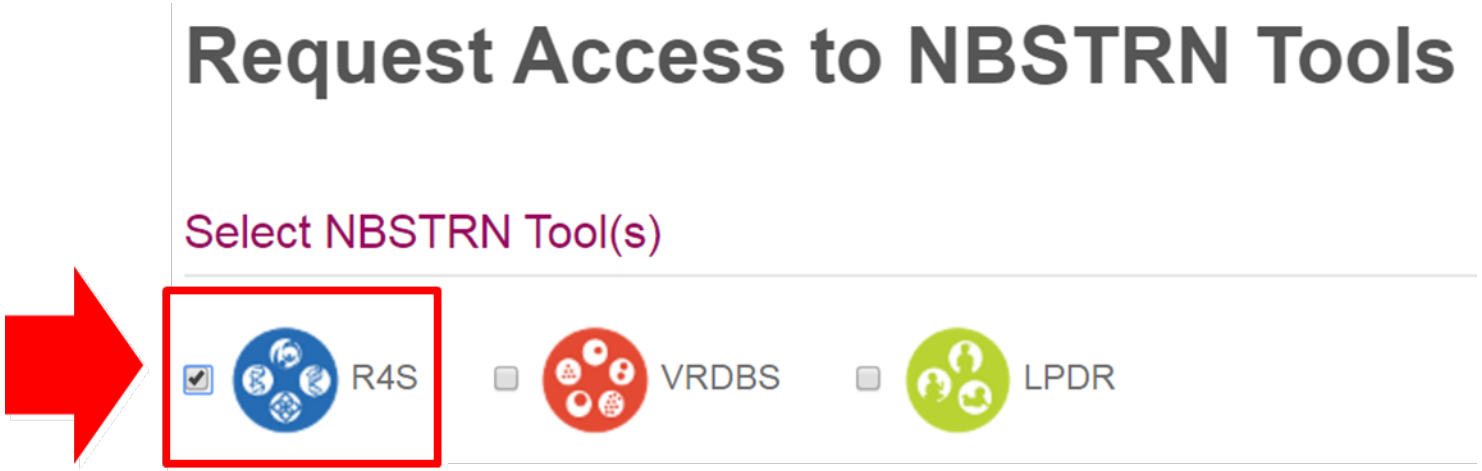
Differences in TOOLS

	R4S	CLIR
Productivity tool types	8	15
Usability enhancements	none	many!
Printable reports (PDF)	basic	customized
Customization of site-specific tools	yes	yes
Configuration of site-specific panels	no	yes



Access to R4S

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



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

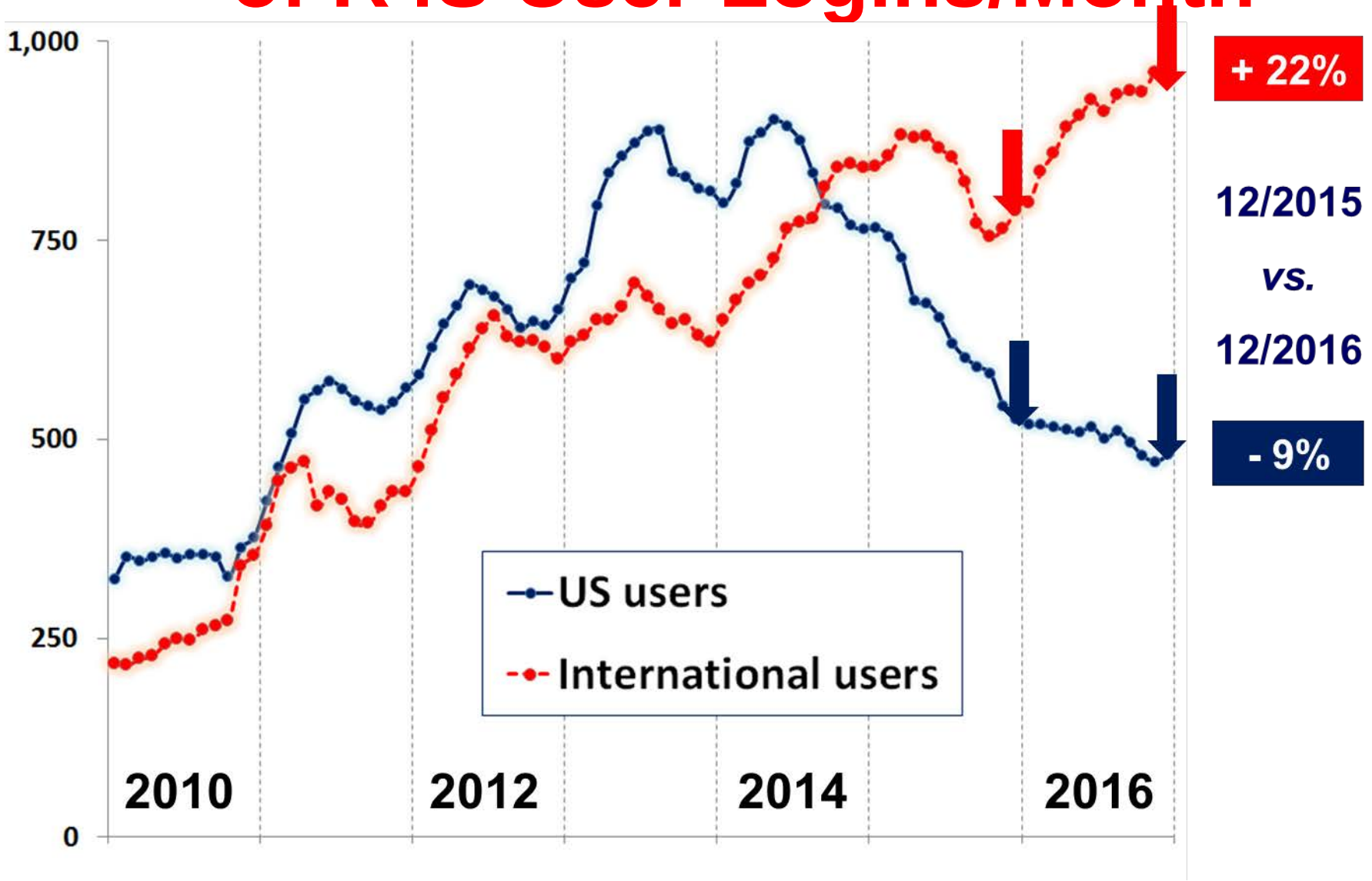
Hello Dr Rinaldo,
I am hoping you can grant me access to your R4S program. I heard about at XXXXX recent conference in XXXXX and know it would be a valuable tool in my role as newborn screen coordinator at XXXXX. I look forward to hearing from you.
Thanks for your consideration,

xxxxxx

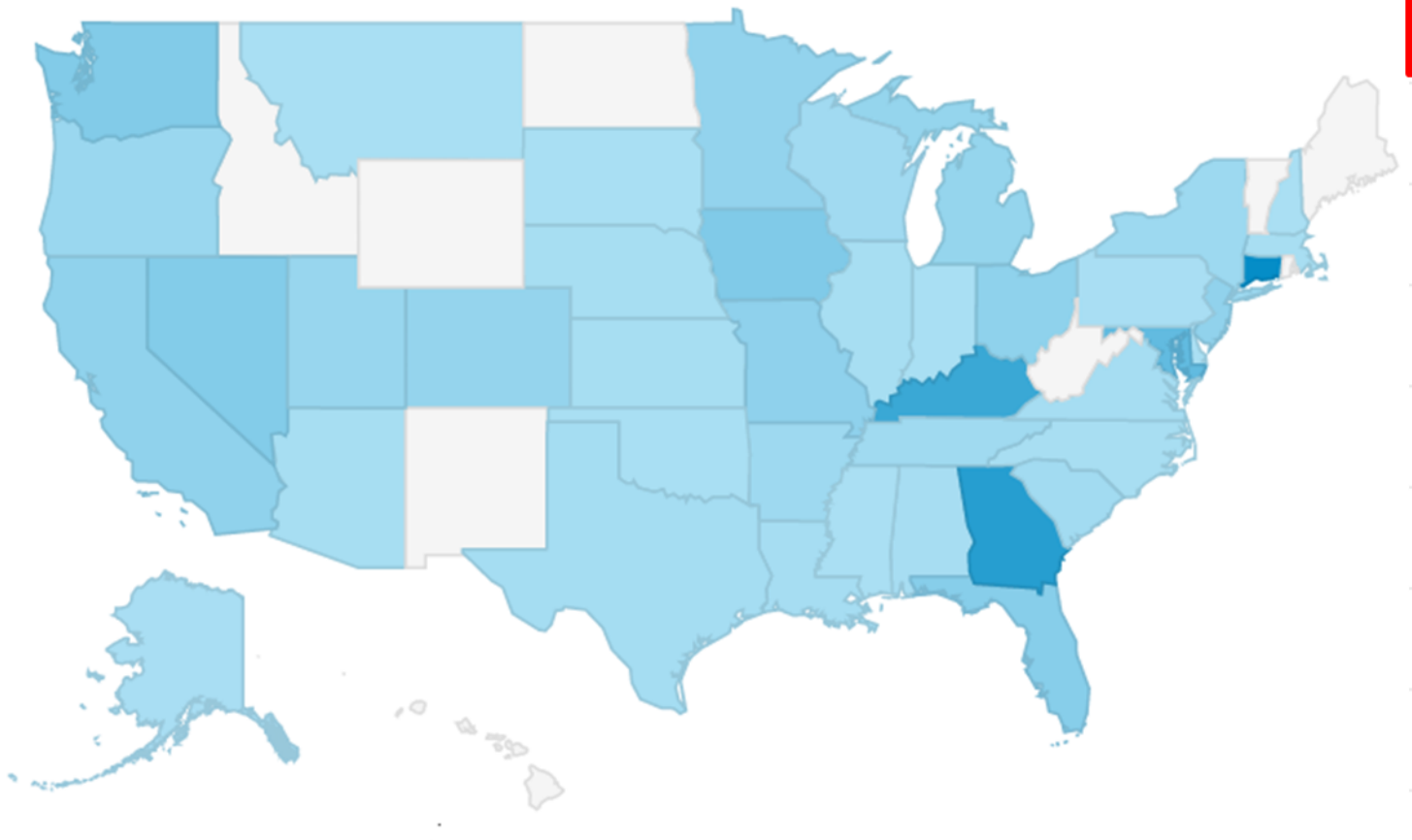
Eligibility (R4S)

- 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 Utilization of R4S
(May 1, 2016 to April 30, 2017)



1. Connecticut
2. Georgia
3. Kentucky
4. Maryland
5. Iowa
6. Washington
7. Nevada
8. Florida
9. Missouri
10. Ohio

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

Request Access

First Name

Middle Name

Last Name

Email Address

Country

City

State/Province

Institution/Company Name

Institution/Company Type

Select Institution Type

Professional Field of User

Select Professional Field

Comments

Enter Comments here

Remaining characters 999

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

Email sent to RSTCLIRsupport@mayo.edu

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

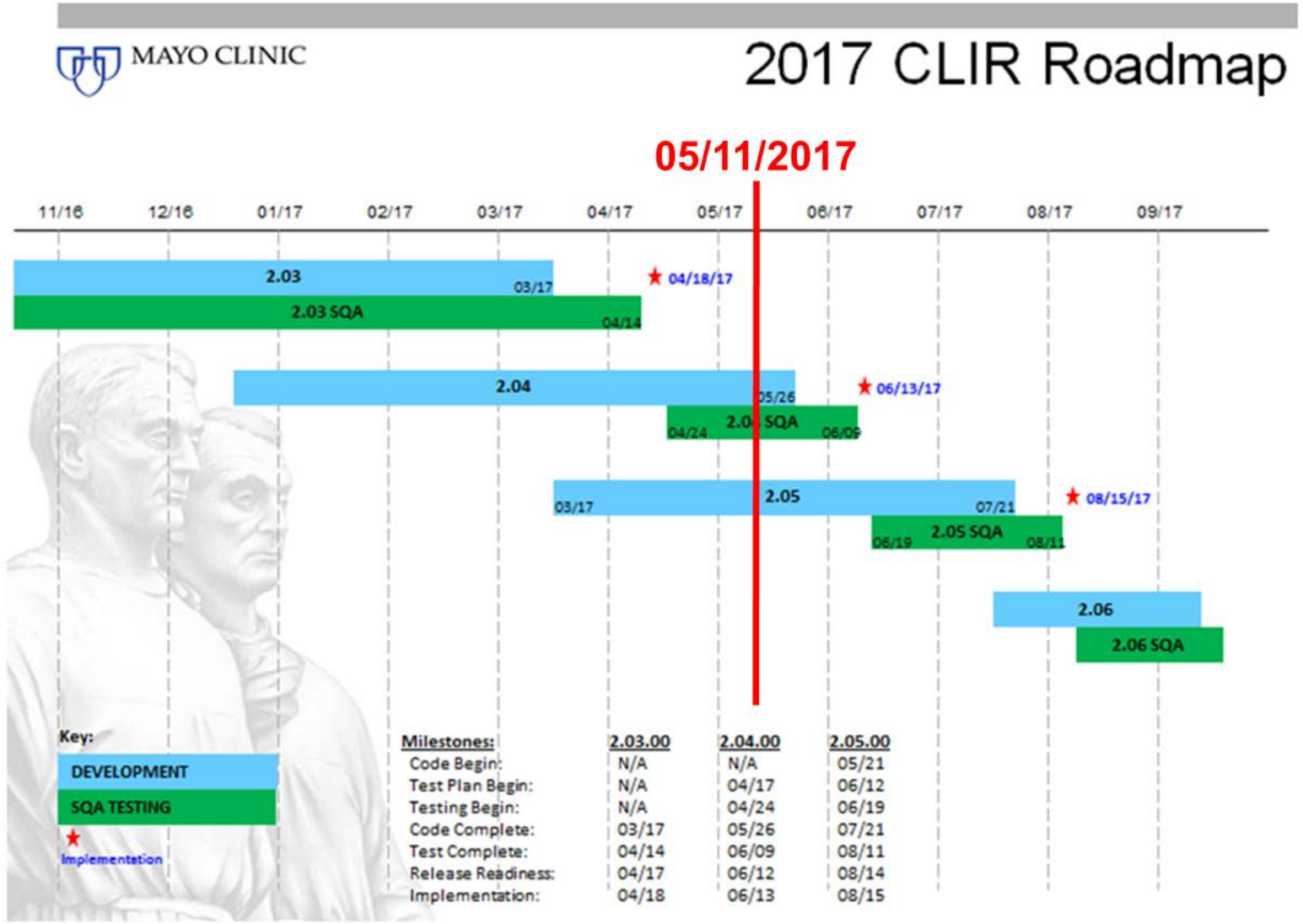
* de-identified data with demographic covariates have been deemed by the Mayo Clinic IRB to still constitute anonymized data

What is the Main Difference in Access/Participation/Utilization between R4S and CLIR?

Examples of Performance (R4S/CLIR Tools without cutoffs)

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

Future Releases of CLIR



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