

# The Impact, Products, and Future Applications of the Region 4 Collaborative Project

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**NEWBORN SCREENING  
COLLABORATIVE PROJECTS**



**2011 NEWBORN SCREENING  
AND GENETIC TESTING SYMPOSIUM**

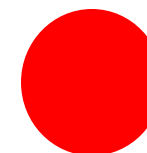
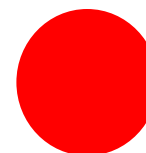
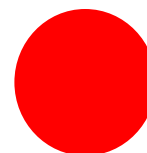
*Fair Winds for the Future*

**San Diego (CA) November 8, 2011**



# Outline

- **Impact of R4S project**
  - **Utilization**
  - **Lessons learned**
- **Products**
- **Future applications**



# Outline

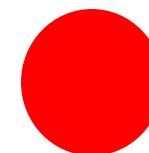
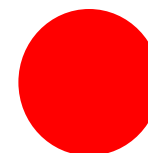
- **Impact of R4S project**

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# R4S Collaborative Project

- HRSA-funded project (2004-2012) aimed initially at laboratory quality improvement of newborn screening by MS/MS
- Standardized collection and objective peer comparison of screening data

# Data Collected



- **Participant profile**  
Method, reagents, derivatization
- **Percentiles of normal population**  
Amino acids, acylcarnitines, ratios
- **Cutoff values**
- **Confirmed positive cases**  
Amino acids, acylcarnitines, ratios
- **Performance metrics**  
Detection rate, FPR, PPV

# Project in Numbers



**11-08-2011**

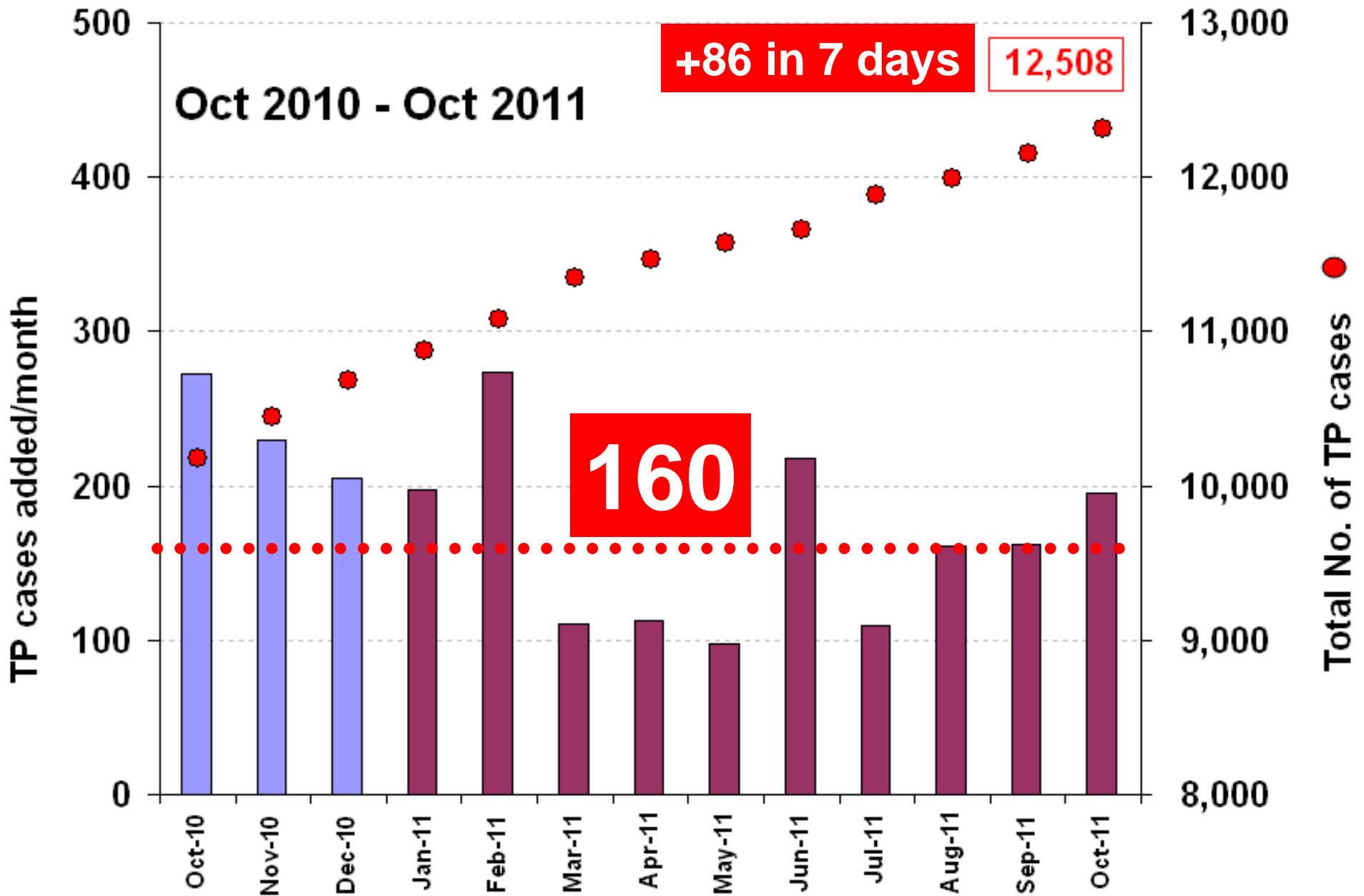
**True positive cases 12,594**

**True positive data points 754,891**

**Percentiles (sites) 29,291 (111)**

**Cutoff values (sites) 6,613 (122)**

# TP Cases Added per Month



# Project Participation

11-07-11

Participating sites  
Users with password  
US states & territories  
Programs  
Countries

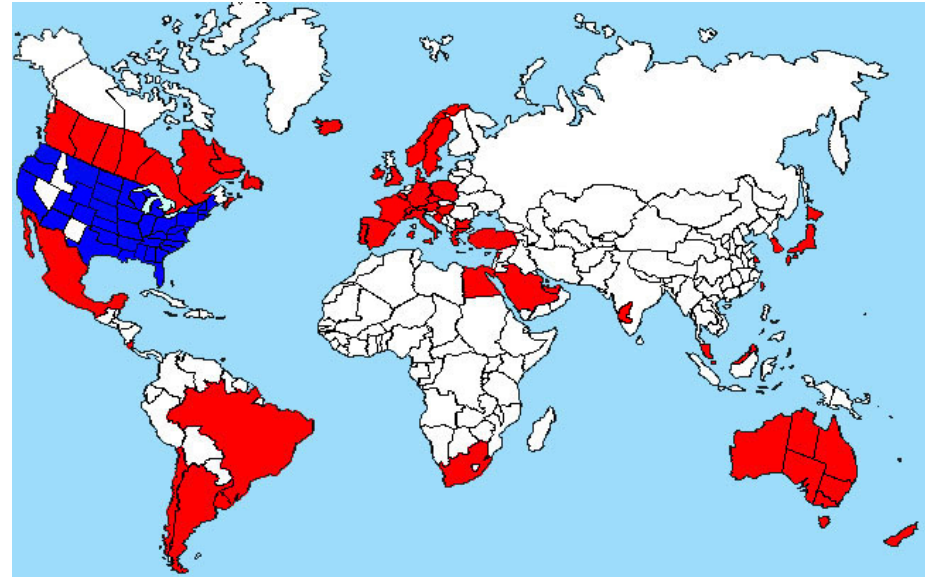
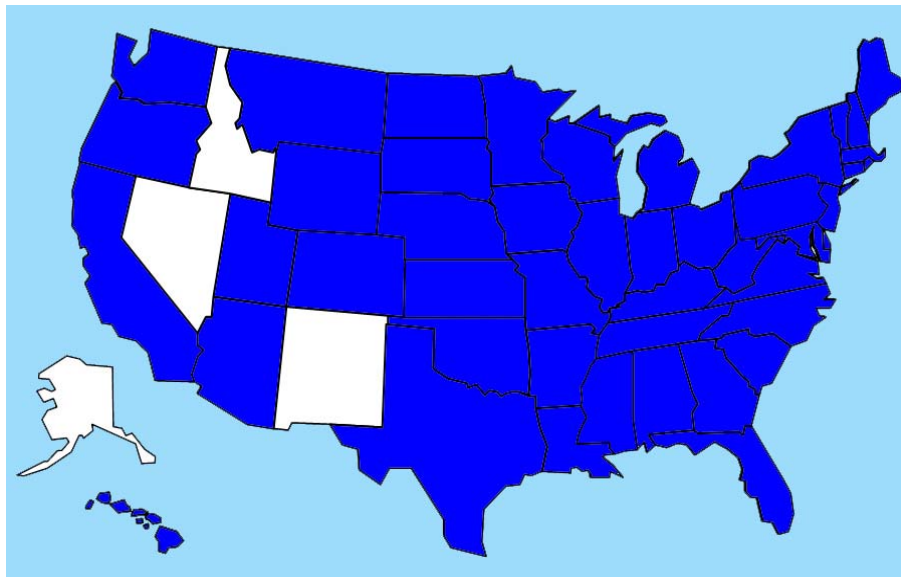
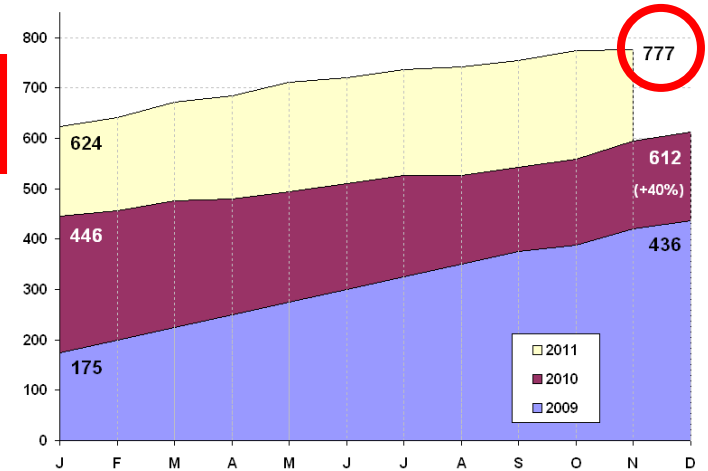
144

777

48

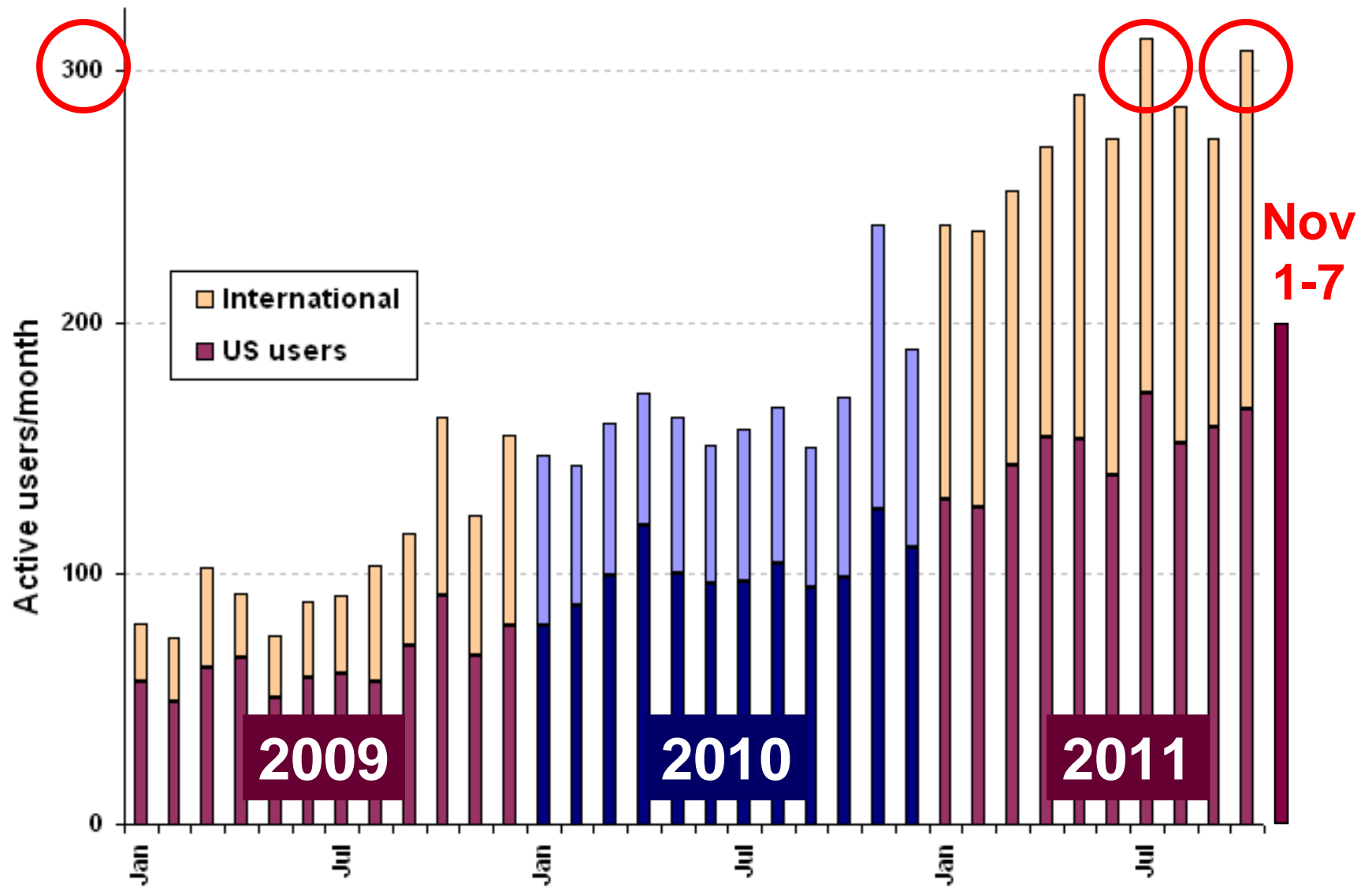
96

49





# Active Users (1/2009-10/2011)



# The R4S Website

**MS/MS COLLABORATIVE PROJECT**



Home    Data Submission    Tools & Reports    User Settings    Documentation    Site Admin    Log Out

Welcome: Piero Rinaldo

## CURRENT DATA POSTED BY YOUR NEWBORN SCREENING LABORATORY

- [Cutoff Values](#)
- [Normal Percentiles](#)
- [True Positives](#)
- [Performance Metrics](#)
- [Last Update](#)

## COMPARE YOUR LABORATORY DATA WITH OTHER PARTICIPANTS

- [Cutoff Values Comparison](#)
- [Percentiles Comparison](#)
- [Performance Metrics Comparison](#)
- [Disease Range](#)
- [Disease Range \(MoM\)](#)
- [Analyte Comparison](#)
- [Profile Comparison](#)

## CUMULATIVE PROJECT DATA

- [Participant Profile](#)    Participant profile summary of all responses
- [Score Cards](#)    Tabular summary of all data (sorted by analyte type)
- [Plots by Target Range](#)    Display of evidence-based and actual cutoff distribution for one analyte
- [Plots by Condition](#)    Which analytes are informative for a specific condition?
- [Plots by Marker](#)    Which conditions present with abnormal levels of a specific analyte?

## INTERACTIVE POST-ANALYTICAL TOOLS

- [Scatter Plot](#)    Compare results of multiple cases to true positives of any condition
- [Post-Analytical Tools](#) **NEW!**    Calculate a condition-specific score for a case based on all clinically significant analytes and ratios

## DOCUMENTATION

- [Procedures](#)    How to use the tools on this web site

## RELATED SITES

- [ACMG act sheets](#)    Newborn screening act sheets and confirmatory algorithms
- [NCC website](#)    National coordinating center for the genetics and newborn screening regional collaborative groups
- [Region 6 Laboratory Quality Assurance project](#)    Exchange of blood spots for educational purposes to improve quality of newborn screening by MS/MS

<http://www.region4genetics.org/>

# Website Utilization (11-07-11)

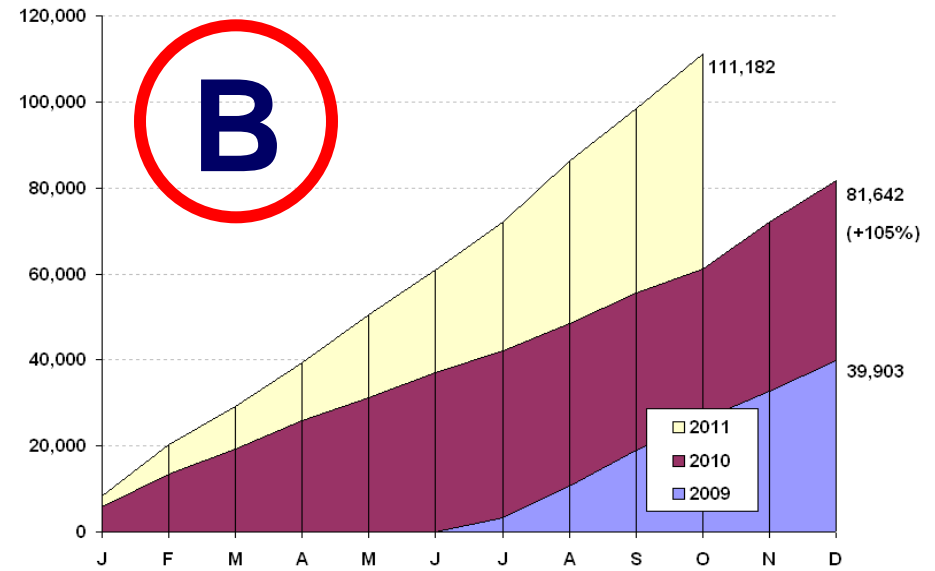
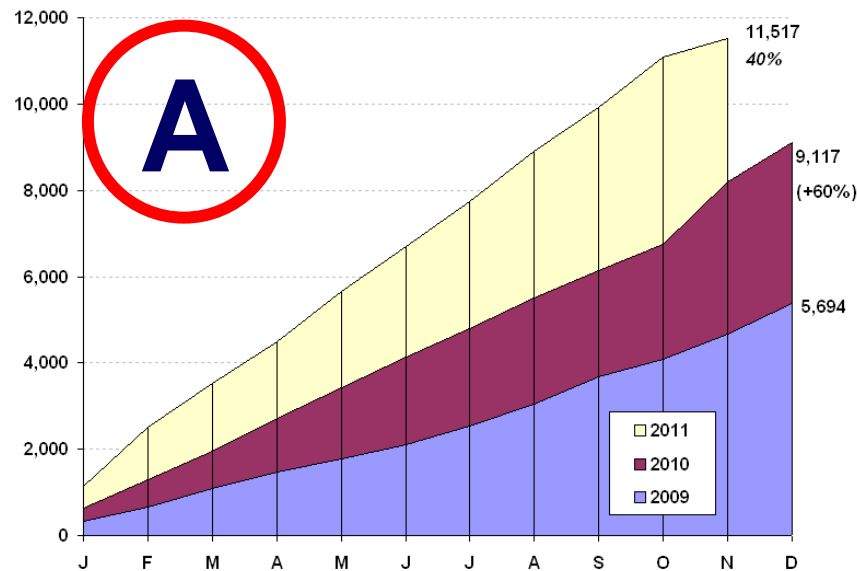
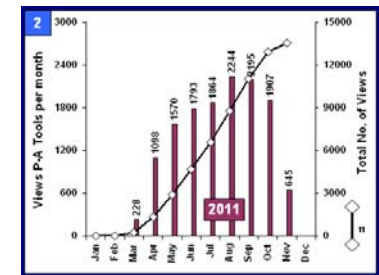
User logins 26,328 (A)

Page views (all) 232,727 (B)

Page views (P-A tools) 13,499 (since 03-2011)

Average time on site (min) 10:49

Average page views/visit 11.5



# Outline

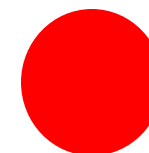
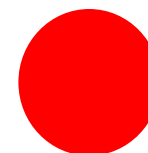
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# Lessons Learned

- **Team effort with different roles**
- **Need to earn the trust of strangers**
- **Drivers of discretionary effort**
- **Three constant needs**

# Diverse Profiles and Roles

- **Project champion (vision, passion, effort)**
- **Super-users (with IT expertise)**
- **Curators (content experts, ideally a team)**
- **Primary contacts (read/write access)**
- **Read-only access (end users doing routine work, the more the better)**



# Diverse Profiles and Roles

- Project champion (vision, passion, effort)
- Super-users (with IT expertise)
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- Read-only access (end users doing **routine work**, the more the better)

# Why Should You Join R4S?

You should get a password if you ever asked

**Assessment of abnormal results for rare conditions**

*is it real??*

**Appreciation of critical values**

*how bad is it??*

**Awareness of additional markers in difficult cases**

*what else? am I getting the whole picture?*

**Avoidance of unnecessary repeat testing & referrals**

*Is it OK to have so many false positives?*

**Analysis of sentinel events**

*was it really “normal”?*

**Attending the training course**

*is it worth the time?*



# How to Earn the Trust of Strangers

- A project like R4S is ENTIRELY based on collaboration and cooperation, which are driven exclusively by **discretionary effort**
- You have to **earn trust** before you get buy in
- First step is to convince users that there is **NO hidden agenda** behind the goals of the project
- Second step is to apply **EQUALITY**, at every level
- Third, the fear of judgment must be replaced by the opportunity to be recognized for good work (**behavior modification**)

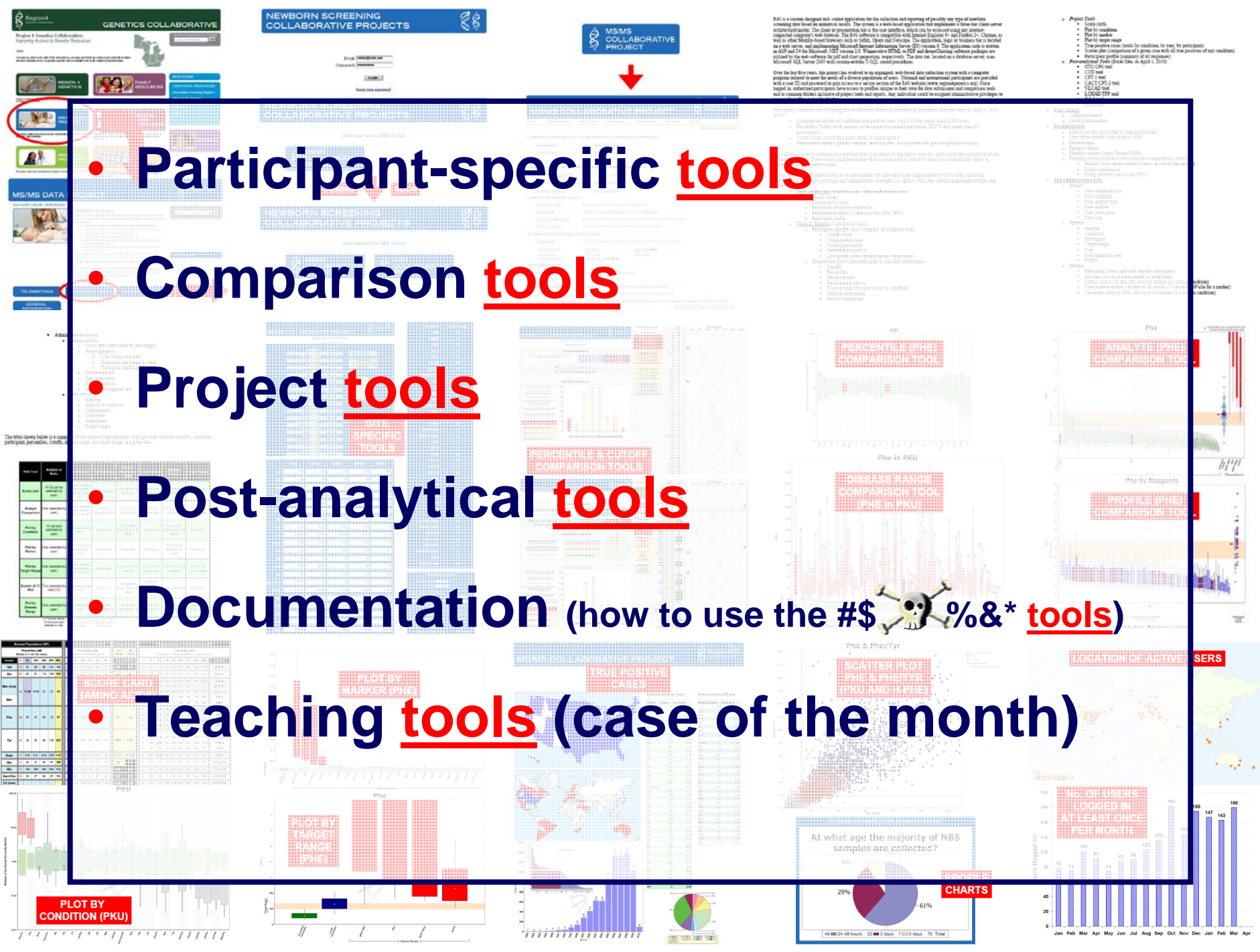
# Drivers of Discretionary Effort

- **Incentives**
- **Incentives**
- **More incentives**

# Incentives

- **Tools (anything that could make daily work better, easier, more effective)**





- Participant-specific tools
- Comparison tools
- Project tools
- Post-analytical tools
- Documentation (how to use the # \$ % & \* tools)
- Teaching tools (case of the month)

R41 is a custom designed and coded application for the collection and reporting of possibly any type of workflow involving data based on scientific research. The system is a web-based application that implements a three-tier client-server architecture model. The client or presentation tier is the user interface, which can be accessed using any internet-connected computer's web browser. The R41 software is developed with Microsoft SQL Server 2008, Oracle, IBM, SAS, and other Microsoft-based servers such as SAP, Open and Vertica. The application, logic or business tier is located on a web server, and implemented Microsoft Business Intelligence Services (BIS) version 6. The application code is written in ASP and C# for Microsoft .NET version 3.0. Web services (WSDL) to PDF and AmazonCloudWatch software packages are utilized by the web software for email alert messages, respectively. The data tier is located on a database server, uses Microsoft SQL Server 2008 with various-queries T-SQL stored procedures.

Over the last few years, this project has evolved to an equipped, web-based data collection system with a complete program related to user interface of diverse applications of users. Detailed and comprehensive techniques are provided with a user ID and password to gain access to a secure section of the R41 website (www.mspcollaborative.org). Once logged in, authorized personnel have access to various reports in real time for data collection and comparison tools used to compare clinical capture of project tools and reports. Any individual could be assigned administrative privileges to

- Project Tools
  - Score cards
  - Plan by condition
  - Plan by center
  - Plan by target range
  - True positive rates (tools by condition, by user, by participant)
  - Scatter plot (comparisons of a given case with all true positives of any condition)
  - Participant profile (summary of all responses)
- Post-analytical Tools (clinical cases, as April 1, 2010)
  - CAC-CR tool
  - C12 tool
  - CPT 3 tool
  - CACT-C-2 tool
  - T12AD tool
  - T12AD-TF tool

R4S Tool	Analyte or Ratio	Condition(s)	Participant(s)	Normal Population %iles	Cutoff Values	Disease Ranges	Target Ranges
Score card	All (by group selected by user)	All with disease range median >99%ile of NP (2)	Total number	Cumulative (by analyte)	Cumulative (by analyte)	Cumulative (by condition)	Shown as values
Analyte Comparison	One (selected by user)	All with disease range median >99%ile of NP	All shown individually (3)	All shown individually	All shown individually	Cumulative (by condition)	Shown as visual range
Plot by Condition	All (groups selected by user)	One (selected by user)	Not shown	Cumulative range shown as MoM	Not shown	Cumulative range shown as MoM	Not shown
Plot by Marker	One (selected by user)	Any (by group selected by user)	Not shown	Cumulative	Not shown	All (by group selected by user)	Not shown
Plot by Target Range	One (selected by user)	All with disease range median >99%ile of NP	Not shown	Cumulative (by analyte)	Cumulative (by analyte)	Cumulative (by condition)	Shown as visual range
Scatter (X-Y) Plot	Two (selected by user) (1)	Any (selected by user)	Not shown	Cumulative range shown as area	Optional display (selected by user)	Individual cases	Not shown
Plot by Disease Range	One (selected by user)	One (selected by user)	All shown individually (3)	All shown individually (3)	All shown individually (3)	All shown individually (3)	Shown as visual range

(1) Optional display of individual case selected by user

(2) Exceptions to this rule are allowed in some cases

(3) All anonymized except participant linked to user (option to hide)

# Incentives

- **Tools (anything that could make their work better, easier, more effective)**
- **Help always available (sharing samples, second opinions, 2<sup>nd</sup> tier tests)**
- **Open channels of communication**
- **Publications (equality rules)**

**Genet in Med**  
**2011;13(3):230-254**

**(submitted)**

**Clinical validation of cutoff target ranges in newborn screening of metabolic disorders by tandem mass spectrometry: A worldwide collaborative project**

David M. S. McHugh<sup>1</sup>, Cynthia A. Cameron, PhD<sup>2</sup>, Jose E. Abdemur, MD<sup>3</sup>, Mahera Abdulrahman, MD, PhD<sup>4</sup>, Ona Adair, PhD<sup>5</sup>,  
Shahira Ahmed Al Nuaimi, BSc<sup>6</sup>, Henrik Ahlman, PhD<sup>7</sup>, Jennifer J. Allen, RN, BSN<sup>7</sup>, Italo Antonozzi, MD<sup>8</sup>, Shaina Archer, MSc<sup>9</sup>,  
Sylvia Au, MS<sup>10</sup>, Christiane Auray-Blais, PhD<sup>11</sup>, Mei Baker, MD<sup>12</sup>, Fiona Bamforth, MD<sup>9</sup>, Kinga Beckmann<sup>13</sup>, Gessi Bentz Pino, CGC<sup>1</sup>,  
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Jose Angel Cocho de Juan, PhD<sup>37</sup>, Maria Elena Colandre, PhD<sup>36</sup>, Veronica Cornejo Espinoza, MD<sup>37</sup>, Timano Corso, MD<sup>38</sup>,  
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Monique G. de Sain-Van der Velden, PhD<sup>42</sup>, Carmen Delgado Pecellin, PhD<sup>43</sup>, Iole Maria Di Gangi, PhD<sup>44</sup>,  
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Mark Dymerski<sup>49</sup>, José Maria Egea Mellado<sup>50</sup>, Bert Elvers<sup>51</sup>, Roger Eaton, PhD<sup>52</sup>, Barbara M. Ecker<sup>53</sup>, Fatma El Mougy, MD<sup>54</sup>,  
Sarah Erol<sup>55</sup>, Mercedes Espada, PhD<sup>26</sup>, Catherine Evans, PhD<sup>56</sup>, Sandy Fawbush, RN, BSN<sup>57</sup>, Kristel F. Fijolek<sup>58</sup>, Lawrence Fisher<sup>28</sup>,  
Leifur Franzson, PhD<sup>58</sup>, Dianne M. Frazier, PhD<sup>59</sup>, Luciana R. C. Garcia<sup>60</sup>, Maria Sierra Garcia-Valdecasas Bermejo, PhD<sup>43</sup>,  
Dimitar Gavrilov, MD, PhD<sup>1</sup>, Rosemarie Gerace<sup>61</sup>, Giuseppe Giordano, PhD<sup>64</sup>, Yolanda González Irazabal<sup>62</sup>,  
Lawrence C. Greed, BS<sup>63</sup>, Robert Griet, PhD<sup>64</sup>, Elyse Grycki, CGC<sup>1</sup>, Yuefan Gu, PhD<sup>65</sup>, Firze Gulamali-Majid, PhD<sup>66</sup>,  
Arthur F. Haggart, PhD<sup>67</sup>, Ligabao Han, MD<sup>68</sup>, W. Harry Hannon, PhD<sup>68</sup>, Christa Hasler<sup>69</sup>, Fayza Abdelhamid Hassan, MD<sup>64</sup>,  
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David M. Hougaard<sup>75</sup>, Cindy Hughes<sup>76</sup>, Ivan Hvalby, PhD<sup>77</sup>, K. G. Hvalby, PhD<sup>77</sup>, Gerardo González, MSc<sup>76</sup>,  
Jón J. Jónsson<sup>78</sup>, J. J. Jónsson<sup>78</sup>, J. J. Jónsson<sup>78</sup>, J. J. Jónsson<sup>78</sup>, J. J. Jónsson<sup>78</sup>, J. J. Jónsson<sup>78</sup>, J. J. Jónsson<sup>78</sup>,  
Dimitris Katakas<sup>79</sup>, Viktor Kozlich, MD, PhD<sup>80</sup>, Ravoul Koungel, PhD<sup>81</sup>, Dirk Kohlmeier, PhD<sup>82</sup>, Ivo Kronensky, MD, PhD<sup>83</sup>,  
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Joyce Lopez<sup>84</sup>, Barbara Luvoshko<sup>86</sup>, Yannis L. Loukas, PhD<sup>87</sup>, Carol Liu, Sharon Liard, MS<sup>29</sup>, Martin Lindner, MD<sup>88</sup>,  
Michele A. Lloyd-Purwar, MD<sup>89</sup>, Louis L. Loring, PhD<sup>90</sup>, M. L. Loring, PhD<sup>90</sup>, M. L. Loring, PhD<sup>90</sup>, M. L. Loring, PhD<sup>90</sup>,  
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Dimitris Nikolopoulos, MSc<sup>107</sup>, Bent Norgaard-Pedersen, MD<sup>75</sup>, Devin Oglesbee, PhD<sup>1</sup>, Martin Ostrowski, PhD<sup>108</sup>,  
Dancica Ombrone<sup>109</sup>, Jenni Ojola, MPhD<sup>110</sup>, Yageis opakonsiaminon, PhD<sup>111</sup>, Sherry Fardo Kezo, MD<sup>30</sup>,  
Hyung-Doo Park, MD, PhD<sup>95</sup>, Marzia Pasquali, PhD<sup>111</sup>, Elisabetta Pasquini, MD<sup>91</sup>, Pallavi Patel<sup>112</sup>, Kenneth A. Pass, PhD<sup>113</sup>,  
Colleen Peterson<sup>100</sup>, Rolf D. Petersen, PhD<sup>114</sup>, James J. Pitt, PhD<sup>115</sup>, Sherry Poh, MSc<sup>80</sup>, Arnold Pollak, MD<sup>83</sup>, Cory Porter<sup>49</sup>,  
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Graham Sinclair, PhD<sup>19</sup>, Sherylkuty Sunny<sup>19</sup>, Kathy Tomashitis, MNS<sup>124</sup>, Sandor Turi, MD, PhD<sup>125</sup>,  
Marcela Vela-Amieva, MD<sup>126</sup>, Laura Vitarmino, PhD<sup>127</sup>, Ulrika von Döbeln, MD, PhD<sup>128</sup>, Marie-Françoise Vincent, MD, PhD<sup>129</sup>,  
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Raquel Yahyaoui Macias, MD<sup>30</sup>, Seiji Yamaguchi, MD<sup>38</sup>, Melissa Yssel<sup>39</sup>, and Wendy M. Zakowicz, BS<sup>79</sup>

**247 authors**  
**124 sites**

**authorship in alphabetical order**

**Enhanced interpretation of newborn screening results without analyte cutoff values**

Running title: Interpretation of newborn screening results  
**Enhanced interpretation  
of newborn screening results  
without analyte cutoff values**

Mark I. Magera<sup>1</sup>, Dietrich Matern, MD<sup>1</sup>, Devin Oglesbee, PhD<sup>1</sup>, Kimiyo Raymond, MD<sup>1</sup>,  
Piero Rinaldo, MD, PhD<sup>1</sup>, Emily H. Smith, PhD<sup>1</sup>, Silvia Tortorelli, MD, PhD<sup>1</sup>, Coleman T.  
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Sandrine Marie, PhD<sup>6</sup>, Marie-Françoise Vincent, MD, PhD<sup>6</sup>, Yuri Cleverthon Sica, MSc<sup>7</sup>,  
Mouseline Torquado Domingos<sup>7</sup>, Khalid Al Thihli, MD<sup>8</sup>, Graham Sinclair, PhD<sup>8</sup>, Osama Y. Al-  
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<sup>21</sup>, Jim Bonham, PhD<sup>22</sup>, Melanie Downing, MSc<sup>22</sup>, Yannis Dotsikas, PhD<sup>23</sup>, Yannis L. Loukas,  
<sup>24</sup>, Ákos Baráth,  
<sup>25</sup>, PhD<sup>26</sup>, Nancy N.  
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# Incentives

- **Tools (anything that could make their work better, easier, more effective)**
- **Help always available (sharing samples, second opinions, 2<sup>nd</sup> tier tests)**
- **Open channels of communication**
- **Publications (equality rules)**
- **Training course (week long, 5 times per year; no registration fee)**

# Training Courses



**What do we do?**

## REGIONAL COLLABORATIVE PROJECT - PRIORITY 1

# TRAINING PROGRAM IN NEWBORN SCREENING BY MS/MS

Biochemical Genetics Laboratory, Mayo Clinic College of Medicine - Rochester (MN), December 5-9, 2011

Personnel	Title
Dimitar Gavrilov, Dietrich Matern, Devin Oglesbee, Kimiyo Raymond, Piero Rinaldo, Silvia Tortorelli	BGL co-directors
A. Studinski, C. Anderson, J. Hesemann	BGL Genetic Counselors
Tricia Hall, Hussain Askree	BGL fellows
Mark Magera	BGL development coordinator
Gregg Marquardt	Software Engineer
David McHugh	Project coordinator



PARTICIPANTS			
Name	State (Reg)	Name	State (Reg)
Jennifer Hesemann	(R4-MN)	Angie Battochio	(INT-CAN)
Carlos Prada	(R4-OH)	Marie Therese Bertier	(INT-CAN)
Laura Davis-Keppen	(R5-SD)	Cong Lu	(INT-CHN)
Hao Tang	(R7-CA)	Jiahua Zhang	(INT-CHN)
Margherita Ruoppolo	(INT-ITA)	Iole Maria DiGangi	(INT-ITA)

	Practical	Presentation	LEGEND	Flex time	Conferences
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TIME	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	TIME
8:00	Introduction to MS/MS analysis <b>(Mark Magera)</b>	2nd tier tests <b>(Dietrich Matern)</b>	REVIEW of results and REPORTING	Tuning & Calibration <b>(Mark Magera)</b>	REVIEW of results and REPORTING	8:00
8:30						8:30
9:00	Introduction to amino acids and acylcarnitines	REVIEW of results and REPORTING <b>(including 2nd tier tests)</b>	REVIEW of results and REPORTING	REVIEW of results and REPORTING	REVIEW of results and REPORTING	9:00
9:30						9:30
10:00						10:00
10:30	Examples of profile interpretation (I)	Break (lunch)	Break (lunch)	Break (lunch)	REVIEW of results and REPORTING	10:30
11:00						11:00
11:30	Lunch in conference room	Break (lunch)	Break (lunch)	Break (lunch)	REVIEW of results and REPORTING	11:30
12:00						12:00
12:30	Examples of profile interpretation (II)	Break (lunch)	Break (lunch)	Break (lunch)	REVIEW of results and REPORTING	12:30
13:00						13:00
13:30	Examples of profile interpretation (II)	Overview & Status of Collaborative Project	MN NBS conference call	Discussion participants comparison tools	REVIEW of results and REPORTING	13:30
14:00						14:00
14:30	Planning of FLEX time	Region 4 Stork (R4S) Project Tools	FLEX TIME	Discussion participants comparison tools	REVIEW of results and REPORTING	14:30
15:00						15:00
15:30	How things look like at Mayo	Region 4 Stork (R4S) Project Tools	FLEX TIME	Discussion participants comparison tools	REVIEW of results and REPORTING	15:30
16:00						16:00
16:30	REVIEW of results and REPORTING	REVIEW of results and REPORTING	REVIEW of results and REPORTING	REVIEW of results and REPORTING	REVIEW of results and REPORTING	16:30
17:00						17:00
17:30	REVIEW of results and REPORTING	REVIEW of results and REPORTING	REVIEW of results and REPORTING	REVIEW of results and REPORTING	REVIEW of results and REPORTING	17:30

FLEX TIME OPTIONS	2nd tier tests (CAH)	2nd tier tests (MMA, SUAC)	MS/MS troubleshooting	QC/QA process & procedures
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**REGIONAL COLLABORATIVE PROJECT - PRIORITY 1**

**TRAINING PROGRAM IN NEWBORN SCREENING BY MS/MS**

Biochemical Genetics Laboratory, Mayo Clinic College of Medicine - Rochester (MN), December 5-9, 2011

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	Practical	Presentation	LEGEND	Flex time	Conferences	

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**PARTICIPANTS**

Name	State (Reg)	Name	State (Reg)
Jennifer Hesemann	<b>CLIN (GC)</b>	Angie Battochio	<b>LAB</b>
Carlos Prada	<b>CLIN</b>	Marie Therese Bertier	<b>LAB</b>
Laura Davis-Keppen	<b>CLIN</b>	Cong Lu	<b>CLIN</b>
Hao Tang	<b>LAB</b>	Jiahua Zhang	<b>LAB</b>
Margherita Ruoppolo	<b>CLIN</b> <b>LAB</b>	Iole Maria DiGangi	<b>LAB</b>

FLEX TIME OPTIONS	2nd tier tests (CAH)	2nd tier tests (MMA, SUAC)	MS/MS troubleshooting	QC/QA process & procedures
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# Three Constant Needs

- **Communication**
  - Keep users informed of what is being done
  - Treasure any feedback they offer!
- **Recruitment of new users**
  - Further growth is critically needed
- **Monitoring of progress**
  - Daily!

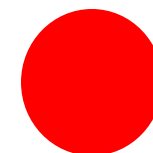
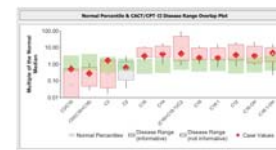
# Outline

- Impact of R4S project
  - Utilization
  - Lessons learned

- **Products**

- Future applications

NEWBORN SCREENING  
COLLABORATIVE PROJECTS





# Project Products

- **Tools and reports**

- ✓ **Training course**

- ✓ **Publications**

- **Sample exchange**

- **Other applications**



# Tools and Reports

- Participant-specific tools

- Comparison tools**

- Project tools

- Post-analytical tools

- Documentation

- Administrative tools

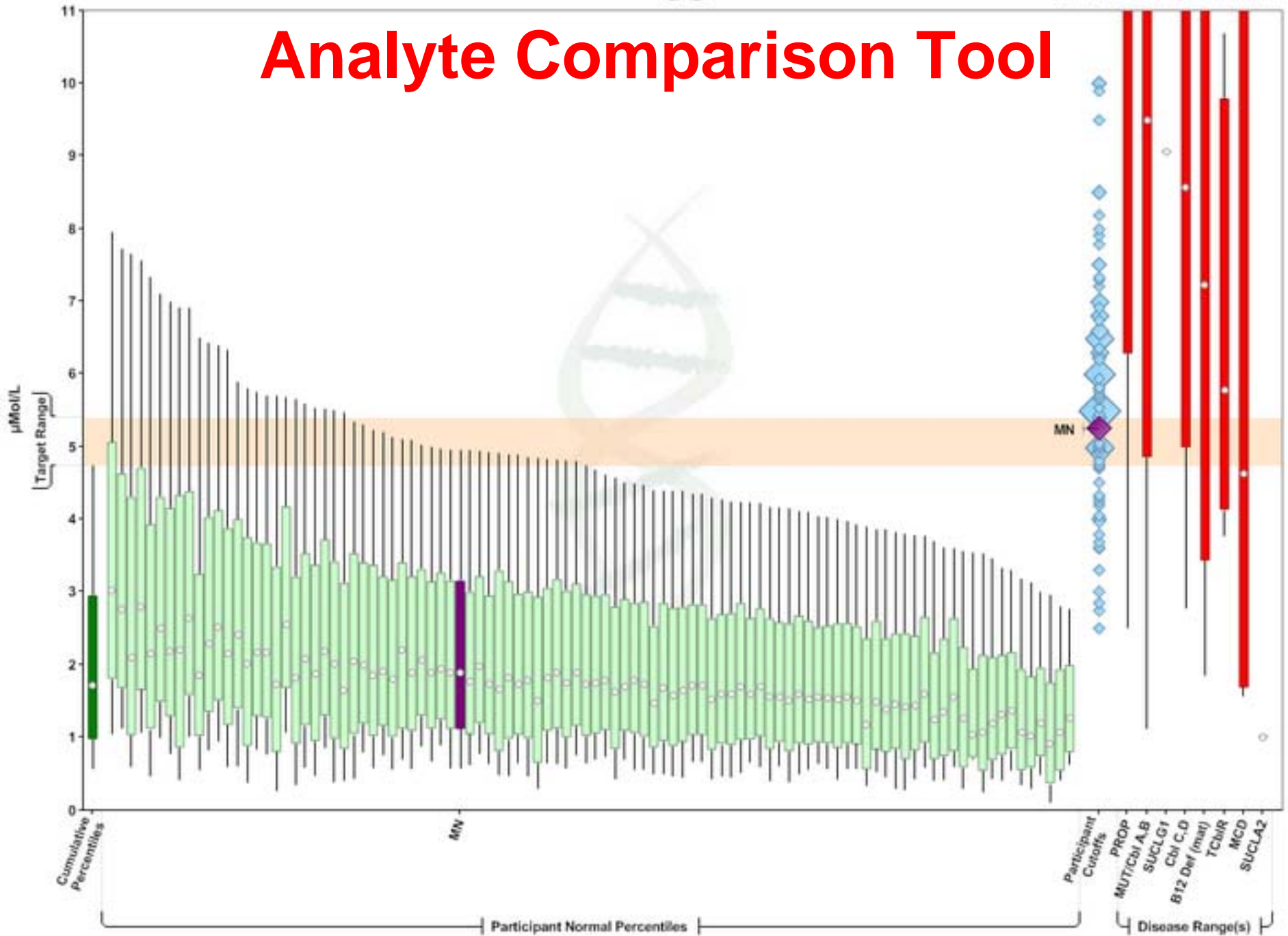
R4S Tool	Analyte or Ratio	Condition(s)	Participant(s)	Normal Population %iles	Cutoff Values	Disease Ranges	Target Ranges
Score card	All (by group selected by user)	All with disease range median >99%ile of NP (2)	Total number	Cumulative (by analyte)	Cumulative (by analyte)	Cumulative (by condition)	Shown as values
Analyte Comparison	One (selected by user)	All with disease range median >99%ile of NP	All shown individually (3)	All shown individually	All shown individually	Cumulative (by condition)	Shown as visual range
Plot by Condition	All (groups selected by user)	One (selected by user)	Not shown	Cumulative range shown as MoM	Not shown	Cumulative range shown as MoM	Not shown
Plot by Marker	One (selected by user)	Any (by group selected by user)	Not shown	Cumulative	Not shown	All (by group selected by user)	Not shown
Plot by Target Range	One (selected by user)	All with disease range median >99%ile of NP	Not shown	Cumulative (by analyte)	Cumulative (by analyte)	Cumulative (by condition)	Shown as visual range
Scatter (X-Y) Plot	Two (selected by user) (1)	Any (selected by user)	Not shown	Cumulative range shown as area	Optional display (selected by user)	Individual cases	Not shown
Plot by Disease Range	One (selected by user)	One (selected by user)	All shown individually (3)	All shown individually (3)	All shown individually (3)	All shown individually (3)	Shown as visual range

(1) Optional display of individual case selected by user  
 (2) Exceptions to this rule are allowed in some cases  
 (3) All anonymized except participant linked to user (option to hide)

C3

◆ Cutoff marker size is proportional to the number of labs using the same value.

# Analyte Comparison Tool

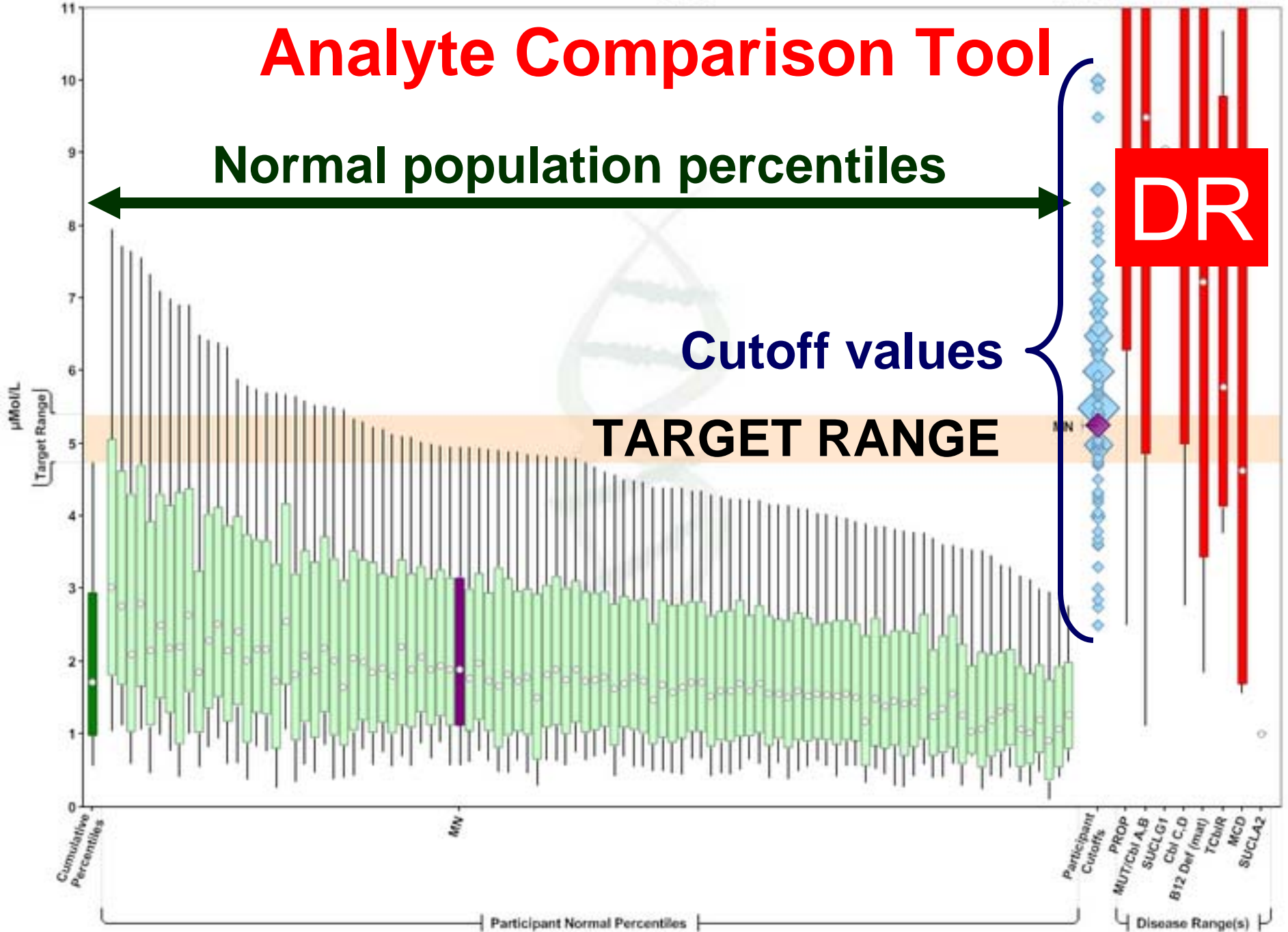


C3

◆ Cutoff marker size is proportional to the number of labs using the same value.

# Analyte Comparison Tool

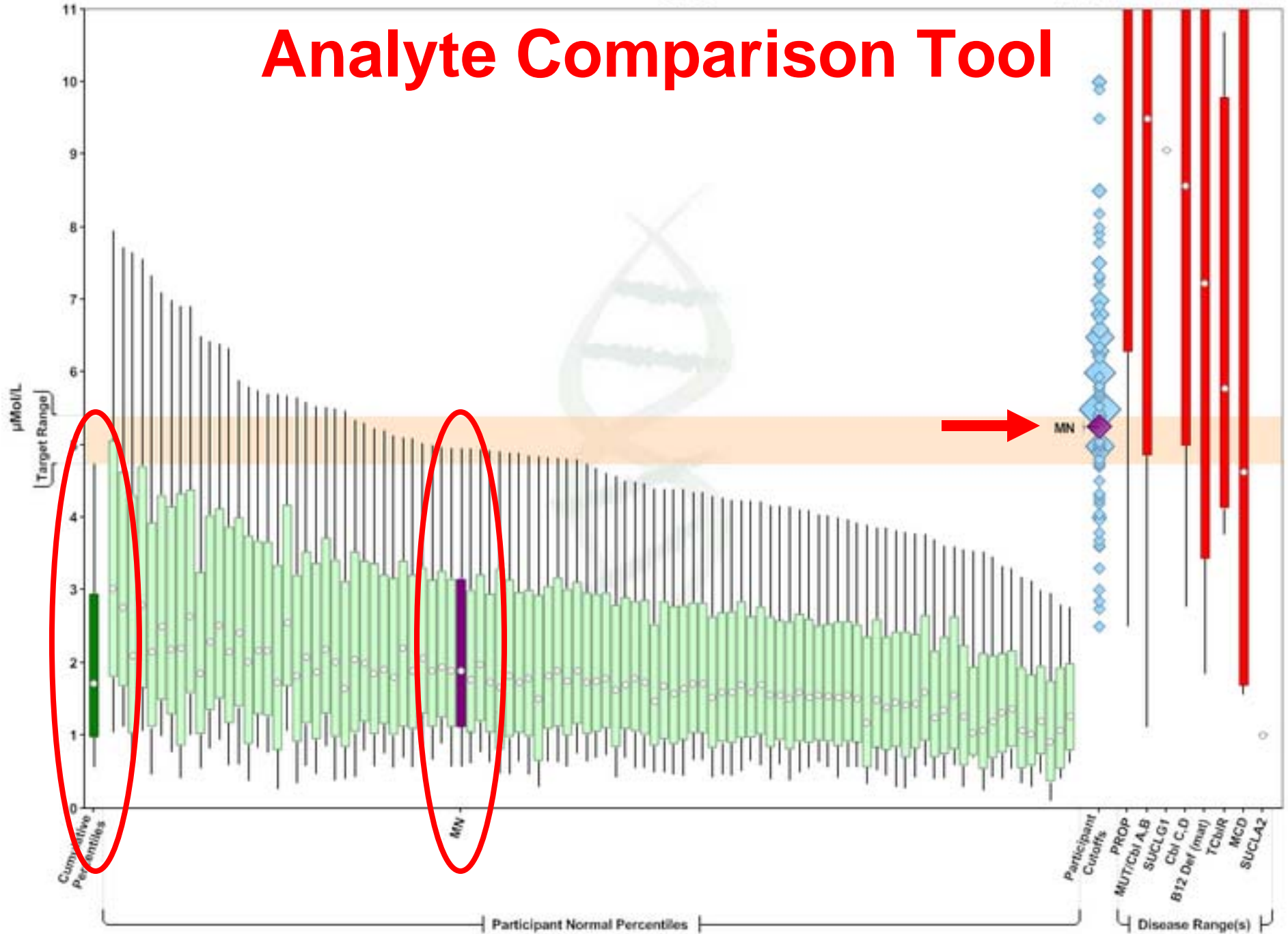
Normal population percentiles



C3

◆ Cutoff marker size is proportional to the number of labs using the same value.

# Analyte Comparison Tool



# Percentile Comparison Tool

## MS/MS COLLABORATIVE PROJECT



### MN 99%ile Comparison Tool

PDF Created On 11/8/2011 10:10 AM

#### Comparison Summary

The 99%ile Comparison Tool compares MN's 99%ile values to percentiles of peer 99%ile values

**60%** of 99%iles are BELOW the median of peer 99%iles

**40%** of 99%iles are ABOVE the median of peer 99%iles

[View detailed analyte comparison](#)

MN has submitted 99%ile values for 113 of the 128 project analytes.

#### Peer 99%ile Comparison

The Peer 99%ile Comparison compares MN's 99%ile values to peer 99%ile percentiles.

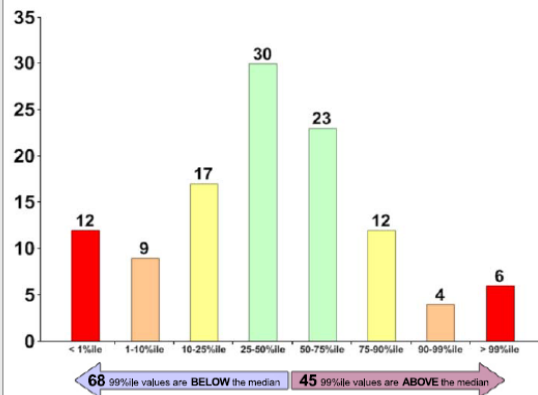
Peer 99%ile percentiles present the distribution of all participant 99%ile values.

(View peer 99%ile percentiles by analyte)

The chart to the right presents the distribution of MN's percentile rank per analyte within peer 99%ile percentiles.

The four ranges below present the distribution of MN's percentile ranks about the median

For example, the 10 - 90%ile count represents the number of MN's 99%ile percentile ranks that fall between the 10 and 90%ile (non-inclusive of the 25 - 75%ile count).



**18** MN values are outliers (high or low)

**13** MN values are within the 1 - 99%ile

**29** MN values are within the 10 - 90%ile

**53** MN values are within the 25 - 75%ile

#### MN 99%ile Values Per Analyte

[View comparison summary](#)

**RED** indicates MN99%ile value is an **OUTLIER** (less than the 1%ile or greater than the 99%ile of all peer 99%ile values.

**ORANGE** indicates MN99%ile value is between the 1 - 10%ile or the 90 - 99%ile of all peer 99%ile values.

**YELLOW** indicates MN99%ile value is between the 10 - 25%ile or the 75 - 90%ile of all peer 99%ile values.

**GREEN** indicates MN99%ile value is between the 25%ile and 75%ile of all peer 99%ile values.

Analyte	MN Values	N	Peer Percentiles						
			1%ile	10%ile	25%ile	50%ile	75%ile	90%ile	99%ile
Val	143	83	141	187	163	217	251	304	442
Xle	207	103	145	188	207	239	265	312	486
Met	57	102	10	30	42	62	65	76	
Phe	100	108	57	73	84	96	106	115	132
Tyr	197	105	129	159	196	219	237	261	321
Suac	1.50	33	0.24	0.57	0.76	1.14	2.19	5.77	15.45
Gln	83	9	83	83	104	123	374	986	1919
Glu	322	32	163	322	330	542	715	821	898
Orn	75	33	53	74	139	186	230	306	409
Pro	776	11	327	327	300	353	776	1165	6485
Cit	20	101	15.13	18	24	30	32	37	66
Asa	0.31	38	0.033	0.11	0.31	0.79	1.43	3.18	7.61
Arg	18	88	10.72	14.87	21	34	44	67	100
Ala	474	66	279	352	431	524	589	693	906
Ser	579	3	184	296	377	579	579	579	579
Gly	576	67	322	458	615	753	934	1131	5933
Thr	79	4	79	79	79	79	98	132	153
ValPhe	2.55	65	2.52	2.72	3.40	3.79	4.46	5.46	13.83
Xle/Phe	3.75	81	3.26	3.44	3.70	4.30	4.91	6.85	11.26
Xle/Ala	1.04	60	0.63	0.75	0.86	1.03	1.23	1.46	3.37
Xle/Tyr	4.27	1	4.27	4.27	4.27	4.27	4.27	4.27	4.27
Met/Phe	0.80	83	0.43	0.66	0.65	0.76	0.94	1.26	1.34
Met/Tyr	0.98	18	0.43	0.52	0.63	0.76	0.84	1.06	1.30
Met/Xle	0.43	23	0.19	0.21	0.25	0.39	0.65	0.66	0.58
Met/Cit	6.40	17	2.07	3.31	3.44	4.40	5.96	6.55	8.42
Phe/Tyr	1.97	102	1.05	1.26	1.40	1.54	1.76	1.92	2.49
Gln/Cit	12.83	6	11.44	12.10	13.16	14.32	58	81	89
Glu/Cit	54	13	19	41	42	57	79	91	93
Ala/Cit	53	3	36	39	44	55	62	67	70
Asn+Orn/Cit	7.41	16	5.23	7.05	12.69	14.36	19	25	30
Cit/Phe	0.41	39	0.38	0.43	0.47	0.67	0.63	0.80	1.80
Arg/Phe	0.018	20	0.073	0.32	0.40	0.58	0.80	1.20	1.67
Arg/Ala	0.004	16	0.011	0.072	0.10	0.13	0.17	0.23	0.34
Arg/Orn	0.31	9	0.17	0.27	0.31	0.35	0.43	1.35	2.09
Ser/Thr	11.14	1	11.14	11.14	11.14	11.14	11.14	11.14	11.14
Cit/Arg	6.10	61	1.26	3.64	4.18	5.06	7.13	11.00	19
Asa/Arg	0.11	16	0.011	0.035	0.076	0.15	0.39	0.49	0.77
Asn+Orn/Phe	1.71	6	1.37	1.53	2.07	3.28	3.86	4.61	5.14
C0	49	100	38	44	48	56	73	83	98
C2	53	84	25	38	44	52	57	64	96
C3	4.95	101	2.80	3.54	4.03	4.74	5.34	6.42	7.72
C4	0.72	97	0.41	0.57	0.69	0.76	0.85	1.03	1.63
C4-OH + C3DC (U)	0.11	17	0.19	0.26	0.26	0.30	0.42	0.84	1.02
C6-OH (D)	0.11	15	0.071	0.079	0.098	0.17	0.23	0.27	0.31
C5	0.49	103	0.24	0.28	0.33	0.39	0.47	0.57	1.00
C5:1	0.068	89	0.019	0.026	0.040	0.070	0.13	0.19	0.55
C5-OH (D)	0.38	73	0.23	0.28	0.33	0.39	0.49	0.59	0.93
C5-OH + C4DC (U)	0.11	37	0.28	0.33	0.37	0.42	0.54	1.62	6.80
C8DC	0.11	74	0.047	0.070	0.099	0.17	0.23	0.29	1.28
C8	0.19	102	0.080	0.10	0.11	0.17	0.23	0.31	0.64
C8:1	0.28	14	0.11	0.11	0.14	0.28	0.34	0.36	0.43
C8	0.22	105	0.080	0.13	0.16	0.19	0.25	0.30	0.41
C10:2	0.056	55	0.020	0.020	0.034	0.070	0.13	0.15	0.26
C10:1	0.18	94	0.099	0.11	0.12	0.17	0.21	0.28	0.42

	MN Values	Peer Percentiles								
		N	1%ile	10%ile	25%ile	50%ile	75%ile	90%ile	99%ile	

**(50%ile normal population)**

C0	<b>21</b>	101	15.40	18	20		24	30	35	39
C2	<b>24</b>	84	8.86	14.95	20		23	25	28	39
C3	<b>1.90</b>	102	1.02	1.26	1.53		1.72	1.93	2.20	2.80
C4	<b>0.22</b>	98	0.16	0.19	0.21		0.23	0.26	0.34	0.56

**(99%ile normal population)**

C0	<b>49</b>	100	38	44	48		58	73	83	98
C2	<b>53</b>	84	25	38	44		52	57	64	96
C3	<b>4.95</b>	101	2.80	3.54	4.03		4.74	5.34	6.42	7.72
C4	<b>0.72</b>	97	0.41	0.57	0.69		0.75	0.85	1.03	1.63

	MN Values	Peer Percentiles								
		N	1%ile	10%ile	25%ile	50%ile	75%ile	90%ile	99%ile	

**(50%ile normal population)**

C0	<b>21</b>	101	15.40	18	20		24	30	35	39
C2	<b>24</b>	84	8.86	14.95	20		23	25	28	39
C3	<b>1.90</b>	102	1.02	1.26	1.53		1.72	1.93	2.20	2.80
C4	<b>0.22</b>	98	0.16	0.19	0.21		0.23	0.26	0.34	0.56

**(99%ile normal population)**

C0	<b>49</b>	100	38	44	48		58	73	83	98
C2	<b>53</b>	84	25	38	44		52	57	64	96
C3	<b>4.95</b>	101	2.80	3.54	4.03		4.74	5.34	6.42	7.72
C4	<b>0.72</b>	97	0.41	0.57	0.69		0.75	0.85	1.03	1.63

	MN Values	Peer Percentiles								
		N	1%ile	10%ile	25%ile	50%ile	75%ile	90%ile	99%ile	

**(50%ile normal population)**

C0	<b>21</b>	101	15.40	18	20		24	30	35	39
C2	<b>24</b>	84	8.86	14.95	20		23	25	28	39
C3	<b>1.90</b>	102	1.02	1.26	1.53		1.72	1.93	2.20	2.80
C4	<b>0.22</b>	98	0.16	0.19	0.21		0.23	0.26	0.34	0.56

**(99%ile normal population)**

C0	<b>49</b>	100	38	44	48		58	73	83	98
C2	<b>53</b>	84	25	38	44		52	57	64	96
C3	<b>4.95</b>	101	2.80	3.54	4.03		4.74	5.34	6.42	7.72
C4	<b>0.72</b>	97	0.41	0.57	0.69		0.75	0.85	1.03	1.63



	MN Values	Peer Percentiles								
		N	1%ile	10%ile	25%ile	50%ile	75%ile	90%ile	99%ile	

**(50%ile normal population)**

C0	<b>21</b>	101	15.40	18	20		24	30	35	39
C2	<b>24</b>	84	8.86	14.95	20		23		25	39
C3	<b>1.90</b>	102	1.02	1.26	1.53		1.72		1.93	2.80
C4	<b>0.22</b>	98	0.16	0.19	0.21		0.23	0.26	0.34	0.56

**(99%ile normal population)**

C0	<b>49</b>	100	38	44	48		58	73	83	98
C2	<b>53</b>	84	25	38	44		52		57	96
C3	<b>4.95</b>	101	2.80	3.54	4.03		4.74		5.34	7.72
C4	<b>0.72</b>	97	0.41	0.57	0.69		0.75	0.85	1.03	1.63

**Cutoff values**

	Target Range	Cutoffs	Peer Percentiles								
			N	1%ile	10%ile	25%ile	50%ile	75%ile	90%ile	99%ile	
C0(low)	7.50 - 12.00	<b>10.00</b>	110	4.77	5.94	7.00	8.75		10.02	13.00	22
C0	58 - 65	<b>65</b>	95	40	54	60		70	97	119	130
C2(low)	7.00 - 9.67	<b>9.50</b>	56	1.50	4.42	5.54	7.75	9.43		11.00	3.66
C3(low)	0.55 - 1.00	<b>0.50</b>	39	0.077	0.30	0.42		0.55	0.62	0.73	0.82
C3	4.74 - 5.40	<b>5.25</b>	108		4.00	5.00		5.50	6.50	7.50	9.99
C4	0.75 - 1.07	<b>1.40</b>	95	0.43	0.71	0.89	1.10	1.32	1.40		1.86

**FP**

**FN**



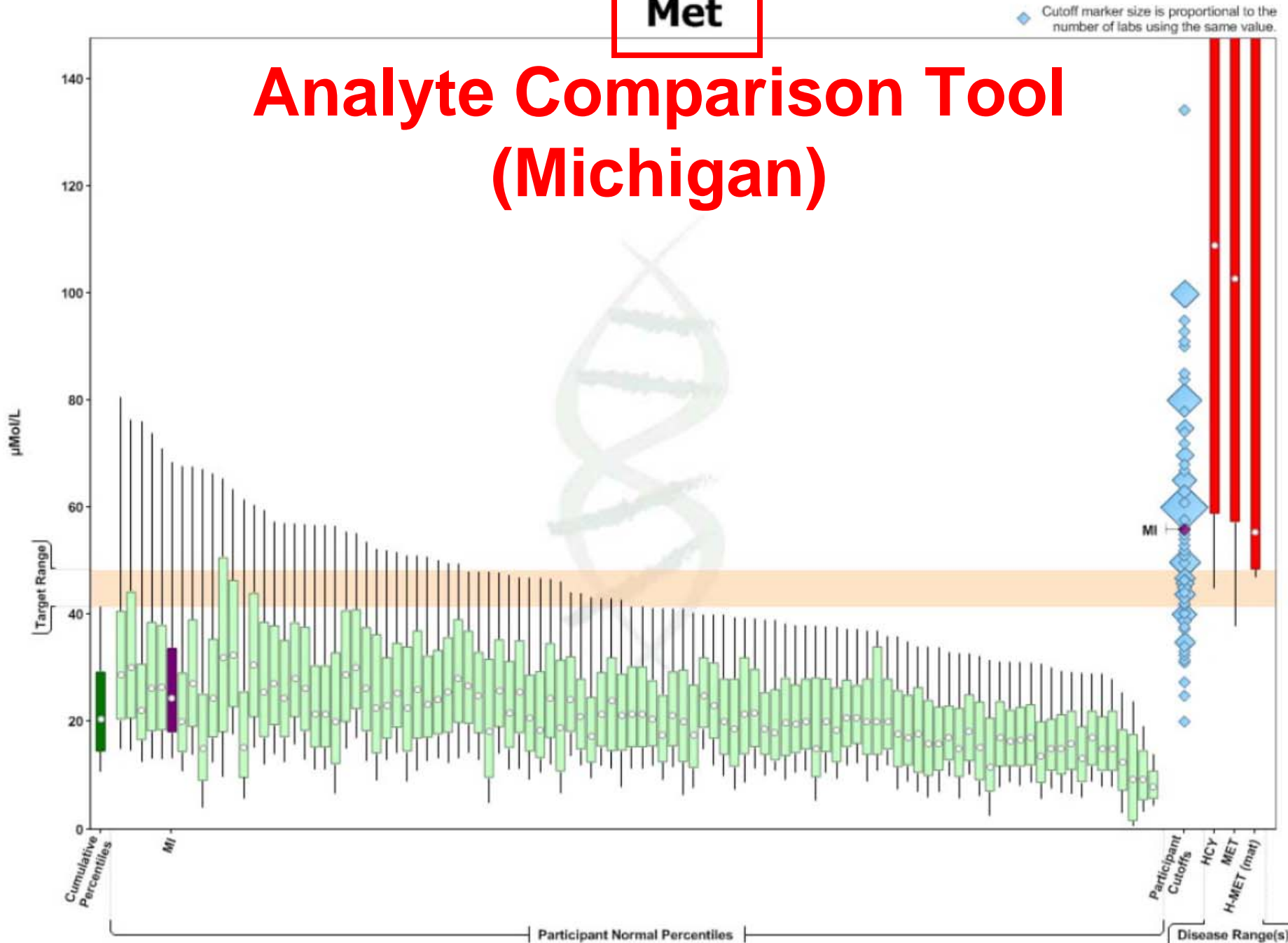
<b>50%ile</b>		Peer Percentiles									
		N	1%ile	10%ile	25%ile	50%ile	75%ile	90%ile	99%ile		
Val	70	94	70		79	91	103	121	147	173	
Xle	90	104	78		91	100	116	135	162	199	
Met	21	103	9.21		15.04	17	21		25	27	32
Phe	53	109	33		41	47		53	58	61	71
Tyr	73	106	48		58	70		80	88	97	109

<b>99%ile</b>		Peer Percentiles										
		N	1%ile	10%ile	25%ile	50%ile	75%ile	90%ile	99%ile			
Val	143	93	141		157	183	217	251	304	442		
Xle	207	103	145		186		207	239	266	312	485	
Met	57	102	19		30	36	42		52		65	76
Phe	100	108	57		73	84	96		106	115	132	
Tyr	197	105	129		159	186		210	237	261	321	

<b>CO</b>	Target Range	Cutoffs	Peer Percentiles								
			N	1%ile	10%ile	25%ile	50%ile	75%ile	90%ile	99%ile	
Val	217 - 230	250	100	153	190	213		250	300	350	453
Xle	239 - 284	250	115	165	220		250	287	312	400	495
Met(low)	10.24 - 10.79	12.00	56	4.91	5.48	6.93	8.60	10.13	11.00		14.25
Met	42 - 48	50	110	25	35	44		56	70	86	100
Phe	96 - 132	130	120	64	97	116		130	150	160	236
Tyr	210 - 229	300	109	130	183	215	260		368	450	599

**Met**

# Analyte Comparison Tool (Michigan)



# Met

◆ Cutoff marker size is proportional to the number of labs using the same value.

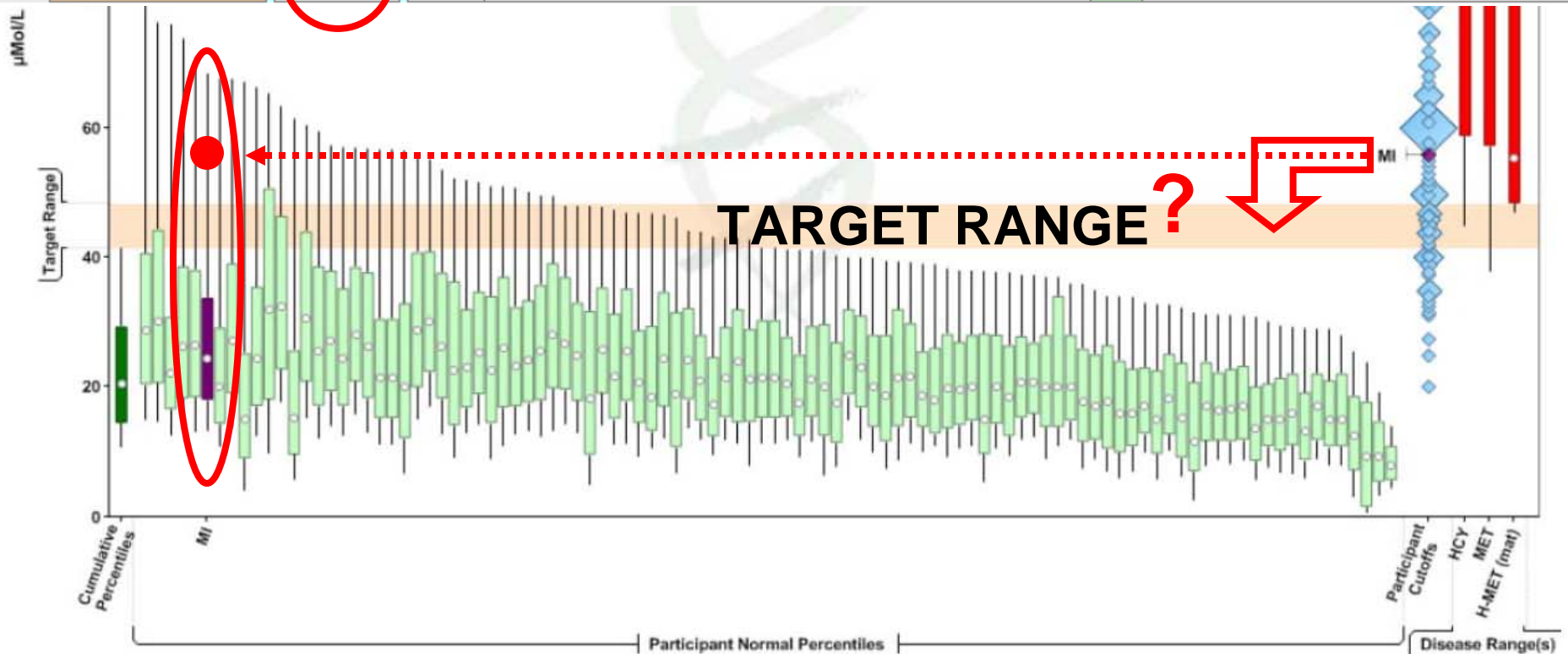
**(50%ile normal population)**



**(99%ile normal population)**



**Cutoff values**



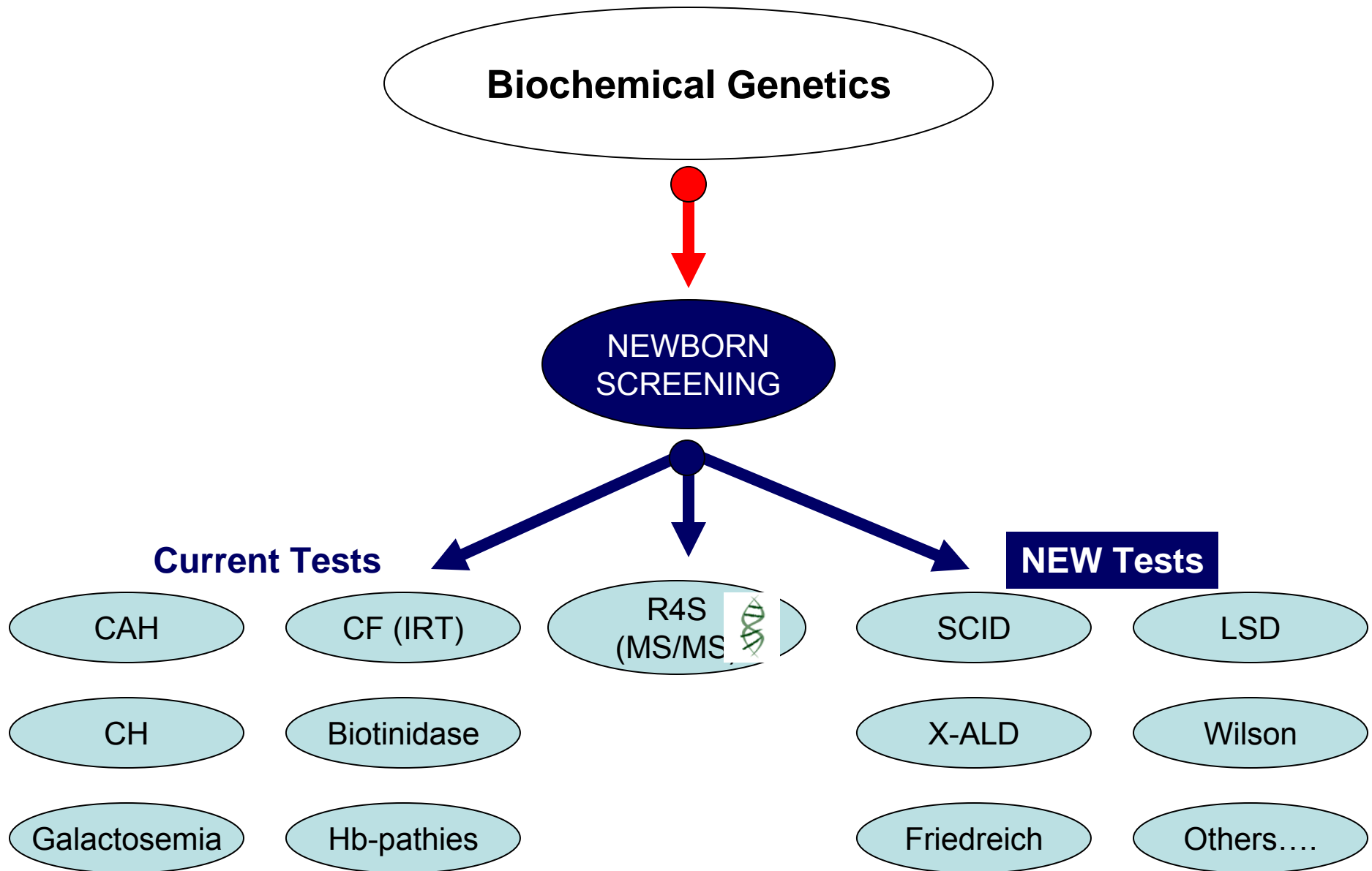
**TARGET RANGE ?**



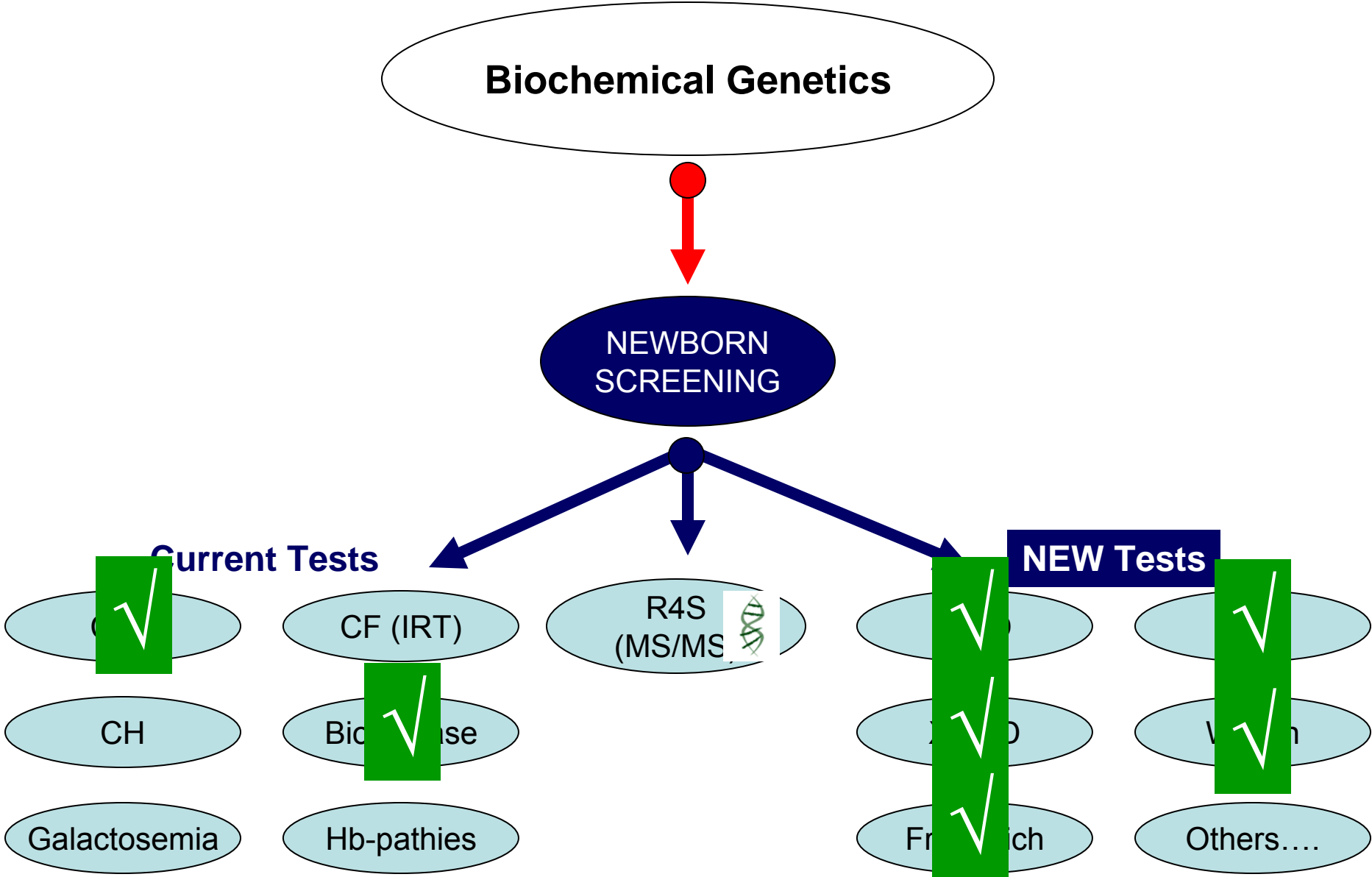
# Project Products

- ✓ **Tools and reports**
- ✓ **Training course**
- ✓ **Publications**
- **Sample exchange**
- **Other applications**

# R4S is a Biochemical Genetics Portal



# R4S is a Biochemical Genetics Portal



# Other Applications

## NEWBORN SCREENING COLLABORATIVE PROJECTS



### Welcome to the Newborn Screening Domain



**MS/MS**

Amino Acids & Acylcarnitines by MS/MS



**CAH**

Congenital Adrenal Hyperplasia

**BIOT**

Biotinidase Deficiency

**MS/MS [2]**

Amino Acids & Acylcarnitines by MS/MS [2nd Sample]

**CH**

Congenital Hypothyroidism

**GALT**

Galactosemia



**SCID**

Severe Combined Immunodeficiency



**LSD**

Lysosomal Storage Disorders



**FRDA**

Friedreich Ataxia



**ALD**

Adrenoleukodystrophy



**WD**

Wilson Disease

**FAO Probe**

Fatty acid oxidation probe assay (fibroblasts)



# Activity Report (11-04-11)



MS/MS



MS/MS

CAH

BIOT

[2]

SCID

LSD

FRDA

ALD

WD

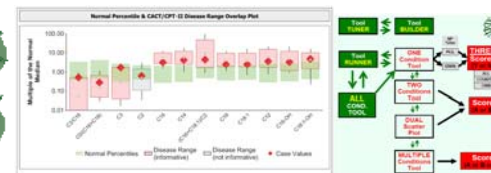
FAO

US sites	48	13	19	9	9	8	1	2	1	2
Int. sites	96	5	15	0	1	4	0	0	0	0
Countries	49	4	3	0	1	4	0	0	0	0
Users	775	42	60	22	42	49	9	15	6	15
TP cases	12,581	57	223	6	29	496	217	50	0	130
TP results	754034	458	828	261	273	2046	681	400	0	12199
Percentiles	25291	63	25	375	100	190	15	40	5	470
contributors	111	2	24	1	4	3	1	1	1	1
Cutoffs	6613	14	7	128	4	19	2	8	1	191
contributors	122	3	5	2	4	4	1	1	1	1

# Outline

- Impact of R4S project
  - Utilization
  - Lessons learned
- Products
- Future applications

NEWBORN SCREENING  
COLLABORATIVE PROJECTS

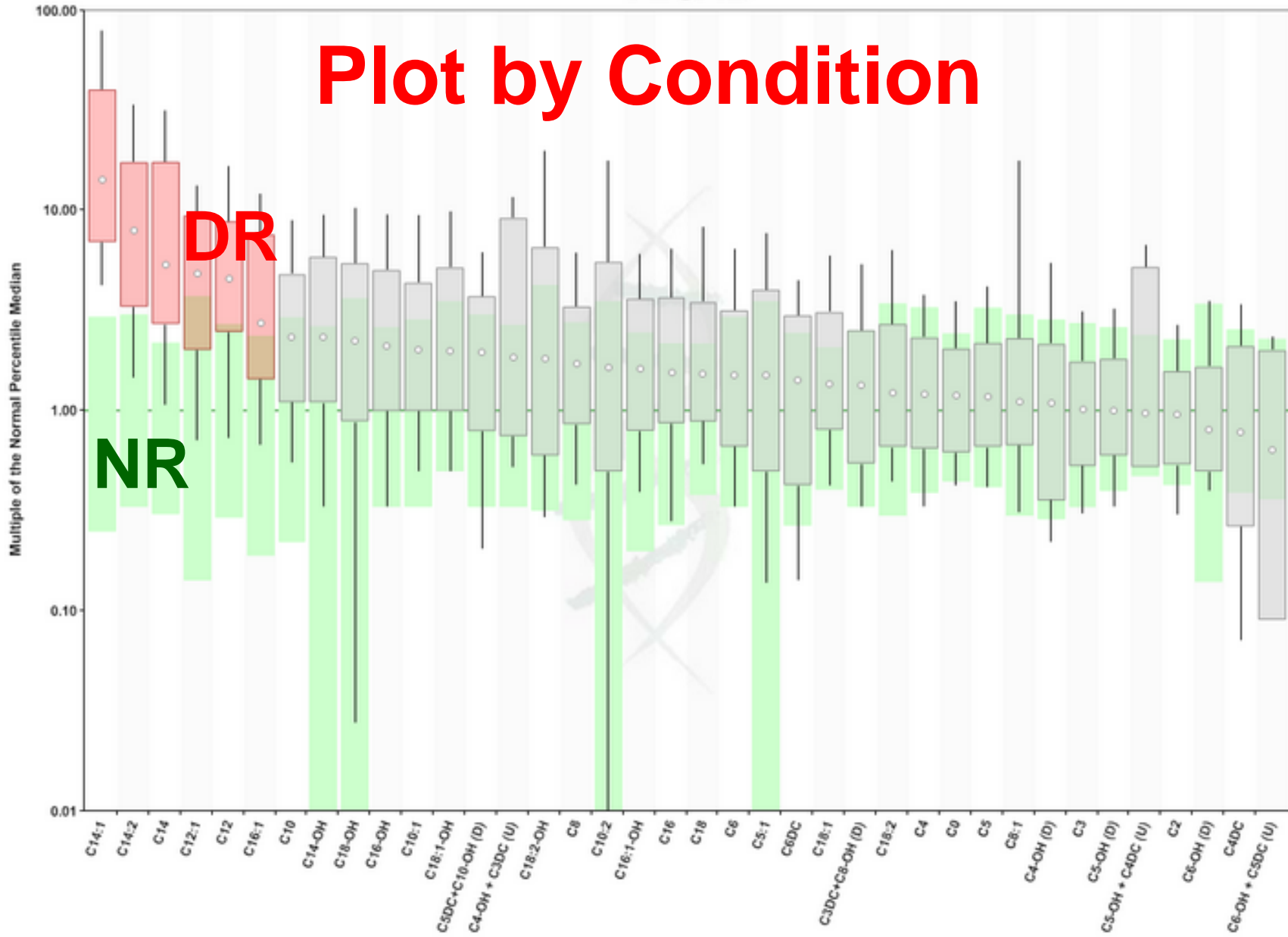


# Post-Analytical Tools

- The rationale to develop post-analytical tools comes from the observation that the diagnosis of most conditions is based on multiple markers, and ratios
- A parallel rather than sequential evaluation could be beneficial toward the achievement of better sensitivity and specificity

# VLCAD

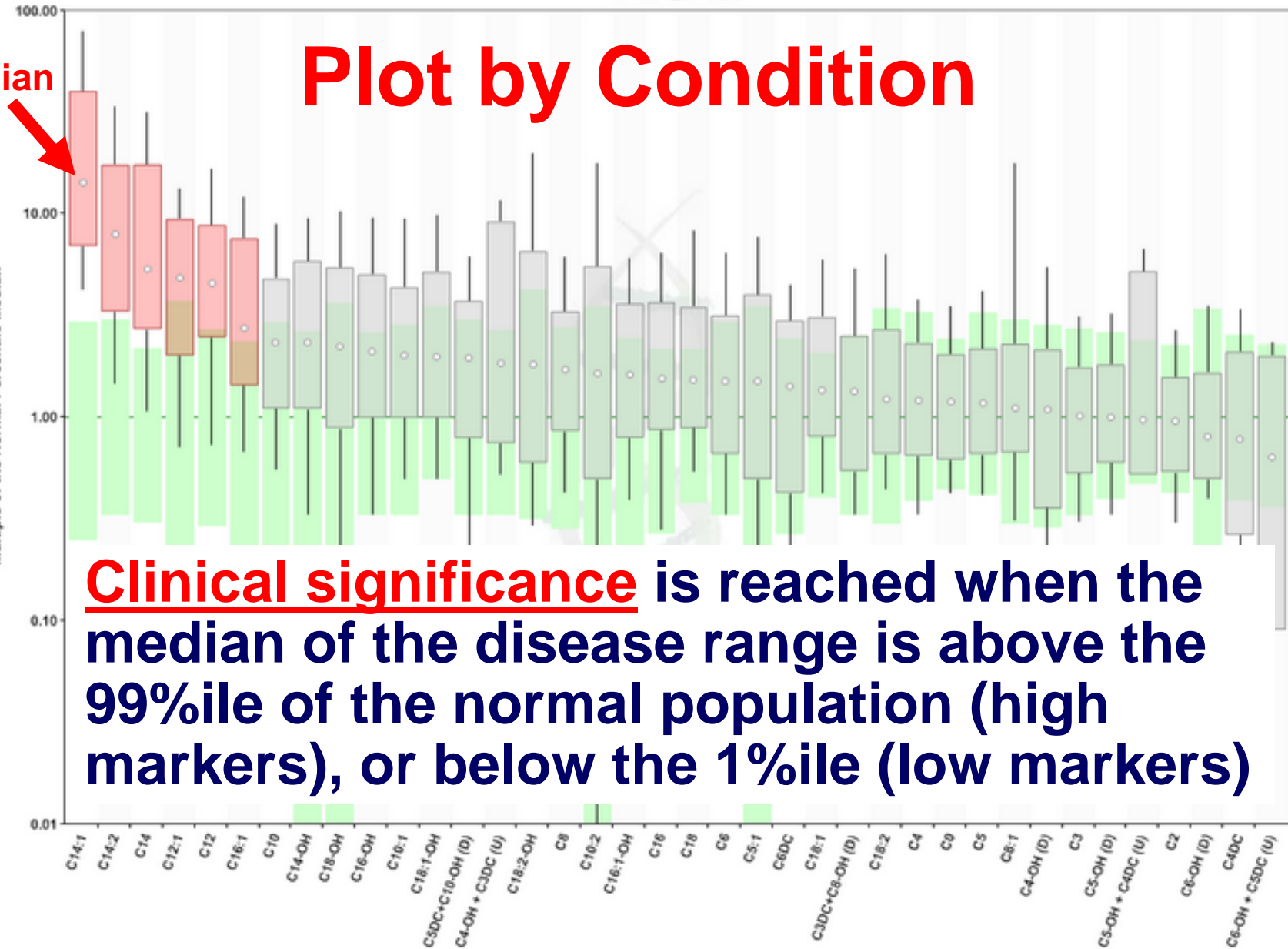
## Plot by Condition



# VLCAD

## Plot by Condition

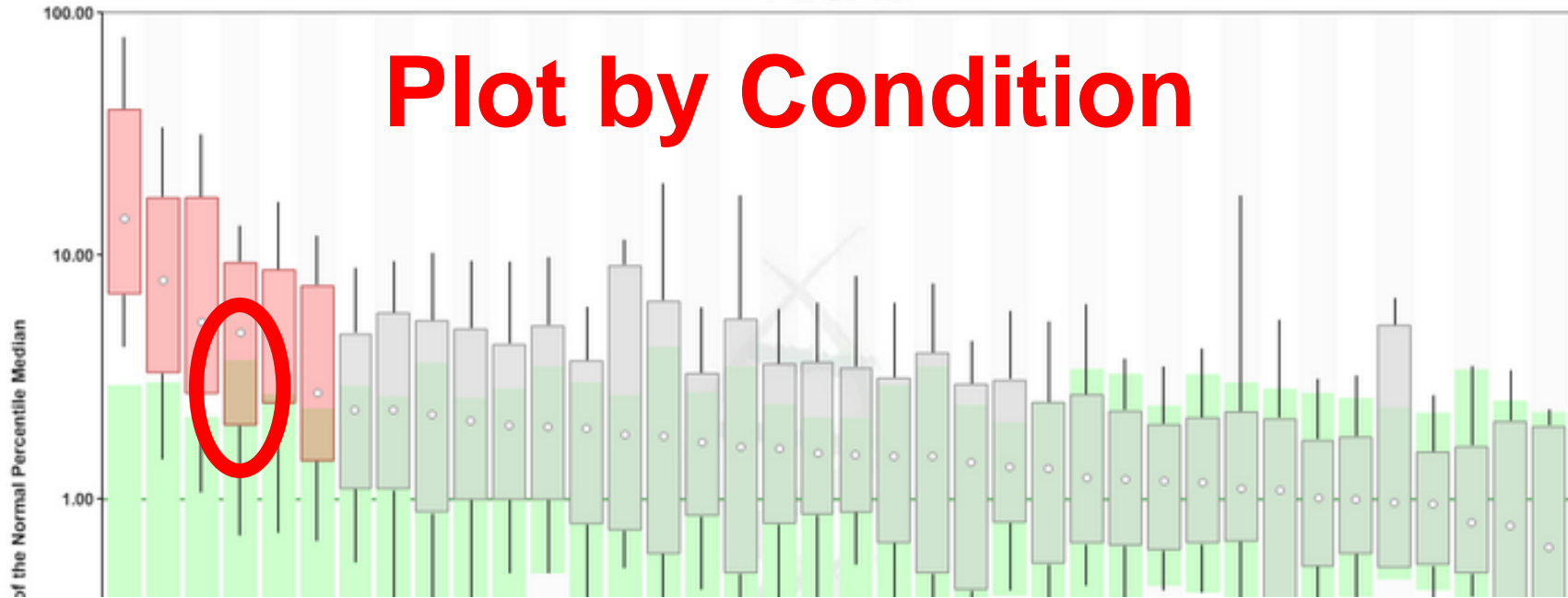
Median



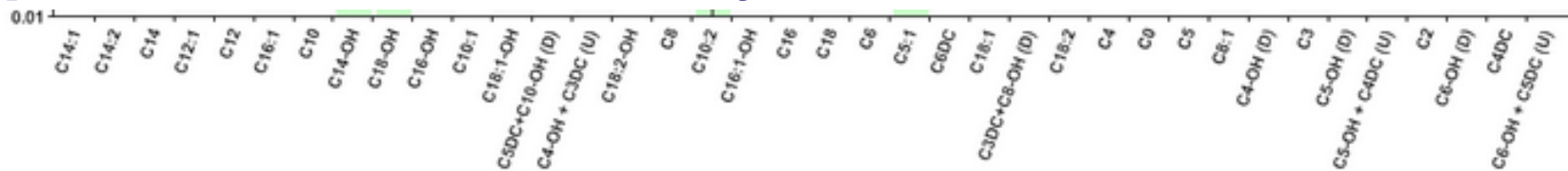
**Clinical significance** is reached when the median of the disease range is above the 99%ile of the normal population (high markers), or below the 1%ile (low markers)

# VLCAD

## Plot by Condition



**The degree of overlap between normal population and disease range is the foundation of a novel method to interpret quantitative results in a way that is unique to each condition and therefore not dependent on fixed analyte cutoff values**



# Post-Analytical Tools

- One Condition
  - These tools generate a score and suggest interpretation guidelines for a specific condition (**answer: Yes or No**)
- Two Conditions
  - These tools generate a score and suggest interpretation guidelines for a specific condition, and a direct comparison with a second related condition (**answer: condition A or condition B**)
- Dual Scatter Plot
  - These tools show the distribution of score pairs for the same case calculated with two of the tools (two conditions) above. The plot provides a **visual report of likelihood** to be one or the other condition
- Multiple Conditions
  - These tools generate a score and suggest interpretation guidelines for a specific condition, and a direct **comparison with other conditions**

# One Condition Tool

MS/MS COLLABORATIVE PROJECT



Post-Analytical Tool  
CACT/CPT-II 002 2011-04-16 [Single]

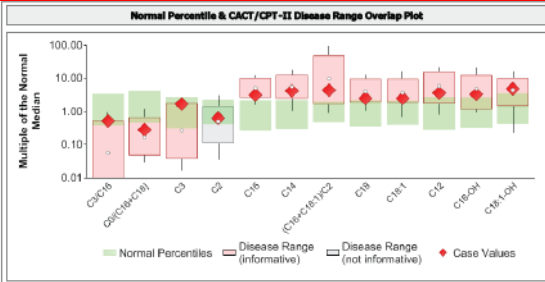
Printed On: 4/20/2011 4:03 PM Participant: Minnesota  
Tool Last Modified: 4/16/2011 11:12 AM Printed By: Piero Rinaldo

Analyte	Normal	Overlap	Disease Range				Case Value
			1%ile	5%ile	10%ile	50%ile	
C3/C16	0.24	12.4 %	0.60	0.41	0.33	0.04	0.33
C0/(C16+C18)	3.06	13.3 %	7.80	4.87	4.31	1.07	1.82
C3	0.57	44.4 %	4.36	3.44	3.06	0.46	3.00
C2	99%ile	%ile	1%ile	5%ile	10%ile	50%ile	Values
	51.25	96.6 %	0.84	1.40	2.62	11.80	15.00
C16	99%ile	%ile	1%ile	5%ile	10%ile	50%ile	Values
	6.01	3.3 %	4.52	7.13	7.62	14.47	9.00
C14	0.50	8.2 %	0.25	0.37	0.59	1.32	1.00
(C16+C18:1)/C2	0.35	11.0 %	0.17	0.24	0.31	1.84	0.80
C18	1.74	13.0 %	0.87	1.09	1.53	3.30	2.00
C18:1	2.48	14.5 %	0.85	1.99	2.27	4.45	3.00
C12	0.37	15.8 %	0.11	0.21	0.24	0.80	0.50
C16-OH	0.08	30.0 %	0.03	0.03	0.04	0.15	0.10
C18:1-OH	0.07	32.6 %	0.00	0.01	0.03	0.09	0.10

Printed On: 4/20/2011 4:03 PM Participant: Minnesota  
Tool Last Modified: 4/16/2011 11:12 AM Printed By: Piero Rinaldo

Normal Percentile & CACT/CPT-II Disease Range Overlap Values

Analyte	Normal	Overlap	Disease Range				Case Values
			99%ile	95%ile	90%ile	50%ile	
C3/C16	0.24	12.4 %	0.60	0.41	0.33	0.04	0.33
C0/(C16+C18)	3.06	13.3 %	7.80	4.87	4.31	1.07	1.82
C3	0.57	44.4 %	4.36	3.44	3.06	0.46	3.00
C2	99%ile	%ile	1%ile	5%ile	10%ile	50%ile	Values
	51.25	96.6 %	0.84	1.40	2.62	11.80	15.00
C16	99%ile	%ile	1%ile	5%ile	10%ile	50%ile	Values
	6.01	3.3 %	4.52	7.13	7.62	14.47	9.00
C14	0.50	8.2 %	0.25	0.37	0.59	1.32	1.00
(C16+C18:1)/C2	0.35	11.0 %	0.17	0.24	0.31	1.84	0.80
C18	1.74	13.0 %	0.87	1.09	1.53	3.30	2.00
C18:1	2.48	14.5 %	0.85	1.99	2.27	4.45	3.00
C12	0.37	15.8 %	0.11	0.21	0.24	0.80	0.50
C16-OH	0.08	30.0 %	0.03	0.03	0.04	0.15	0.10
C18:1-OH	0.07	32.6 %	0.00	0.01	0.03	0.09	0.10



**Case Score**

**50**

%ile Rank of all CACT/CPT-II Scores

**14 %**

Count of CACT/CPT-II Scores

**30**

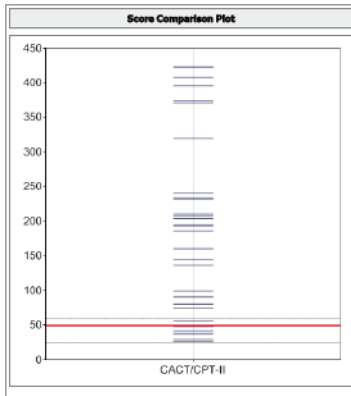
Score Interpretation Guidelines

This tool has been validated only for neonatal (<10 days) blood spots. Use of this tool is not advised to calculate scores for older patients.

Score  $\geq$  60  
Condition is most likely CACT/CPT-II.

Score  $\geq$  25 and  $<$  60  
Condition is likely CACT/CPT-II.

Score  $<$  25  
Profile is not informative.



NP - DR Overlap



# One Condition Tool

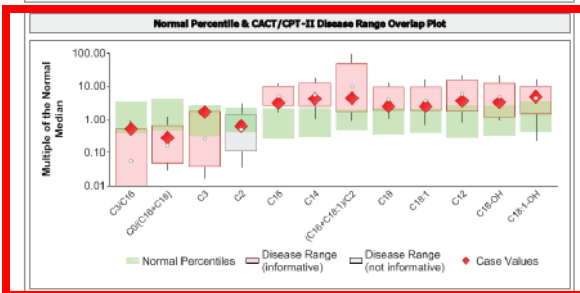
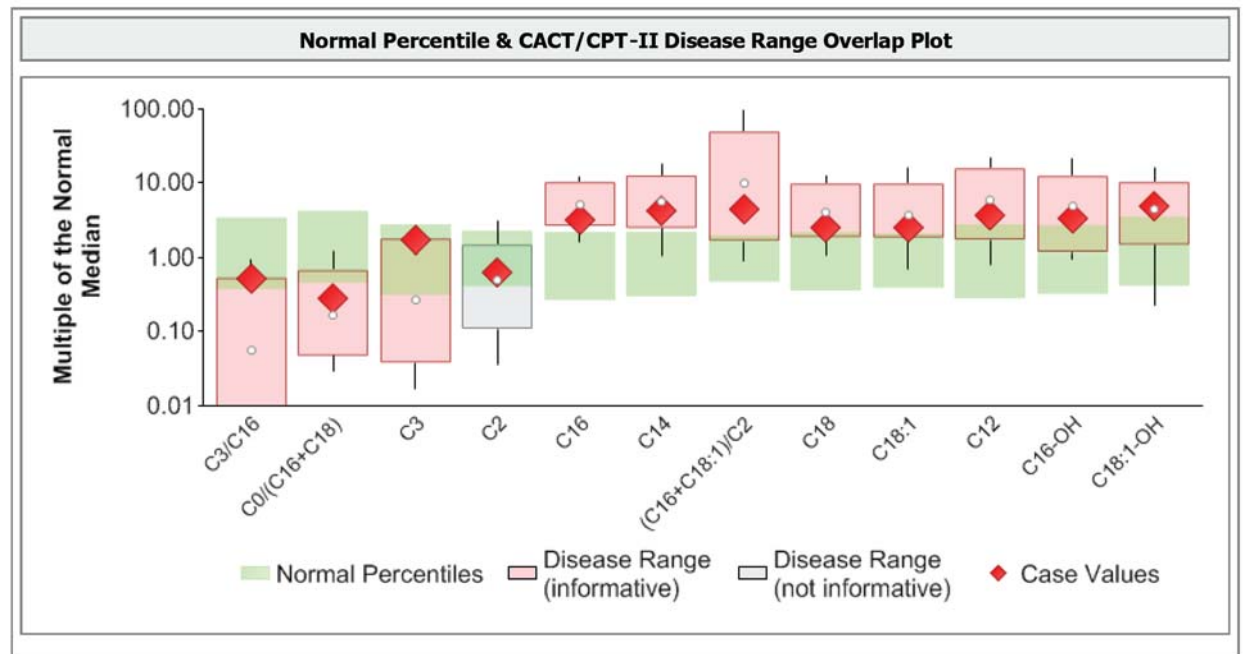
MS/MS COLLABORATIVE PROJECT



Post-Analytical Tool  
CACT/CPT-II 002 2011-04-16 [Single]

Printed On: 4/20/2011 4:03 PM Participant: Minnesota  
Tool Last Modified: 4/16/2011 11:12 AM Printed By: Piero Rinaldo

Analyte	Normal Value	Overlap %	Disease Range				Case Value
			99%ile	95%ile	10%ile	50%ile	
C3/C16	0.24	12.4 %	0.60	0.41	0.33	0.04	0.33
C0(C16+C18)	3.06	13.3 %	7.80	4.87	4.31	1.87	1.82
C3	0.57	44.4 %	4.36	3.44	3.06	0.46	3.00
C2	99%ile	%ile	99%ile	95%ile	10%ile	50%ile	Value
	51.25	96.6 %	0.84	1.40	2.62	11.80	15.00
C16	6.01	3.3 %	4.52	7.13	7.62	14.47	9.00
C14	0.50	8.2 %	0.25	0.37	0.59	1.32	1.00
(C16+C18)/C2	0.35	11.0 %	0.17	0.24	0.31	1.84	0.80
C18	1.74	13.0 %	0.87	1.09	1.53	3.30	2.00
C18:1	2.48	14.5 %	0.85	1.99	2.27	4.45	3.00
C12	0.37	15.8 %	0.11	0.21	0.24	0.80	0.50
C16-OH	0.08	30.0 %	0.03	0.03	0.04	0.15	0.10
C18:1-OH	0.07	32.6 %	0.00	0.01	0.03	0.09	0.10



**Case Score**

**50**

%ile Rank of all CACT/CPT-II Scores:

**14 %**

Count of CACT/CPT-II Scores:

**30**

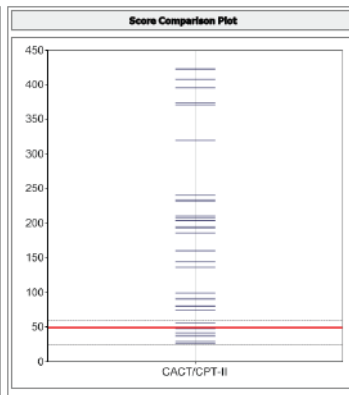
Score Interpretation Guidelines

This tool has been validated only for neonatal (<10 days) blood spots. Use of this tool is not advised to calculate scores for older patients.

Score  $\geq$  60  
Condition is most likely CACT/CPT-II.

Score  $\geq$  25 and  $<$  60  
Condition is likely CACT/CPT-II.

Score  $<$  25  
Profile is not informative.

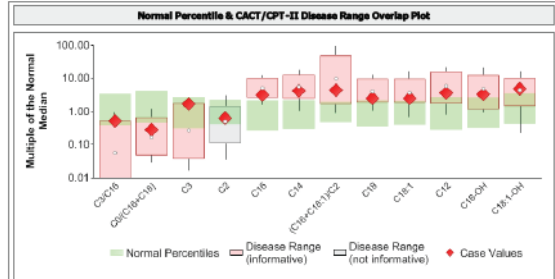


# One Condition Tool

Post-Analytical Tool  
CACT/CPT-II 002 2011-04-16 [Single]

Printed On: 4/20/2011 4:03 PM Participant: Minnesota  
Tool Last Modified: 4/16/2011 11:12 AM Printed By: Piero Rinaldo

Analyte	Normal 2%ile	Overlap %ile	Disease Range				Case Value
			99%ile	95%ile	10%ile	50%ile	
C1/C16	0.24	12.4 %	0.60	0.41	0.33	0.04	0.33
C0(C16+C19)	3.06	13.3 %	7.80	4.87	4.31	1.87	1.82
C3	0.57	44.4 %	4.36	3.44	3.06	0.46	3.00
C2	51.25	96.6 %	0.84	1.40	2.62	11.80	15.00
		99%ile					
C16	6.01	3.3 %	4.52	7.13	7.62	14.47	9.00
C14	0.90	8.2 %	0.25	0.37	0.59	1.32	1.00
(C16+C18)/C2	0.35	11.0 %	0.17	0.24	0.31	1.84	0.80
C18	1.74	13.0 %	0.87	1.09	1.53	3.30	2.00
C18:1	2.48	14.5 %	0.85	1.99	2.27	4.45	3.00
C12	0.37	15.8 %	0.11	0.21	0.24	0.80	0.50
C16-OH	0.08	30.0 %	0.03	0.03	0.04	0.15	0.10
C18:1-OH	0.07	32.6 %	0.00	0.01	0.03	0.09	0.10



**Case Score**

**50**

%ile Rank of all CACT/CPT-II Scores:

**14 %**

Count of CACT/CPT-II Scores

**30**

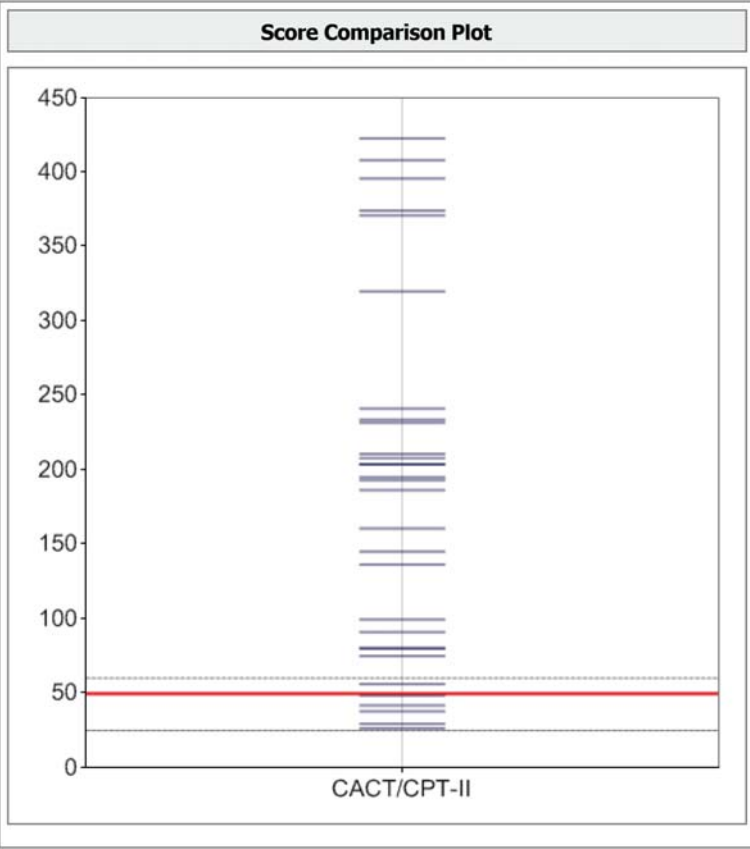
**Score Interpretation Guidelines**

This tool has been validated only for neonatal (<10 days) blood spots. Use of this tool is not advised to calculate scores for older patients.

**Score is >= 60**  
Condition is most likely CACT/CPT-II.

**Score is >= 25 and < 60**  
Condition is likely CACT/CPT-II.

**Score is < 25**  
Profile is not informative.



**Case Score**

**50**

%ile Rank of all CACT/CPT-II Scores:

**14 %**

Count of CACT/CPT-II Scores

**30**

**Score Interpretation Guidelines**

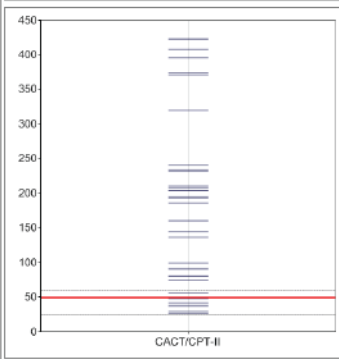
This tool has been validated only for neonatal (<10 days) blood spots. Use of this tool is not advised to calculate scores for older patients.

**Score is >= 60**  
Condition is most likely CACT/CPT-II.

**Score is >= 25 and < 60**  
Condition is likely CACT/CPT-II.

**Score is < 25**  
Profile is not informative.

**Score Comparison Plot**

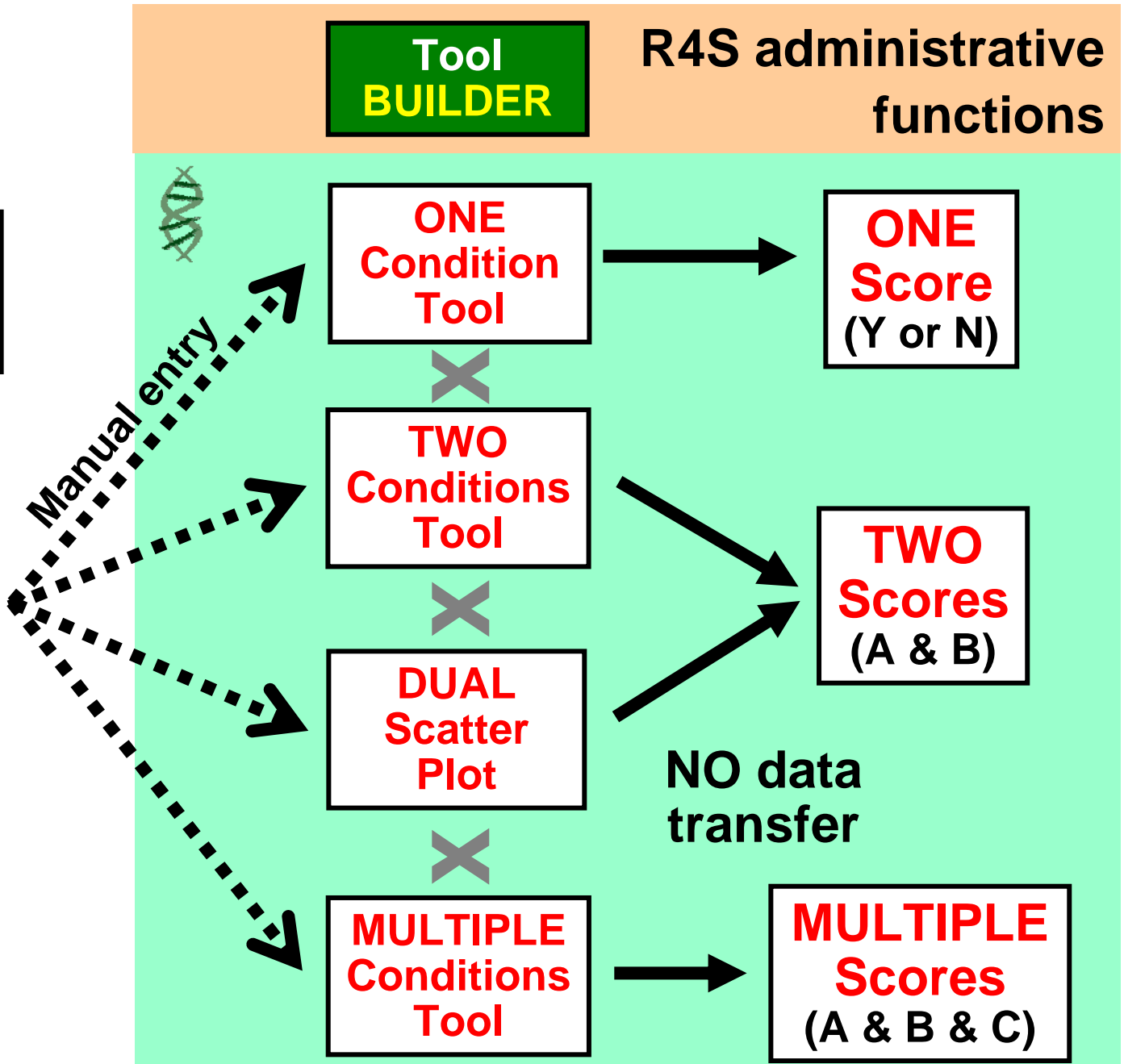


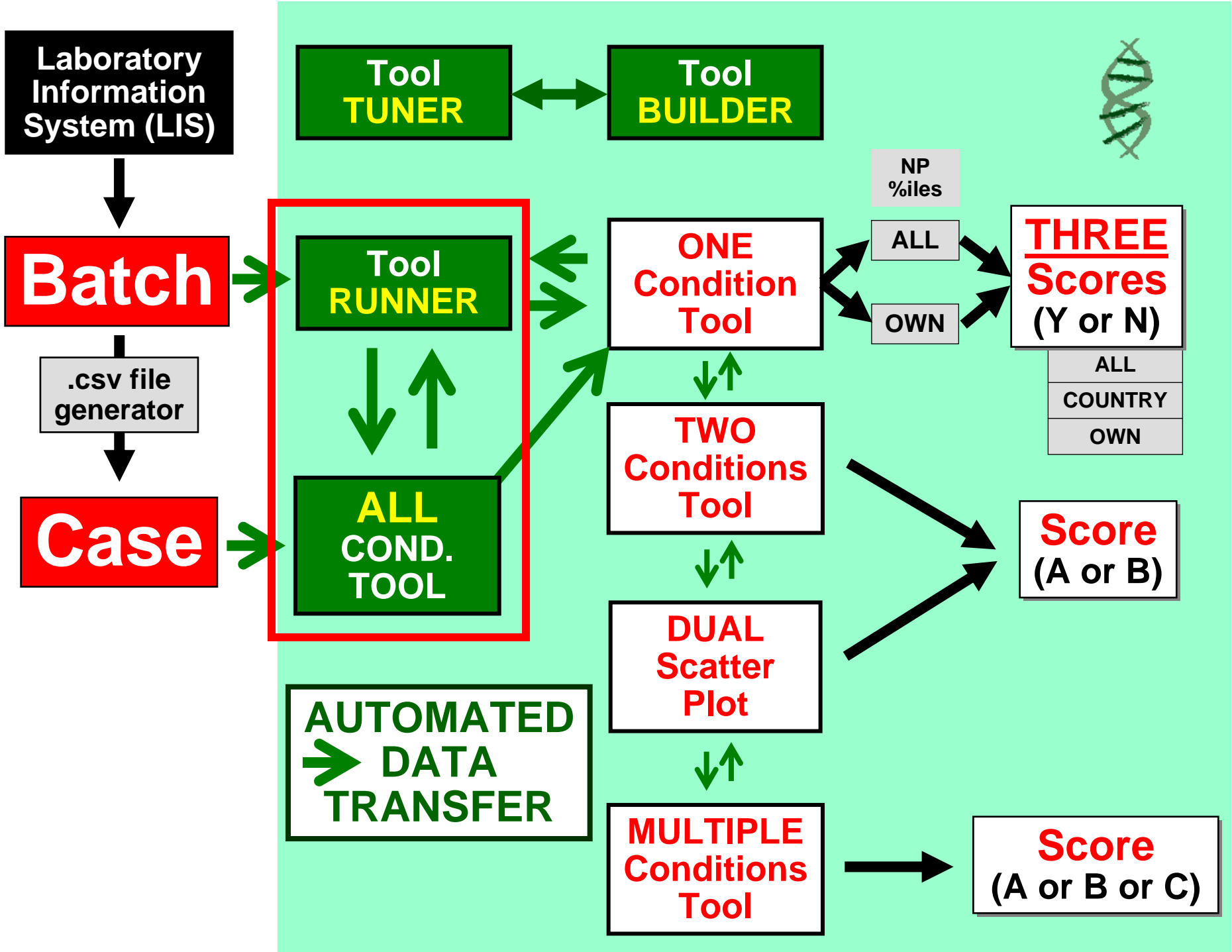
~~ANALYTE~~ ➔ **CONDITION**

cutoff cutoff

Laboratory Information System (LIS)

Case





# What is the Tool Runner?

- **The tool runner is a process to upload to the website whole batches of raw data after conversion to .csv files**
- **The tool calculates automatically every possible score (or a chosen subset) for each case in a batch (i.e., a 96 well plate)**
- **It generate a report of all instances with a score greater than 0%ile rank**

# Tool Runner Report

Case ID: 27 All Conditions Tool

Percentile	Tool	Guideline
0	LCHAD/TFP 005 2011-08-31 [Single-Derivatized]	Condition is possibly LCHAD/TFP. (Score of 11 $\geq$ 10 AND $<$ 20)

Case ID: 31 All Conditions Tool

Percentile	Tool	Guideline
0	LCHAD/TFP 005 2011-08-31 [Single-Derivatized]	Condition is possibly LCHAD/TFP. (Score of 11 $\geq$ 10 AND $<$ 20)

Case ID: 37 All Conditions Tool

Percentile	Tool	Guideline
1	LCHAD/TFP 005 2011-08-31 [Single-Derivatized]	Condition is possibly LCHAD/TFP. (Score of 12 $\geq$ 10 AND $<$ 20)
6	CACT/CPT-II 003 2011-08-23 [Single]	Condition is likely CACT/CPT-II. (Score of 37 $\geq$ 25 AND $<$ 60)

Case ID: 69 All Conditions Tool

Percentile	Tool	Guideline
2	HCY 005 2011-10-26 [Single]	Condition is possibly HCY. Consider performing 2nd tier test for homocysteine. If negative, rule out hyper-methioninemia. (Score of 24 $\geq$ 10 AND $<$ 50)
1	H-PHE 003 2011-04-15 [Single]	Condition is possibly H-PHE. Consider excluding TPN. (Score of 33 $\geq$ 20 AND $<$ 50)

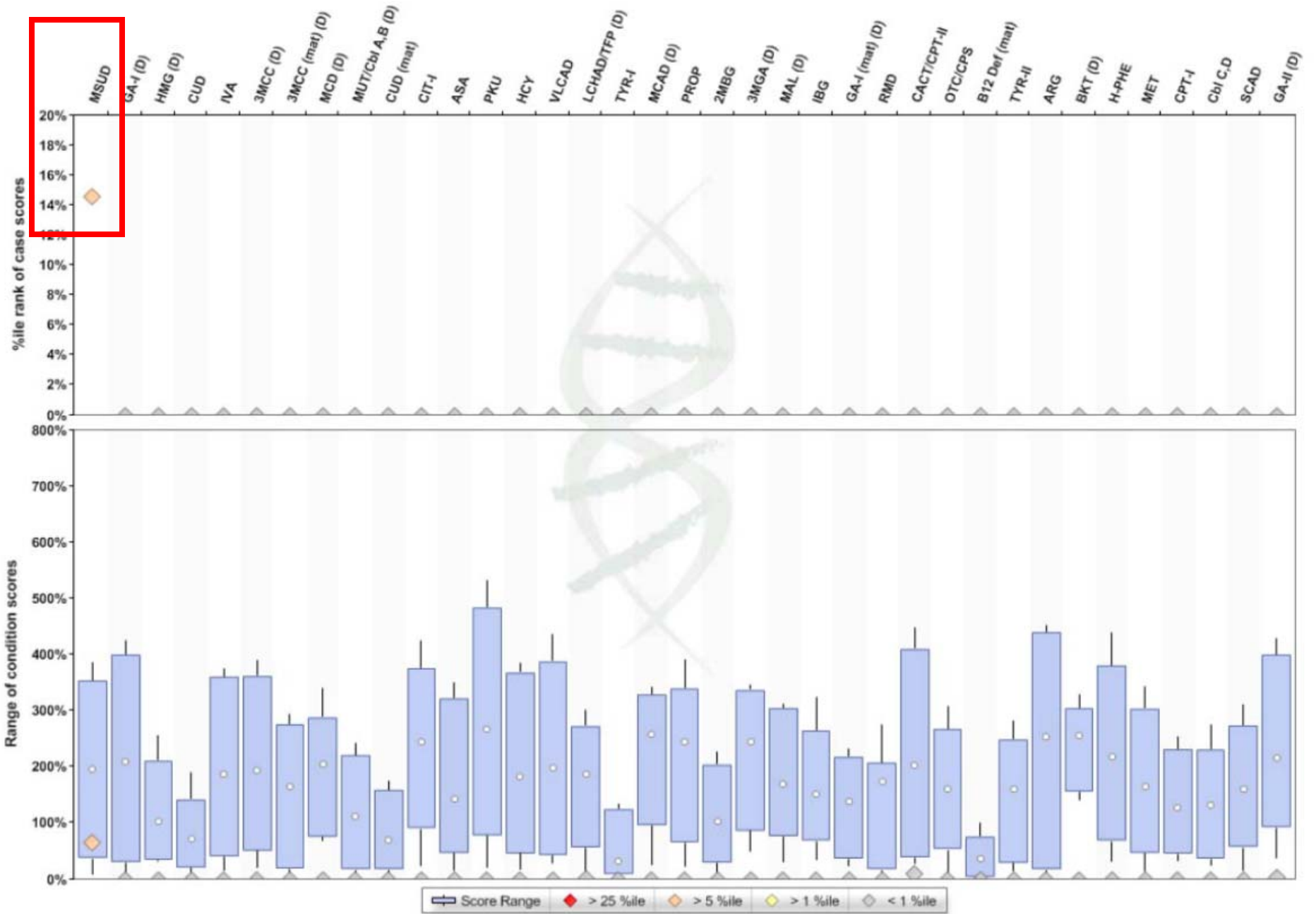
Case ID: 84 All Conditions Tool

Percentile	Tool	Guideline
1	MET 003 2011-10-26 [Single]	Consider performing 2nd tier test for homocysteine. If negative, condition is likely MET. (Score of 13 $\geq$ 10 AND $<$ 50)

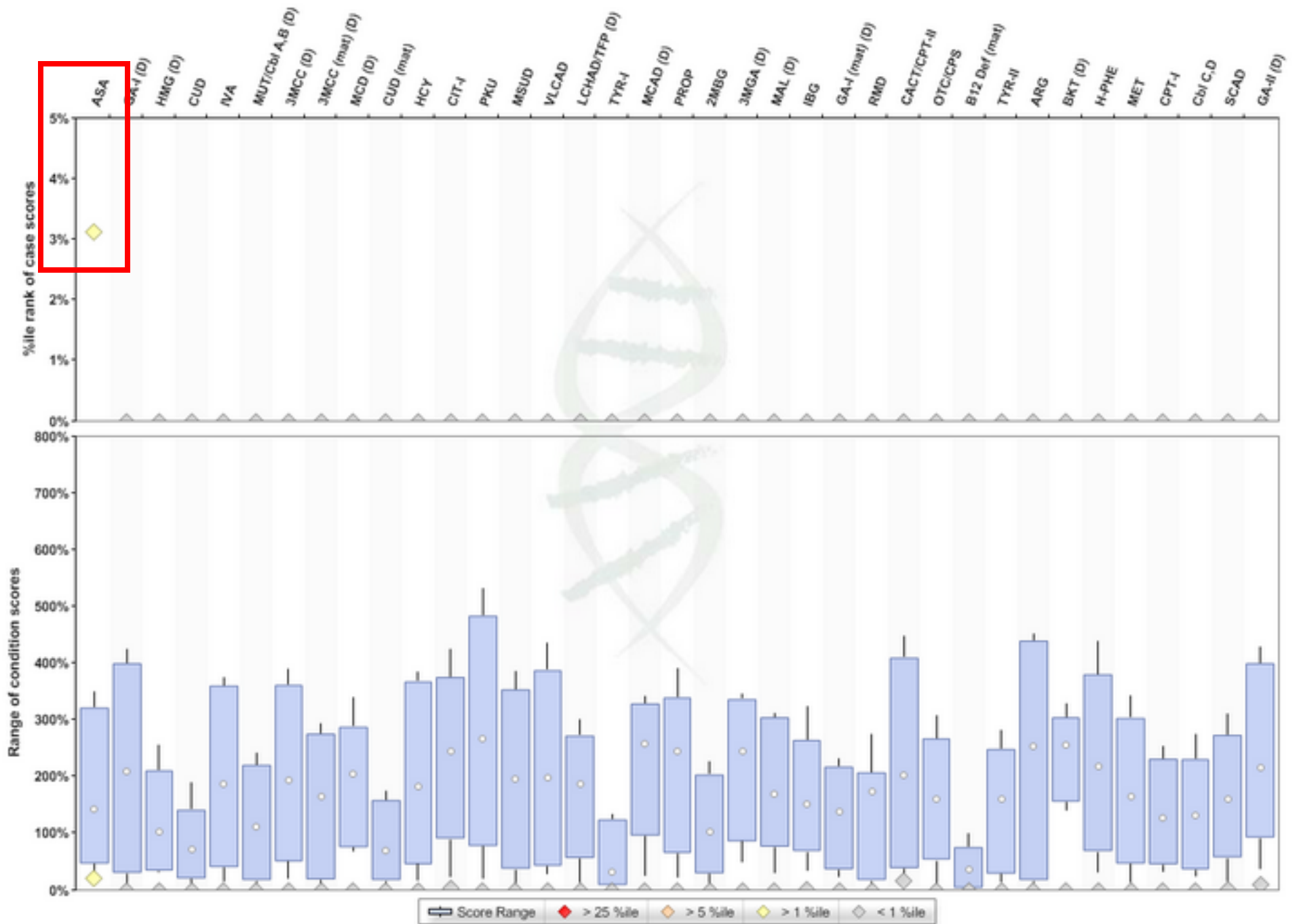
**In this plate, only 5 cases (27,31,37,69,84) had one or more scores above the threshold of clinical significance which is set for each condition separately**

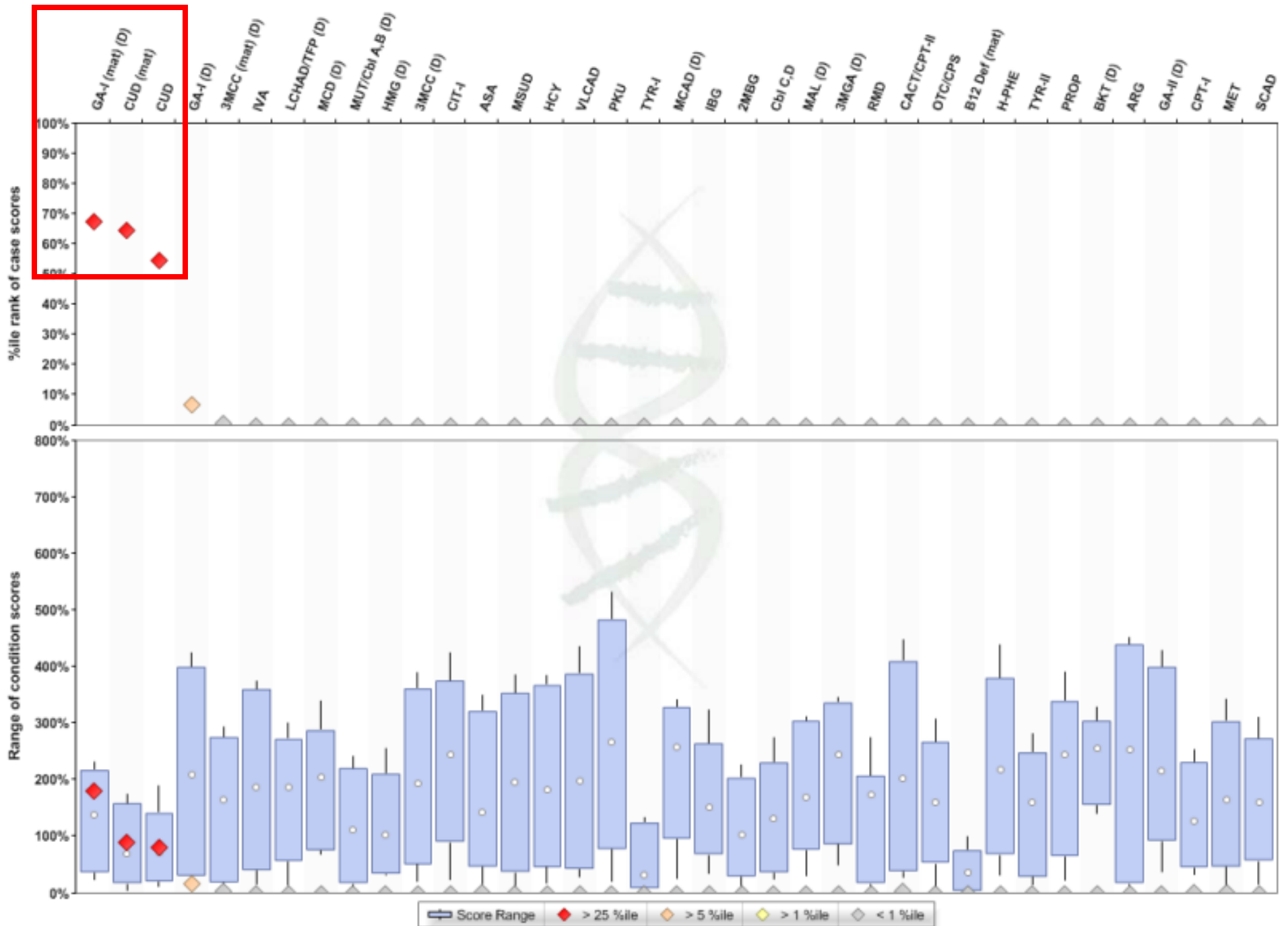
# What is the All Conditions Tool?

- **The All Conditions tool is similar to the tool runner but it processes one case at the time (either uploaded as .csv file or entered manually) and provides a visual, not tabular output of the results**
- **The tool calculates automatically every possible score (if all required data are available) for that case**

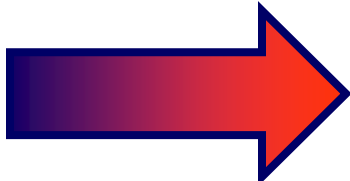


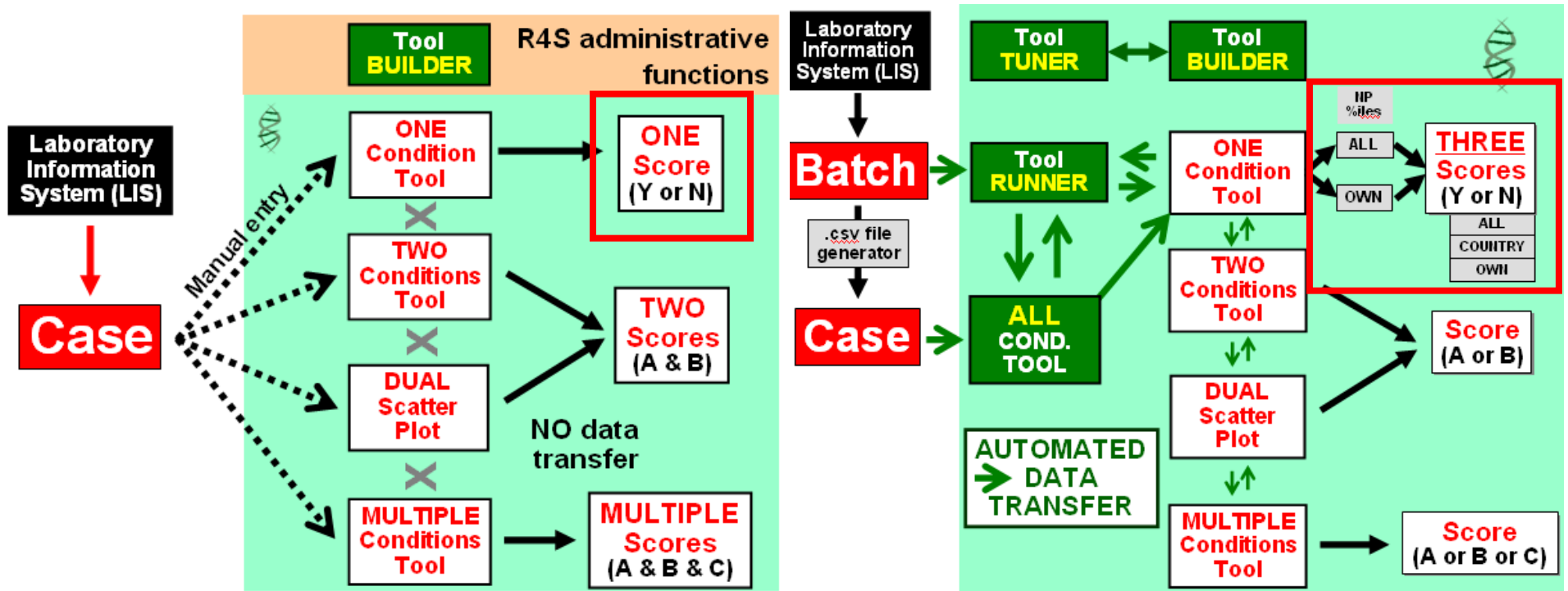






# User Customization of Tools

Old R4S  NEW R4S



# The NEW One Condition Tool

**Upload Values By Loinc**

Choose File

Populate

**Normal Percentiles**

Cumulative

Minnesota

All Values Required to Generate a Score

**Low Markers**

*No values required.*

**Differentiators**

C16

C18

C2

**High Markers**

C16-OH

C18-OH

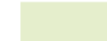
C18:1-OH

C14:1

C16:1-OH

Calculate

Cumulative Normal Percentile & LCHAD/TFP Disease Range Overlap Values							
Analyte	Normal 99%ile	Overlap %ile	Disease Range				Case Values
			1%ile	5%ile	10%ile	50%ile	
C16	6.08	92.5 %	0.90	1.23	1.63	3.41	
C18	1.74	94.5 %	0.18	0.45	0.53	0.95	
C2	51.70	99.5 %	2.70	4.50	6.62	19.95	
	99%ile	%ile	1%ile	5%ile	10%ile	50%ile	Values
C16-OH	0.08	0.0 %	0.13	0.19	0.27	0.73	
C16OH/C16	0.03	0.0 %	0.05	0.08	0.10	0.26	
C18-OH	0.06	2.2 %	0.05	0.09	0.12	0.57	
C18-OH/C18	0.11	3.7 %	0.05	0.12	0.16	0.67	
C18:1-OH	0.07	3.8 %	0.03	0.09	0.14	0.54	
C14:1	0.35	23.1 %	0.08	0.14	0.20	0.62	
C14:1/C2	0.02	23.4 %	0.00	0.01	0.01	0.04	
C14:1/C16	0.13	24.9 %	0.04	0.05	0.07	0.19	
C16:1-OH	0.12	26.1 %	0.04	0.07	0.09	0.18	

 NP - DR Overlap

### Case Score

**12**

All

**13**

United States

**8**

Minnesota

### %ile Rank of all LCHAD/TFP Scores:

**1 %**

All

**0 %**

United States

**0 %**

Minnesota

### Count of LCHAD/TFP Scores

**73**

All

**38**

United States

**5**

Minnesota

### Score Interpretation Guidelines

This tool has been validated only for neonatal (<10 days) blood spots. Use of this tool is not advised to calculate scores for older patients.

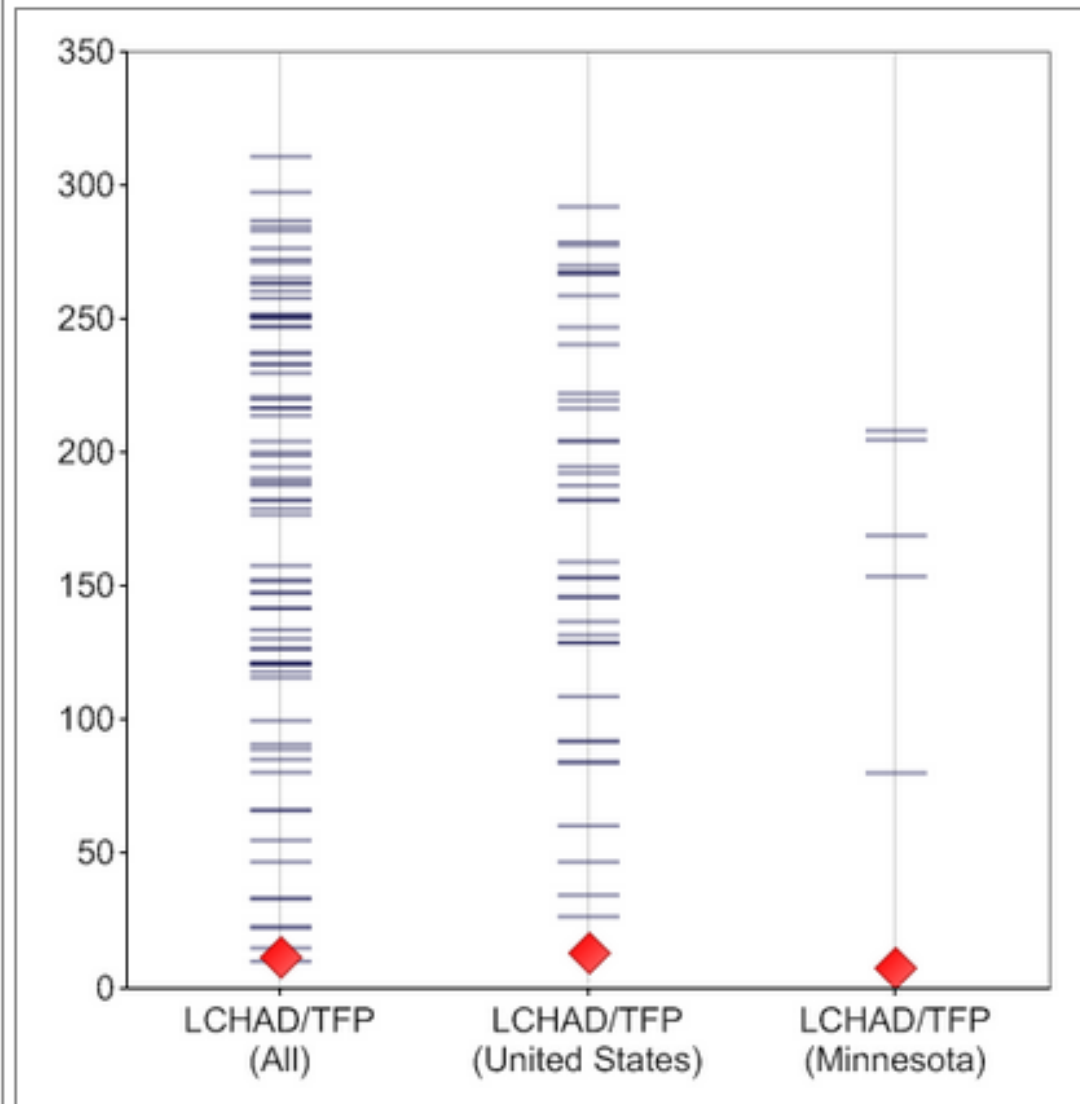
**Score is  $\geq 40$**   
Condition is most likely LCHAD/TFP.

**Score is  $\geq 20$  and  $< 40$**   
Condition is likely LCHAD/TFP.

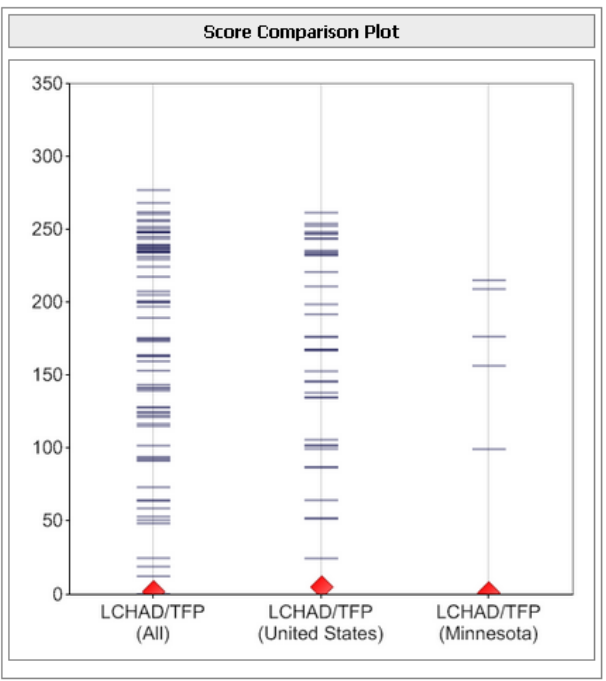
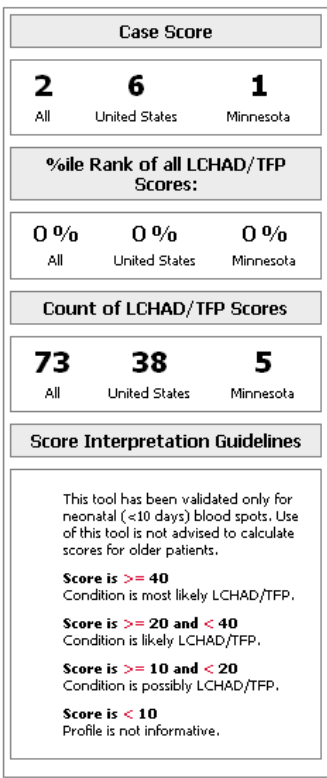
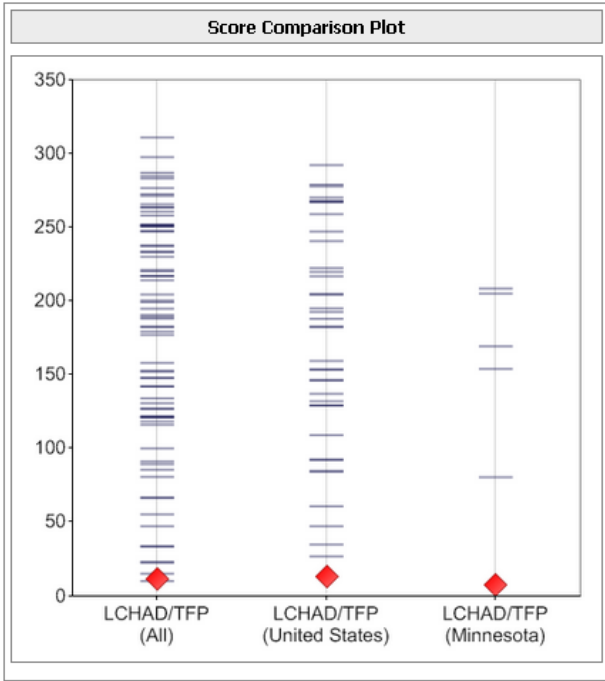
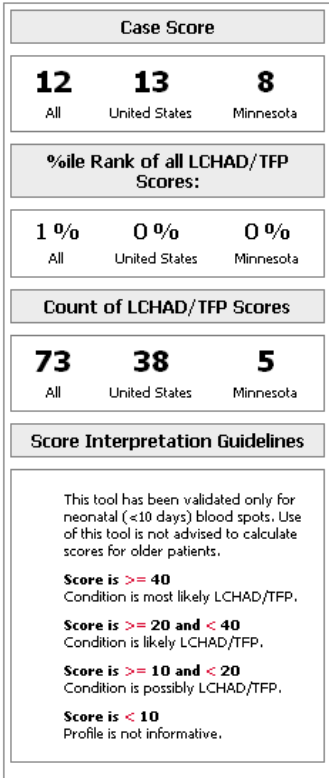
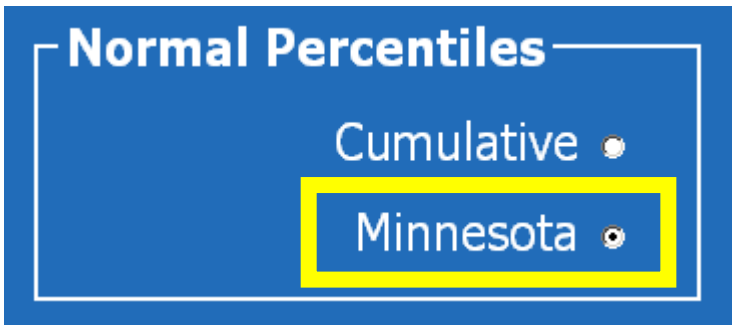
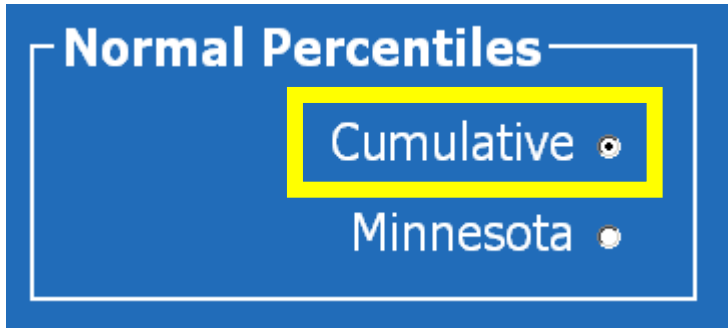
**Score is  $\geq 10$  and  $< 20$**   
Condition is possibly LCHAD/TFP.

**Score is  $< 10$**   
Profile is not informative.

### Score Comparison Plot

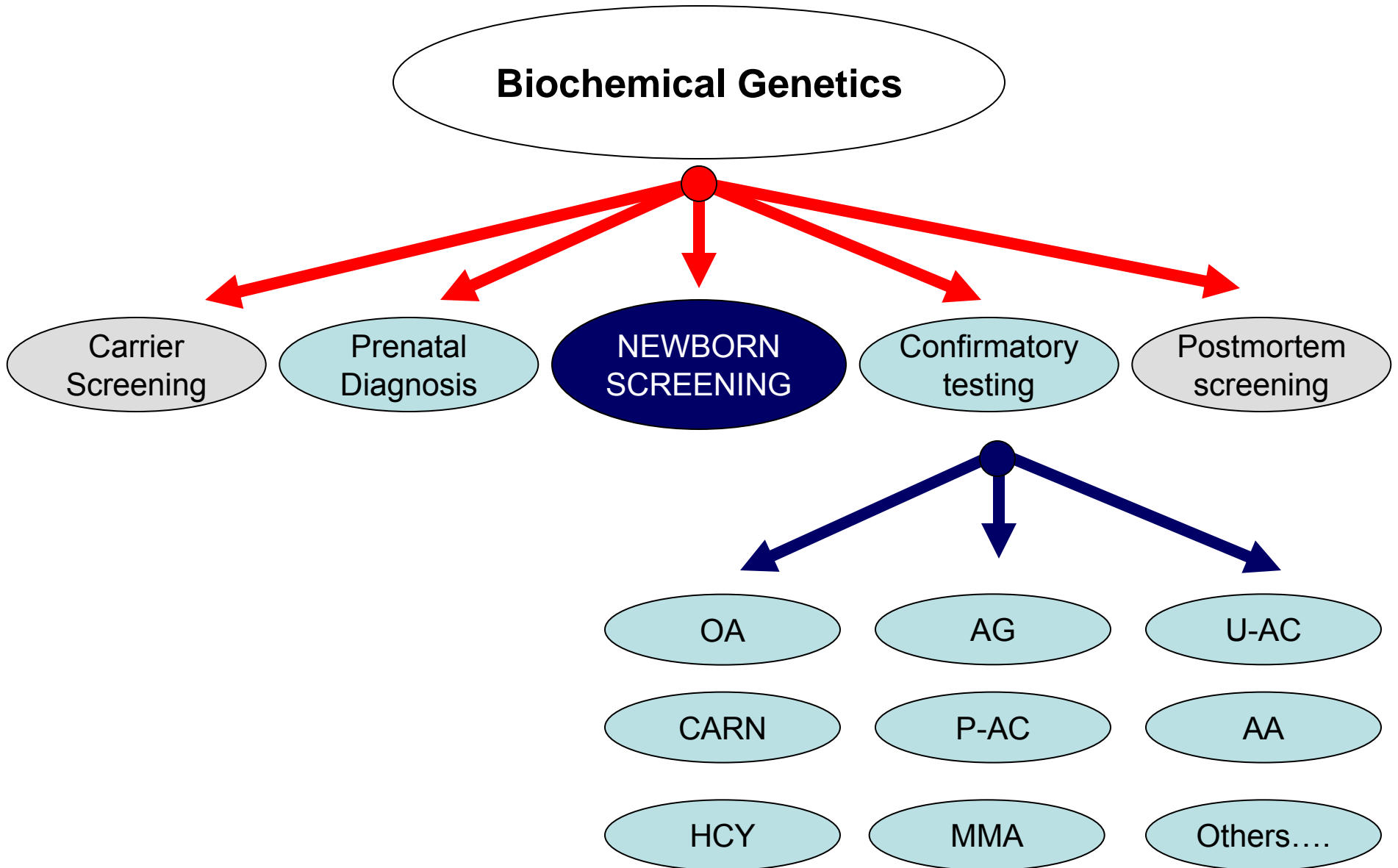


**ALL** COUNTRY OWN  
(USA)



The new tools can be customized to calculate scores based on **OWN** %iles and **OWN** cases

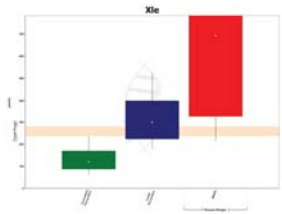
# R4S is a Biochemical Genetics Portal



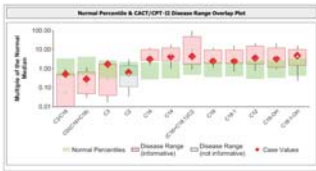
# Conclusions



- Please join R4S. To get a password send e-mail to [rinaldo@mayo.edu](mailto:rinaldo@mayo.edu)



- Analyte cutoff values could be replaced by score interpretation guidelines for a specific condition



- The tools are in constant development, with your help (and more data) they could get much better of what they are



- The new tools allow automated data submission, score customization, and discretionary modifications of the tools



# Thank You for Your Attention

## 2011 NEWBORN SCREENING AND GENETIC TESTING SYMPOSIUM

*Fair Winds for the Future*



*Fair winds!  
Bob*

NEWBORN SCREENING COLLABORATIVE PROJECTS

