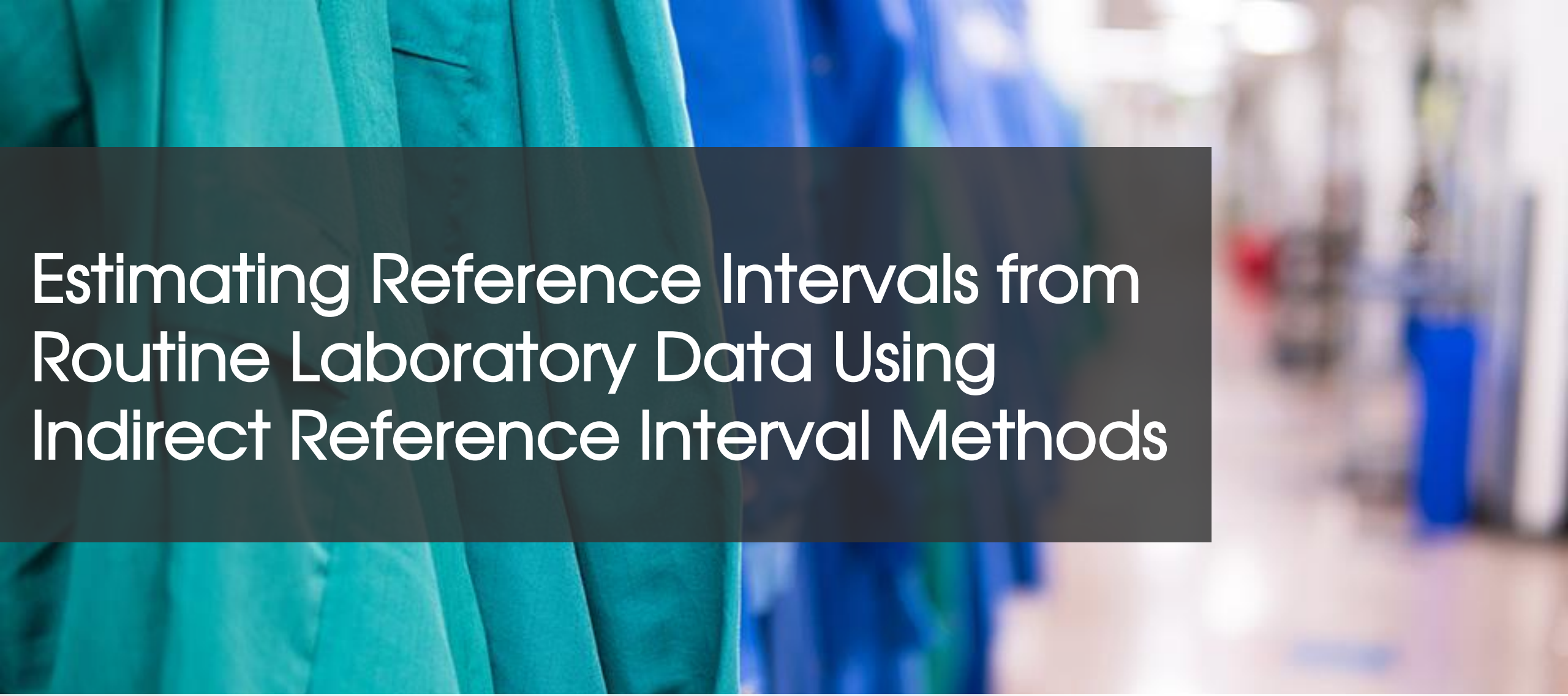

Estimating Reference Intervals from Routine Laboratory Data Using Indirect Reference Interval Methods

Kelly Doyle, PhD, DABCC, FADLM

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Medical Director of Special Chemistry and Endocrinology, ARUP Laboratories

ARUP INSTITUTE FOR LEARNING

AUGUST 2024

OBJECTIVES

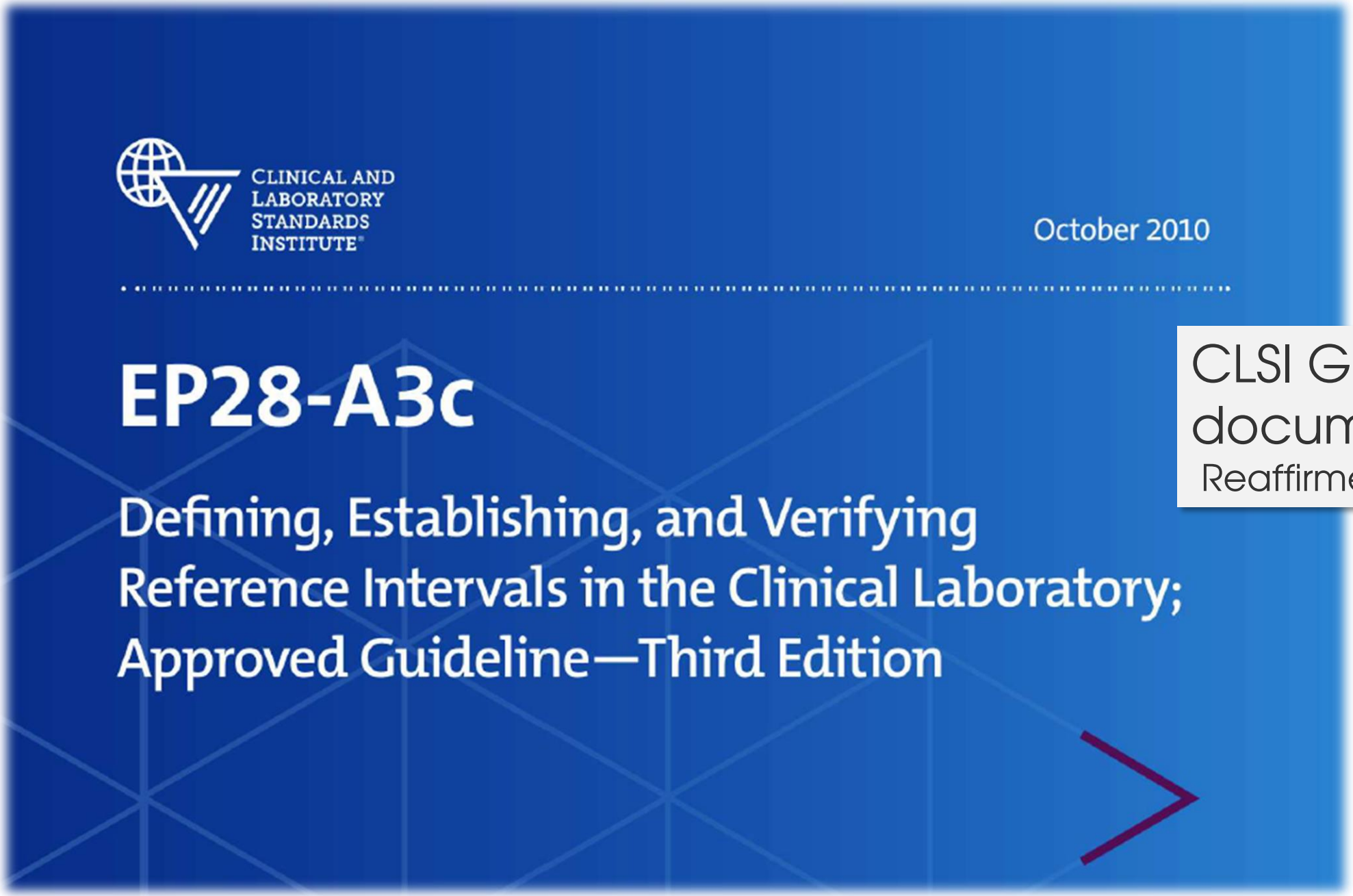
1. Summarize the establishment and use of reference intervals in clinical laboratory practice.
2. Discuss the application of direct and indirect methods to determine population/sex/age-based reference intervals.
3. Describe how different estimation methods can overcome analyte specific challenges including skewed, partial, or overlapping distributions.

Reference Intervals (RIs)

- *Are:*
  - » a representation of the typical distribution of analyte values observed in a healthy reference population
  - » are reported to clinicians to support the interpretation of clinical pathology results
- *Are not:*
  - » the same as clinical decision limits (CDL)

Regulatory requirements in US and ISO:

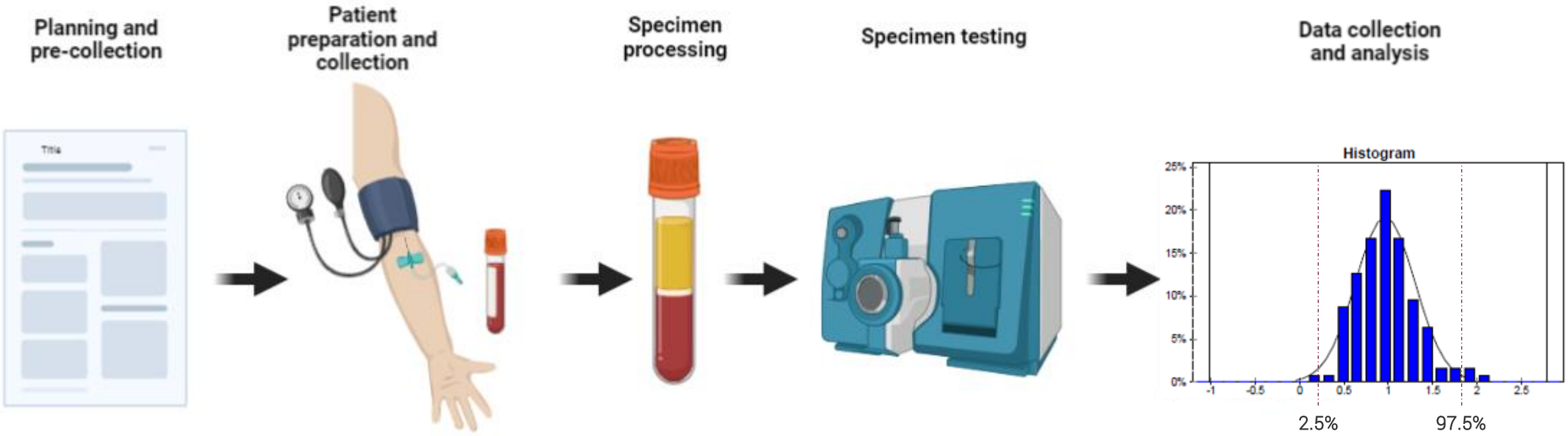
- » CLIA: RIs must be provided with lab results when applicable
- » CAP: Each laboratory to establish or verify RIs
- » ISO15189: Verify RIs
  - When new clinical data is available
  - When a method has been in use for an extended time



CLSI Guidance document

Reaffirmed April 2016

Direct Method



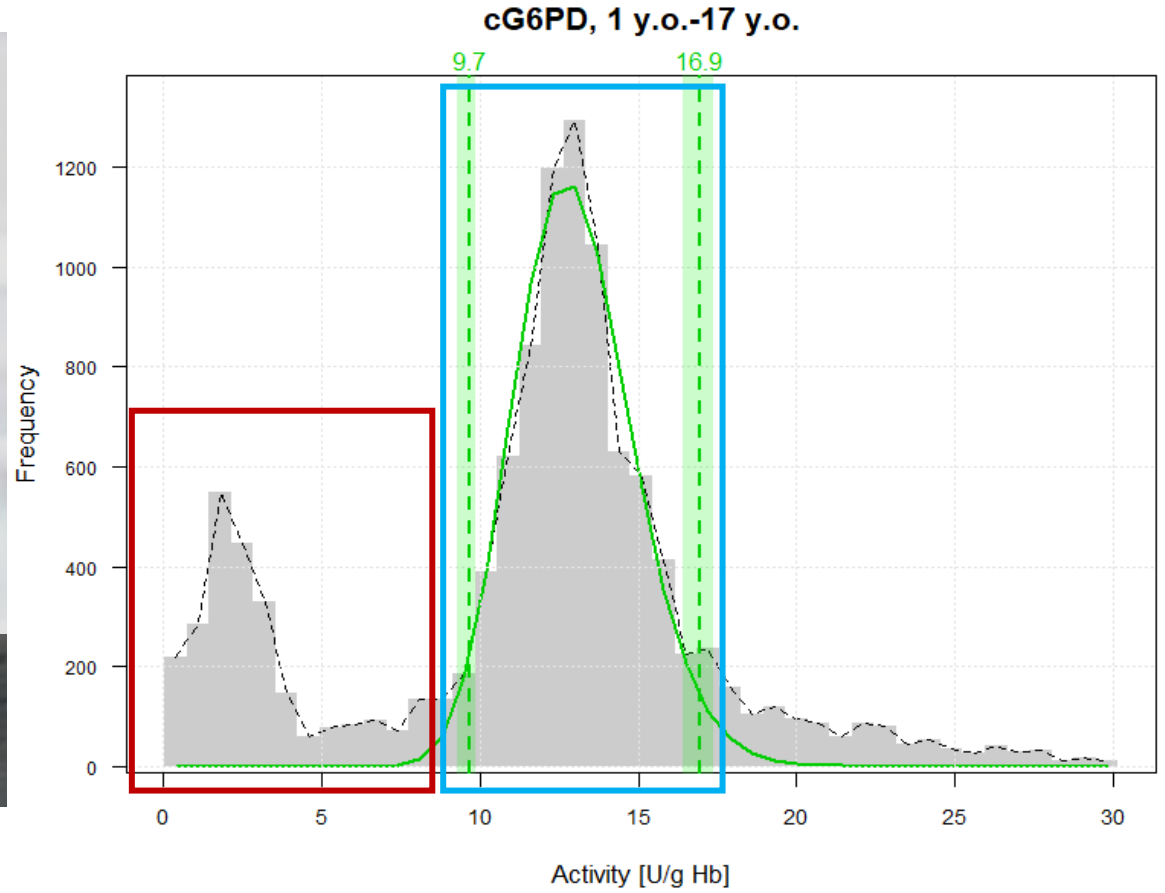
Created with BioRender.com and EP Evaluator

Benefits and Limitations

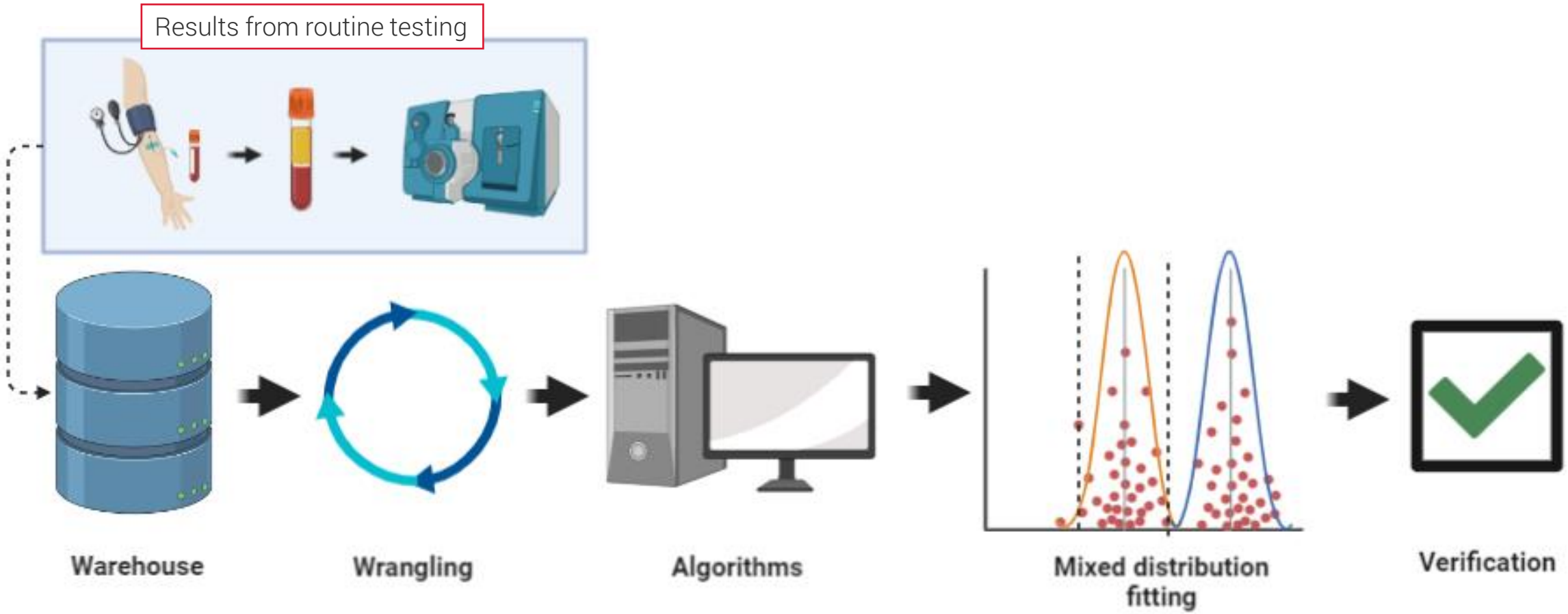
- Benefits
  - » Controlled, well-characterized reference group
  - » Defined protocols for volunteer preparation, specimen collection, and analysis
  - » Simple statistical methods used
- Limitations
  - » Cost
  - » Time
  - » Ethical issues – e.g., pediatric or pregnant individuals
  - » Selection bias – volunteer reference group may not be truly representative
  - » Challenge to encompass all groups – pediatrics, pregnant, elderly, ethnic
  - » Preanalytical conditions may not fully represent all variables
  - » Possible harm to subjects – bruising, time
  - » Difficult to define/assure health of subjects

Martinez-Sanchez et al. Adv Lab Med 2(1) 2021

Indirect Methods



Indirect Method



Created with BioRender.com.

Benefits and Limitations

- Benefits
  - » Cost
  - » Time
  - » Ethical advantages
  - » Mixed datasets – i.e., pathological and non-pathological test results
  - » Data collected under routine lab processes
  - » Difficult to collect scenarios (e.g., 24-hour urine)
  - » When many in the general population may be excluded (e.g., PTH in elderly)
- Limitations
  - » Useful after the testing has commenced - need data!
  - » There may be too little data for some partitions
  - » May be too challenging to minimize the influence of pathological results

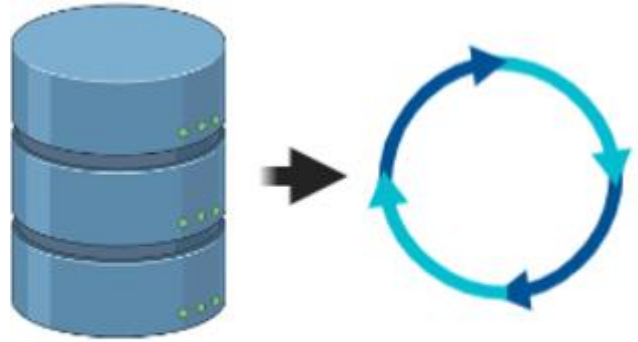
Farrell and Nguyen. Clin Biochem Rev 40 (2) 2019

Conducting an Indirect Reference Interval Study

Overview and Use of the Indirect Methods

Initial Process Steps

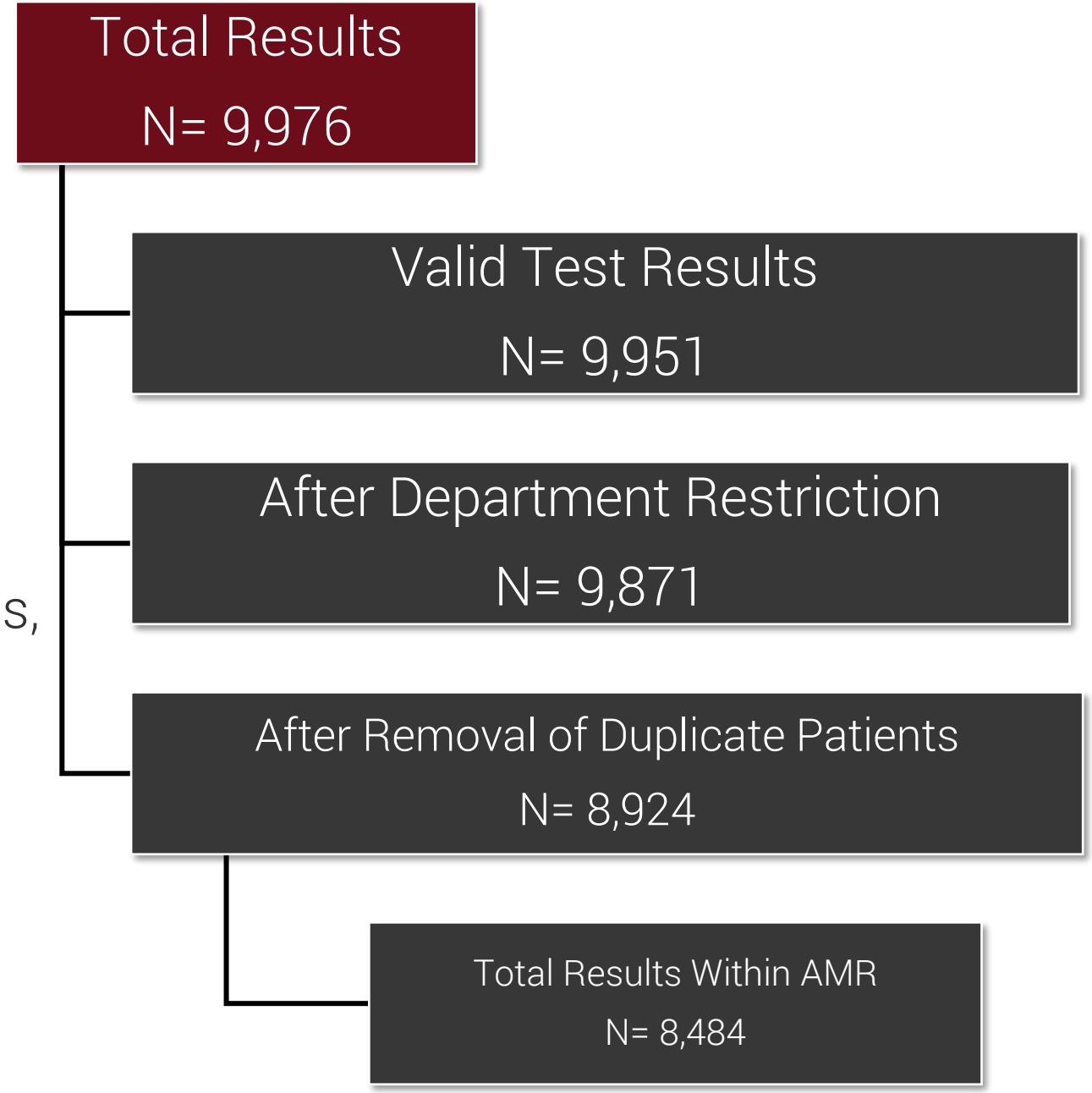
- Step 1: Feasibility – analytic and population stability
  - » QC review, moving medians, proficiency testing result review, method history, draw site/patient mix history (pathological fraction <30%)
- Step 2: Pre-Data Collection
  - » IRB, data sources, data sets
- Step 3: Data Collection
  - » Deidentification
  - » Age (decimal), sex, result time, instrument ID, collection site, result
- Step 4: Data Cleanup
  - » Collection sites (e.g., oncology, diabetes clinics), repeat patients (or repeat test results), test specimens, result truncation



Created with BioRender.com.

Data Cleanup

- Document the process!
  Exclusion criteria, data cleanup steps, transformations, truncation, etc.



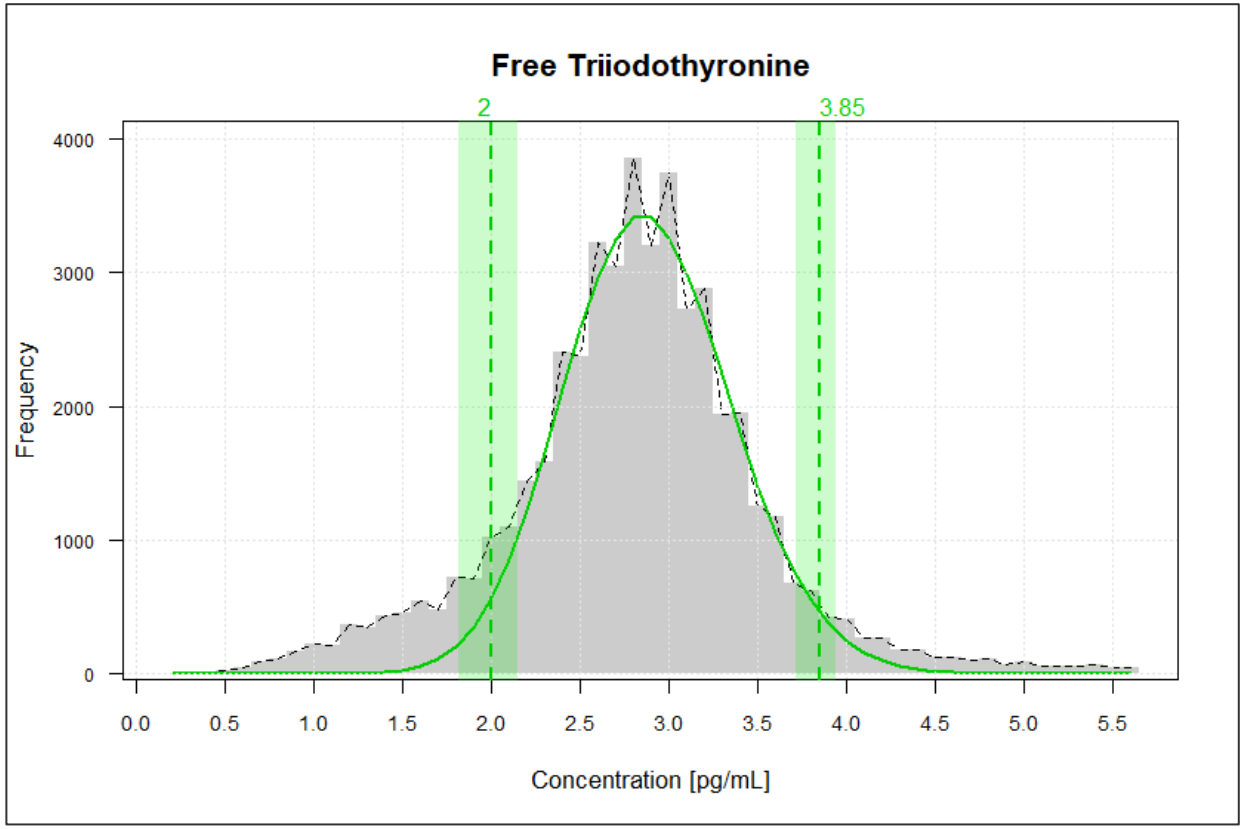
Dataset Structure

Patient_ID	Age_decimal	Sex	Result	Verified_time	Device_ID
00001	27.29	M	1.34	05/22/2022 12:32:00	5500-6
00002	18.75	F	1.17	05/22/2022 12:33:00	5500-6

Recommendation: keep all data together as a single .csv file, perform filtering in R.

Step 5 – Data Processing and Distribution Modeling

- Initial review of data set
  - » Distribution
    - Skew
    - < or > impact on histogram
- Choose an appropriate indirect method

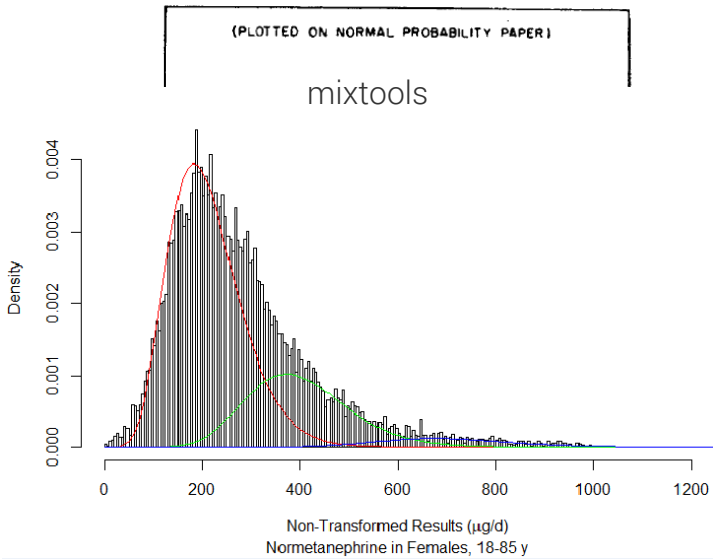


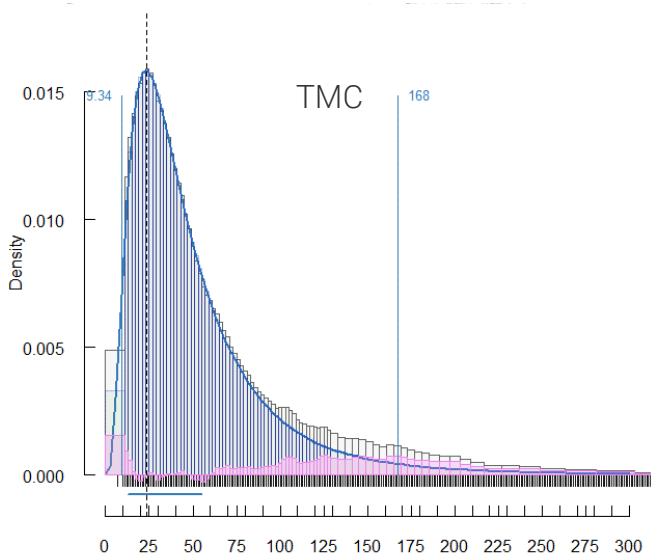
INDIRECT METHOD

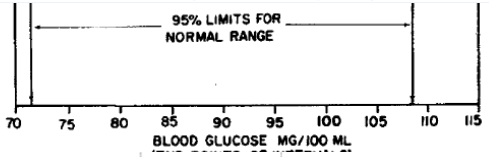
Methods/Algorithms

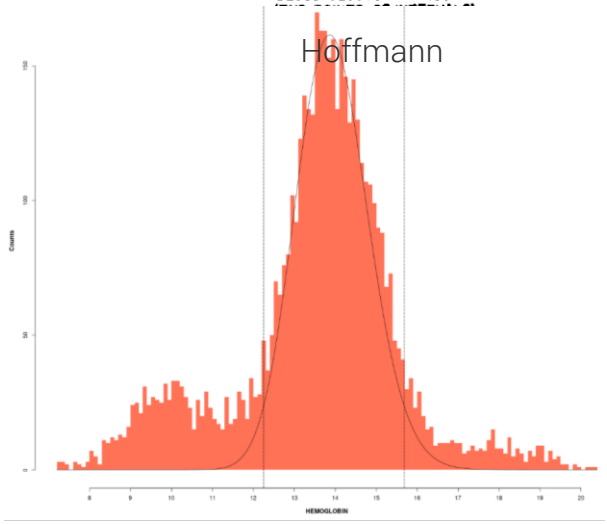
Hoffmann
Bhattacharya

Mixtools
Truncated Minimum Chi-Square (TMC)
Kosmic
refineR

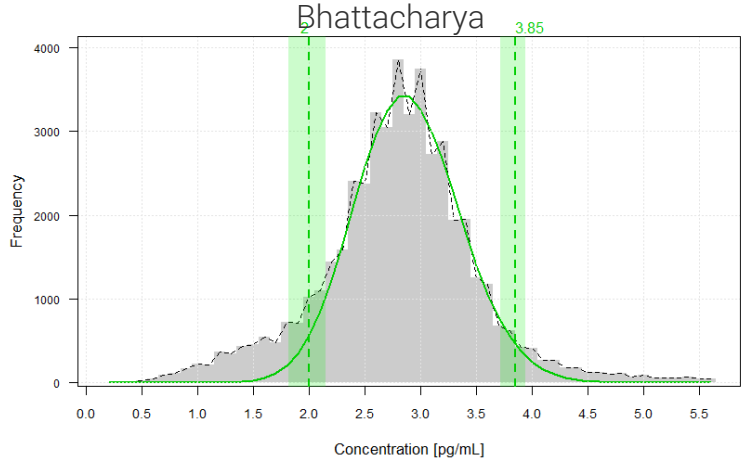








kosmic



refineR

RStudio

RStudio

File Edit Code View Plots Session Build Debug Profile Tools Help

Go to file/function | Addins | Project: (None)

Reference Interval.R | IGF_refineR_script.R | FIG3_script.R | Rolling_Median_refineRv1_5.R | 17OHP_refineR.R* | Rolling_Median_disacs

Source on Save | Run | Source

```
76  rollmedian_data <- rollmedian(Data.DF$RESULT, k = N+1, fill = NA, align = 'right')
77  Data_median.DF <- Data.DF %>% mutate(rollmedian_data)
78  RM.plot <- ggplot(Data_median.DF, aes(VER.WHEN, rollmedian_data)) +
79    geom_line() +
80    coord_cartesian(ylim = c(0,100)) +
81    scale_x_datetime (date_breaks = "1 year",date_minor_breaks = "1 month", date_labels = ("%b %y")) +
82    labs(title= "Rolling Median", y = "Median", subtitle = ANALYTE, caption = paste("Based on N =", N))
83  RM.plot
84
85  #refineR ("BoxCox", "modBoxCoxFast", "modBoxCox")
86  #is.na(Data.DF$RESULT)
87  Data.DF[is.na(Data.DF$RESULT),]
88  Data.RI<- Data.DF[!is.na(Data.DF$RESULT),]
89
90  fit_OHP_F_16_17 <- findRI(Data = Data.RI$RESULT,
91                            model = "BoxCox",
92                            NBootstrap = 1200,
93                            seed = 123)
94  print(fit_OHP_F_16_17)
95  ri <- getRI(fit_OHP_F_16_17, RIperc = c(0.025, 0.975), CIprop = 0.95, pointEst ="medianBS")
96  plot(fit_OHP_F_16_17, RIperc = c(0.025, 0.975), CIprop = 0.95, pointEst ="medianBS",
97       xlim = c(0,300), xlab = "Concentration [ng/dL]", title = "17-hydroxyprogesterone, Females, 16-17 y.o.",
98  Nhist=50, showValue = FALSE)
99  mtext(text = round(ri$PointEst, 0), at = ri$PointEst, col = "green3", cex = 1.0)
100
101 save(fit_OHP_F_16_17, file = "./refineR_model_OHP_F_16_17.RData")
102
103
104 # to load again into the workspace to use the model for further plots or additional analysis
105 fit_OHP_F_16_17 <- get(load(file = "./refineR_model_OHP_F_16_17.RData"))
106
```

82:62 | 17-OHP, Females, 16-17 y.o. | R Script

Console | Terminal | Background Jobs

R 4.2.2 · U:/Stats math/Reference Intervals/Indirect RI/Tools/refineR/refineR_TestScripts/test_data/

```
      sigma: 1.95
      shift: 0
       cost: -14.2
NP fraction: 0.941
> ri <- getRI(fit_OHP_F_16_17, RIperc = c(0.025, 0.975), CIprop = 0.95, pointEst ="medianBS")
> plot(fit_OHP_F_16_17, RIperc = c(0.025, 0.975), CIprop = 0.95, pointEst ="medianBS",
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>
> save(fit_OHP_F_16_17, file = "./refineR_model_OHP_F_16_17.RData")
> Data.DF[is.na(Data.DF$RESULT),]
[1] PatId       RESULT      AGE.DECIMAL SEX         VER.WHEN    Device
<0 rows> (or 0-length row.names)
> Data.RI<- Data.DF[!is.na(Data.DF$RESULT),]
>
> fit_OHP_F_16_17 <- findRI(Data = Data.RI$RESULT,
+                           model = "BoxCox",
+                           NBootstrap = 1200,
+                           seed = 123)
```

Environment | History | Connections

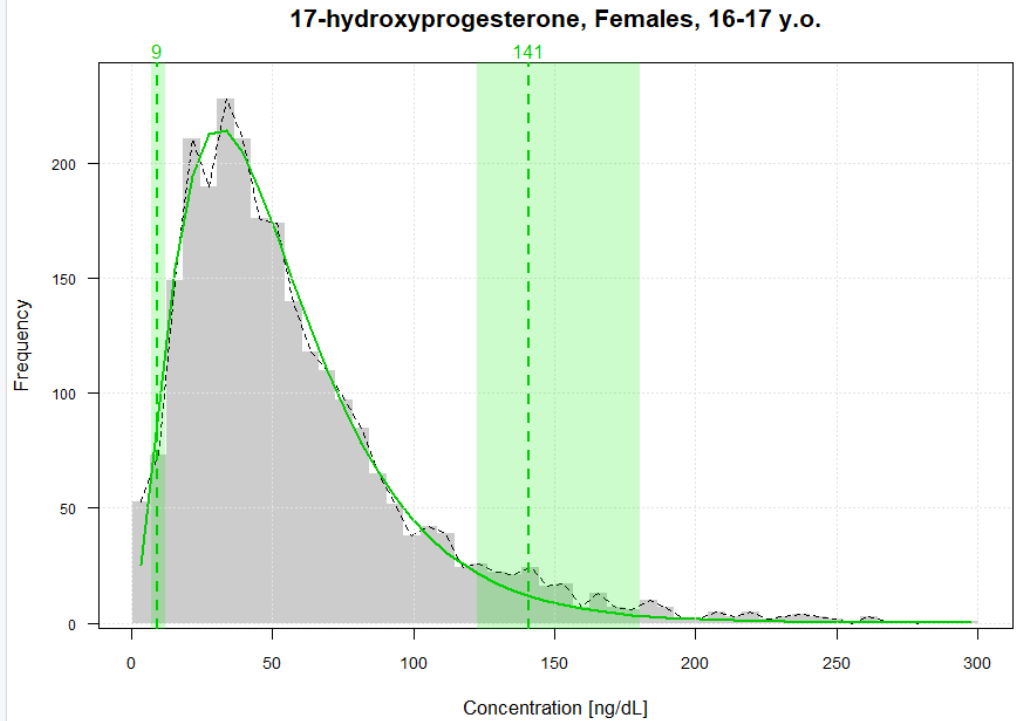
Import Dataset | 358 MiB | List

R | Global Environment

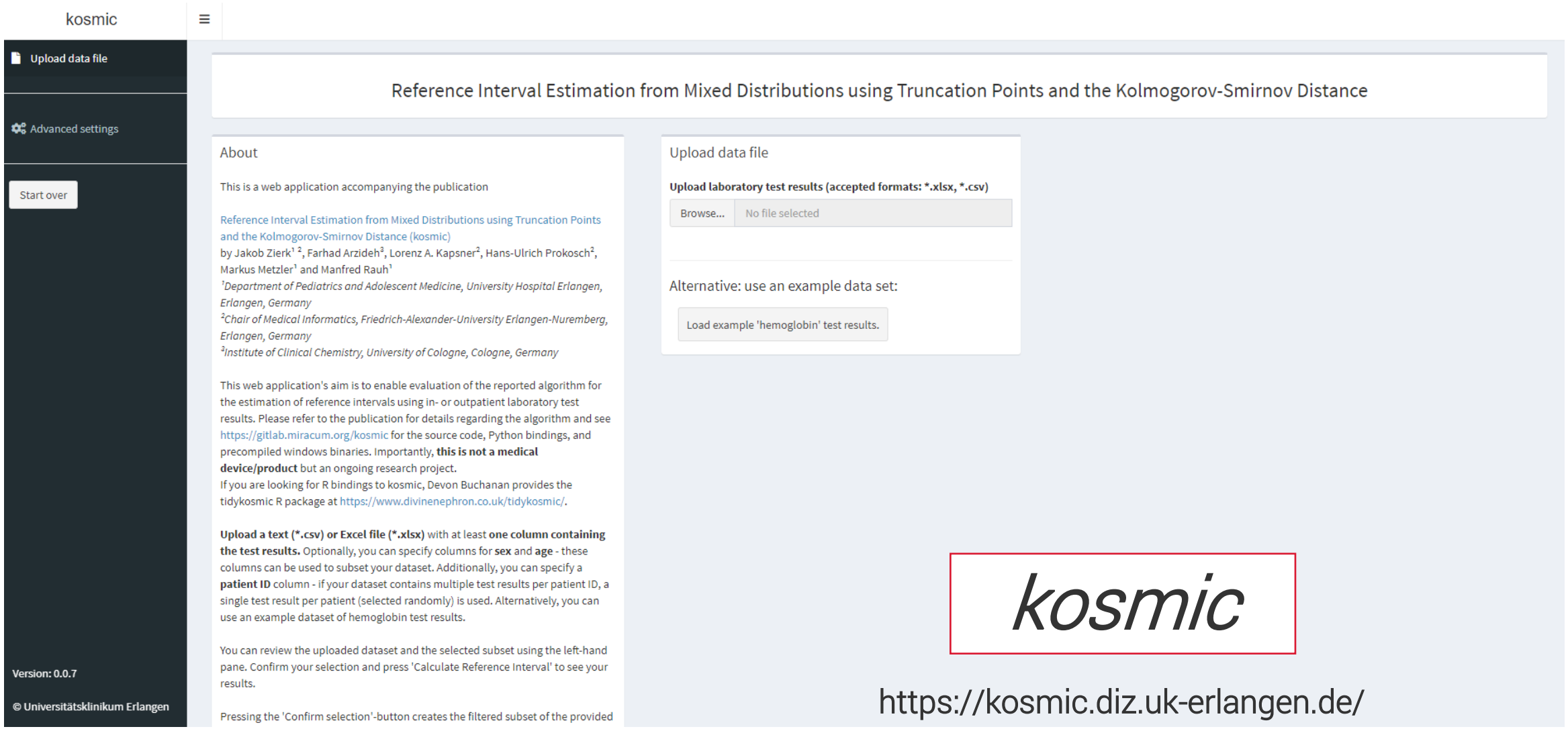
rawData.DF	123565 obs. of 6 variables
ri	2 obs. of 4 variables
RM.plot	List of 9
values	
ANALYTE	"17-OHP, Females, 16-17 y.o."
myPaths	chr [1:2] "C:/Program Files/R/R-4.2.2/library" "C:/Users/204783/Documents/R/R...
N	50
rollmedian_data	num [1:2505] NA NA NA NA NA NA NA NA NA NA NA ...

Files | Plots | Packages | Help | Tutorial | Viewer | Presentation

Zoom | Export | Publish



What if I Don’t Know a Coding Language?



kosmic

https://kosmic.diz.uk-erlangen.de/

Upload data file

Upload laboratory test results (accepted formats: *.xlsx, *.csv)

Browse... No file selected

Alternative: use an example data set:

Load example 'hemoglobin' test results.

Select Columns

Decimals

1

Caution: Increasing the number of decimals results in a substantially longer computation time.

- [x] Test result (required): HEMOGLOBIN
- [ ] Patient ID (optional): HEMOGLOBIN
- [x] Age (optional): AGE
- [x] Sex (optional): SEX

Specify age range

Age

0.4 — 18

0.4 2.16 3.92 5.68 7.44 9.2 10.96 12.72 14.48 16.24 18

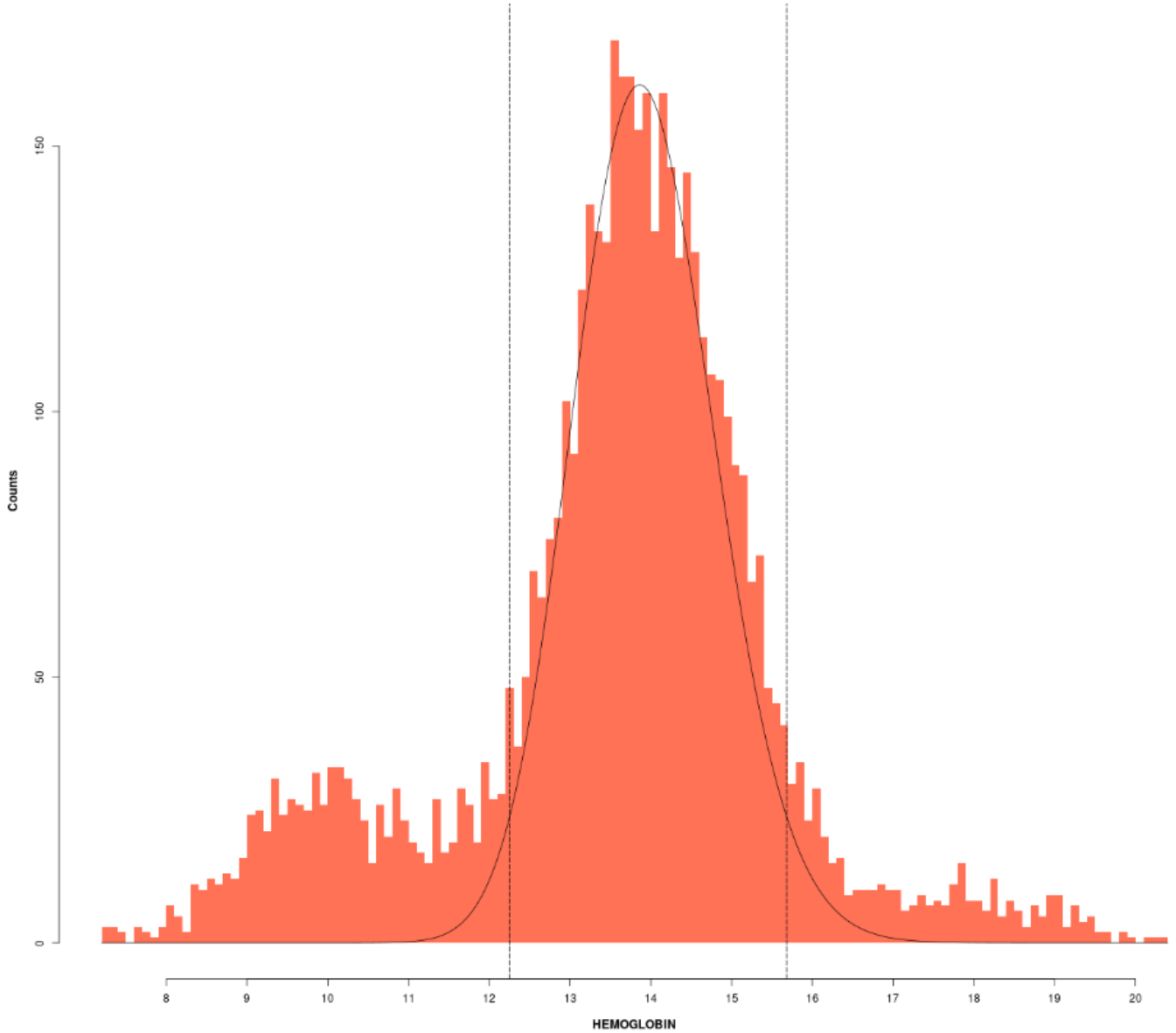
Specify gender

Male: m

Female: w

Select gender subset:

(•) Female ( ) Male



Download Plot | Download Report

N:	5016
2.5 % Percentile:	12.2496
50 % Percentile:	13.8606
97.5 % Percentile:	15.6834
Lambda:	0
Mu:	2.62905
Sigma:	0.0630387
T1:	12.6
T2:	14.4
Decimals:	1
T1 min:	0.05
T1 max:	0.3
T2 min:	0.7
T2 max:	0.95
SD:	0.8
Tolerance:	1e-07

RStudio

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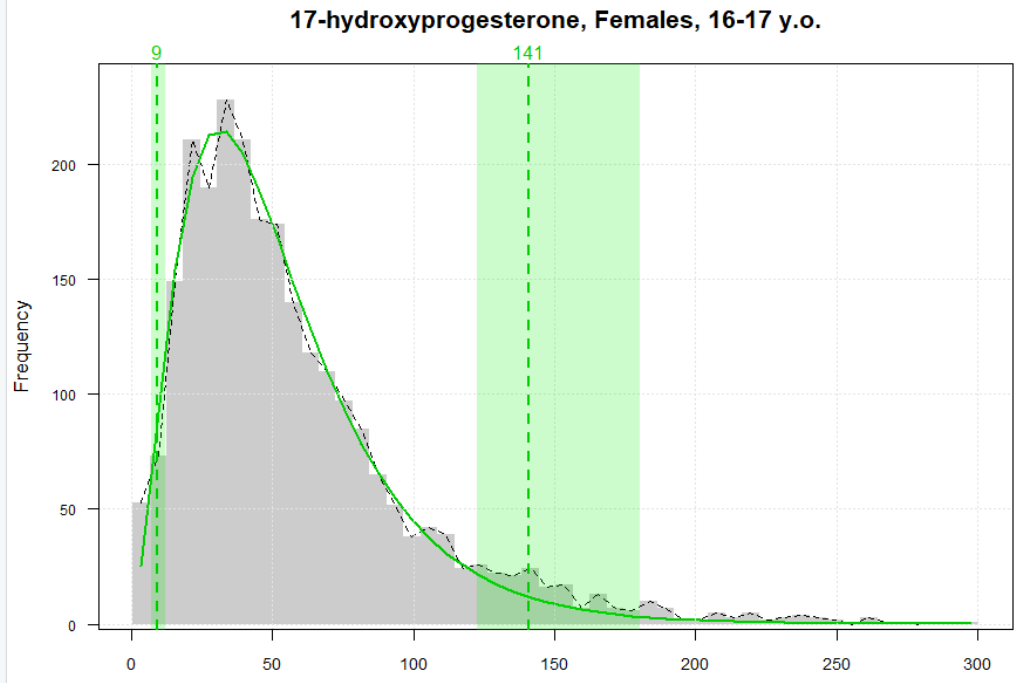


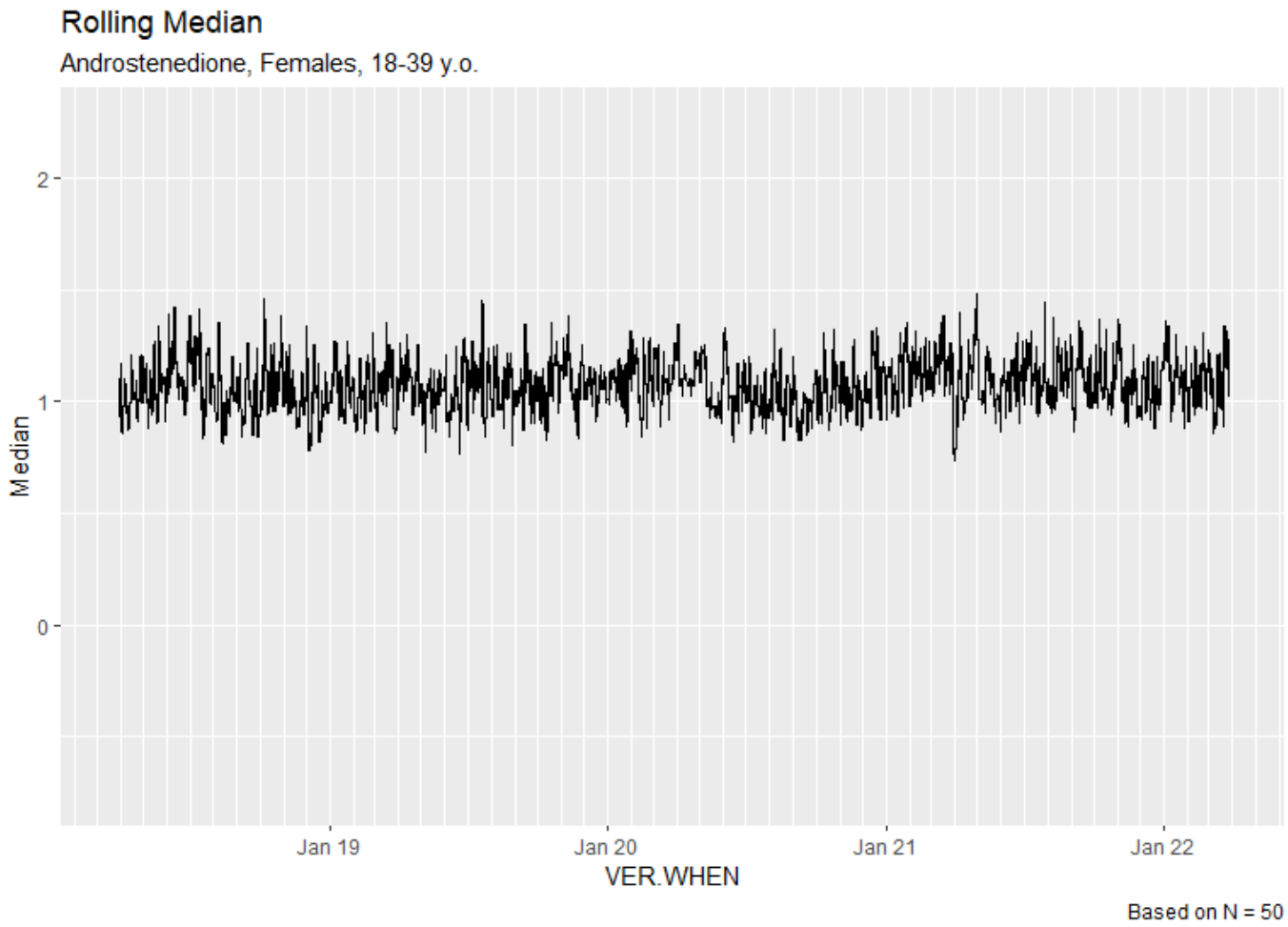
Data Review: Moving Medians

Highly recommended to review data integrity across data set

Rolling median:

library(zoo)
rollmedian(data, K (block size), align = 'right')

library(ggplot2)
ggplot(data, aes(date, results))

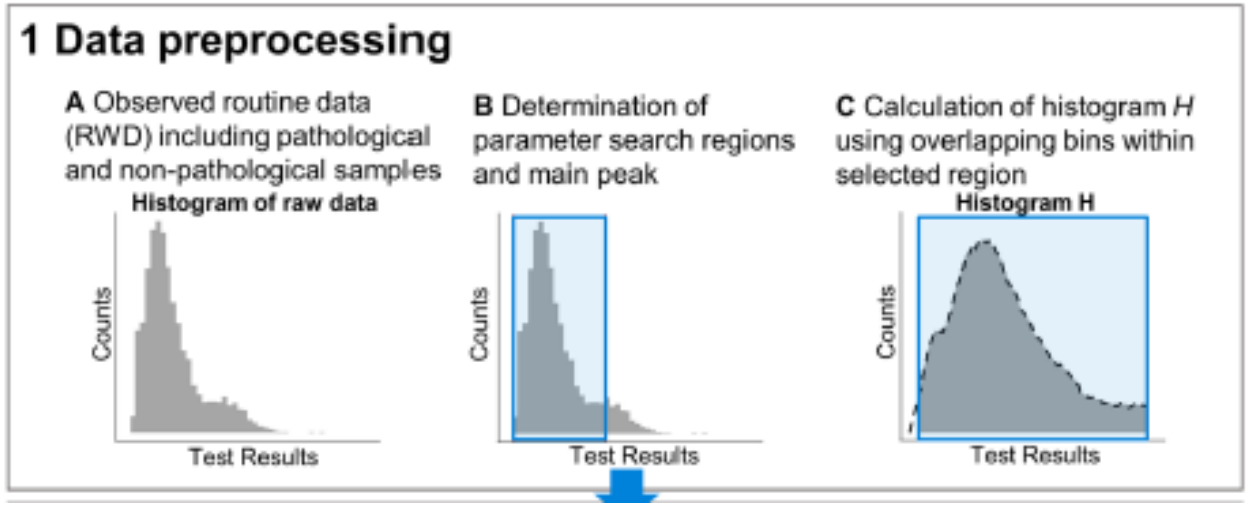


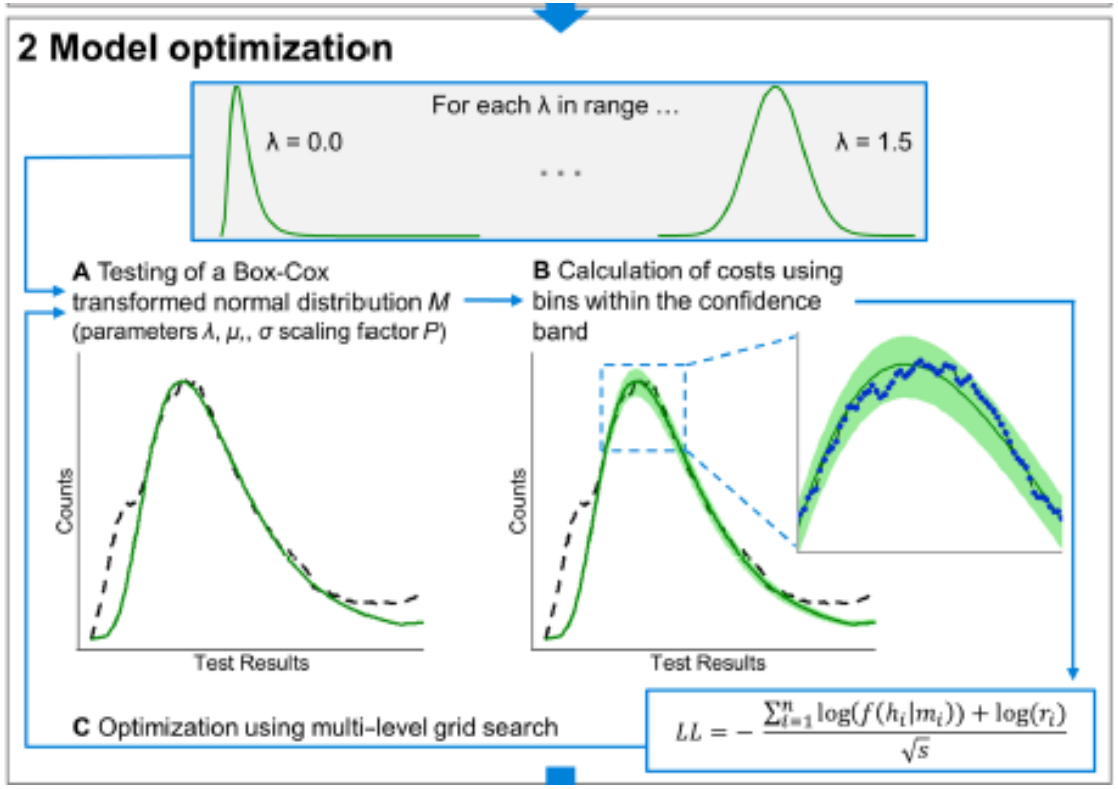
refineR Package - R

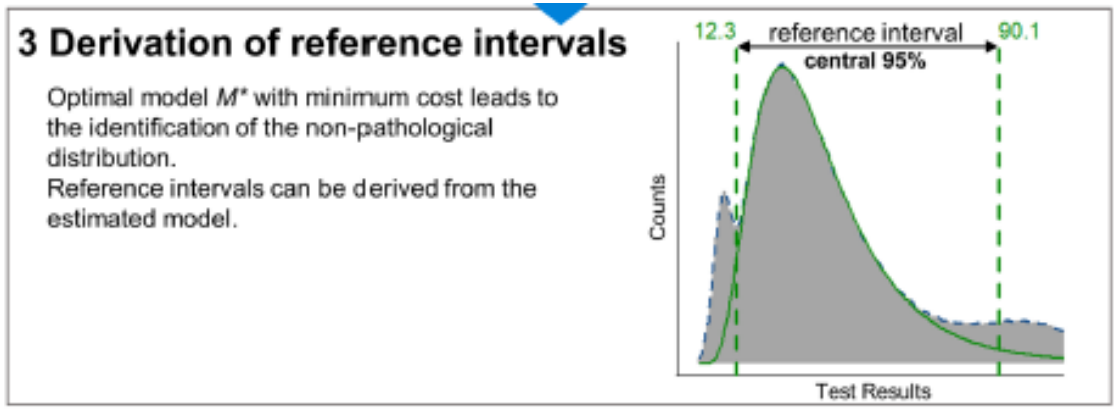
refineR: A Novel Algorithm for Reference Interval Estimation from Real-World Data

Tatjana Ammer[1,2]✉, André Schützenmeister[2], Hans-Ulrich Prokosch[1], Manfred Rauh[3], Christopher M. Rank[2,5] & Jakob Zierk[3,4,5]

PMID: 34362961







Ammer T et al. Sci Rep. 2021 Aug 6;11(1):16023

refineR Package - R

JOURNAL ARTICLE

Estimation of Reference Intervals from Routine Data Using the refineR Algorithm—A Practical Guide

Tatjana Ammer ✉, André Schützenmeister, Christopher M Rank, Kelly Doyle

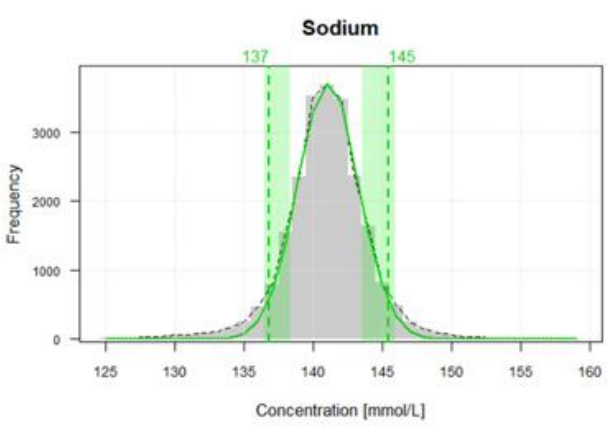
Author Notes

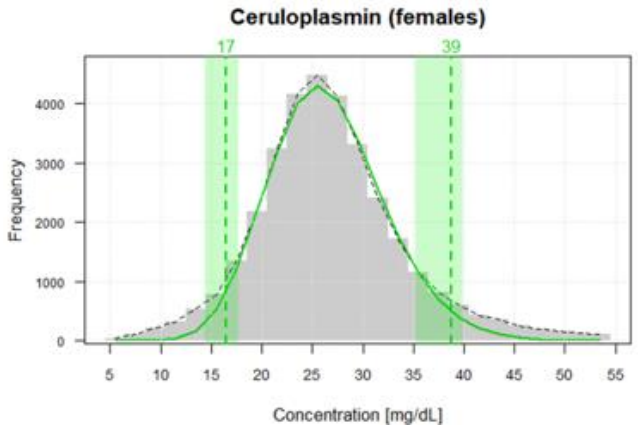
The Journal of Applied Laboratory Medicine, Volume 8, Issue 1, January 2023, Pages 84–91, https://doi.org/10.1093/jalm/jfac101

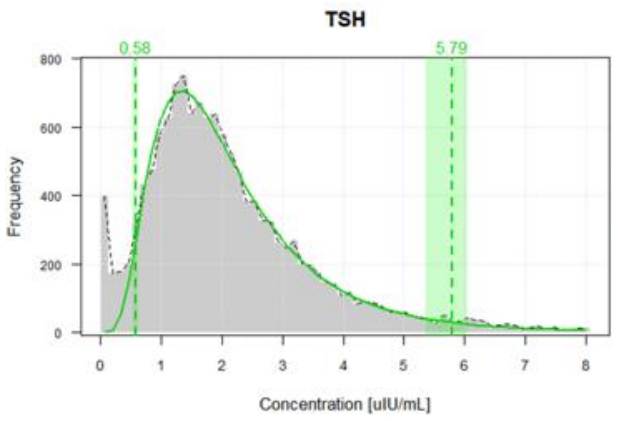
Published: 04 January 2023 **Article history** ▾

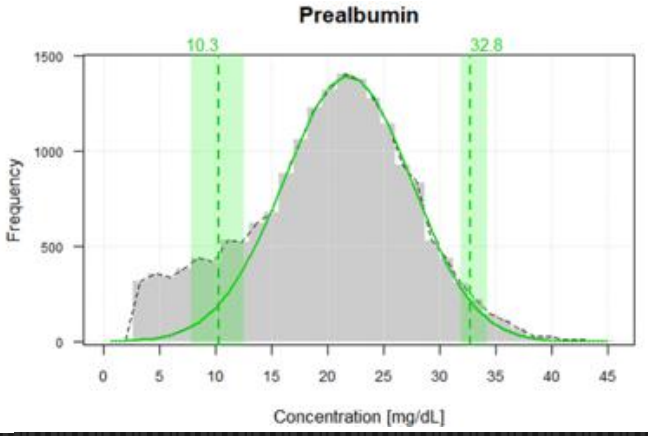
PMID: 36610416

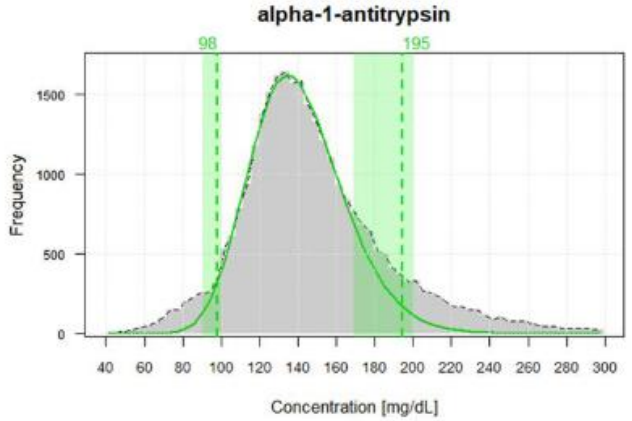
refineR: Various Distributions

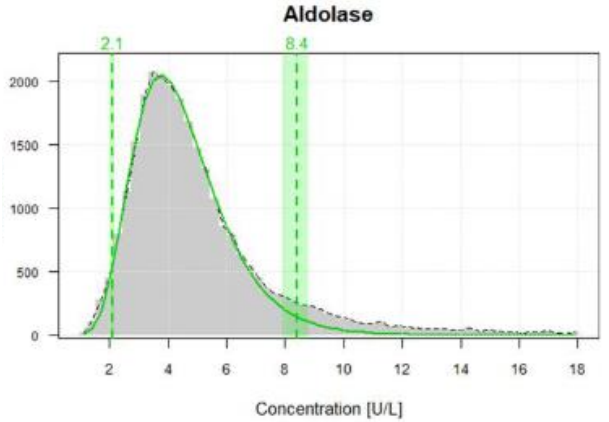


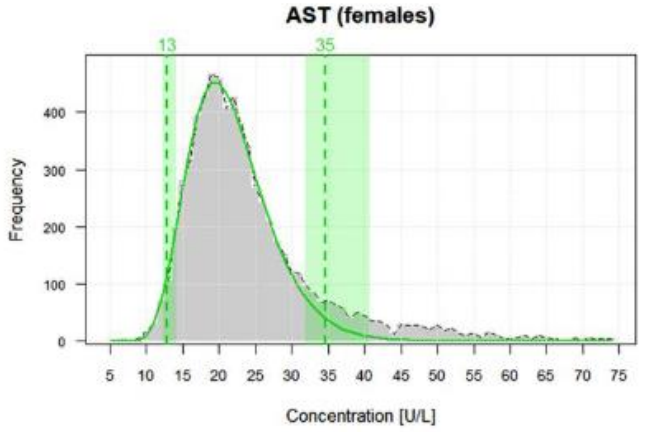


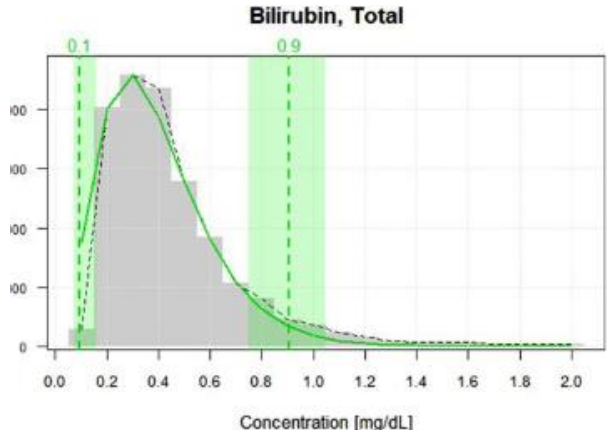


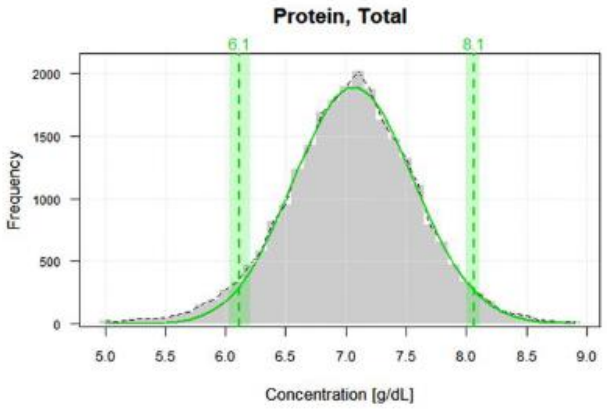


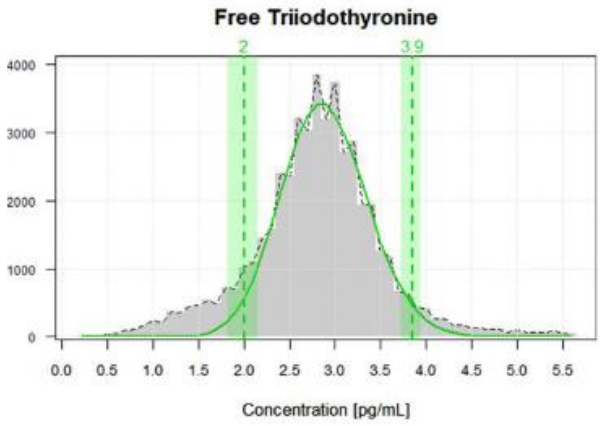












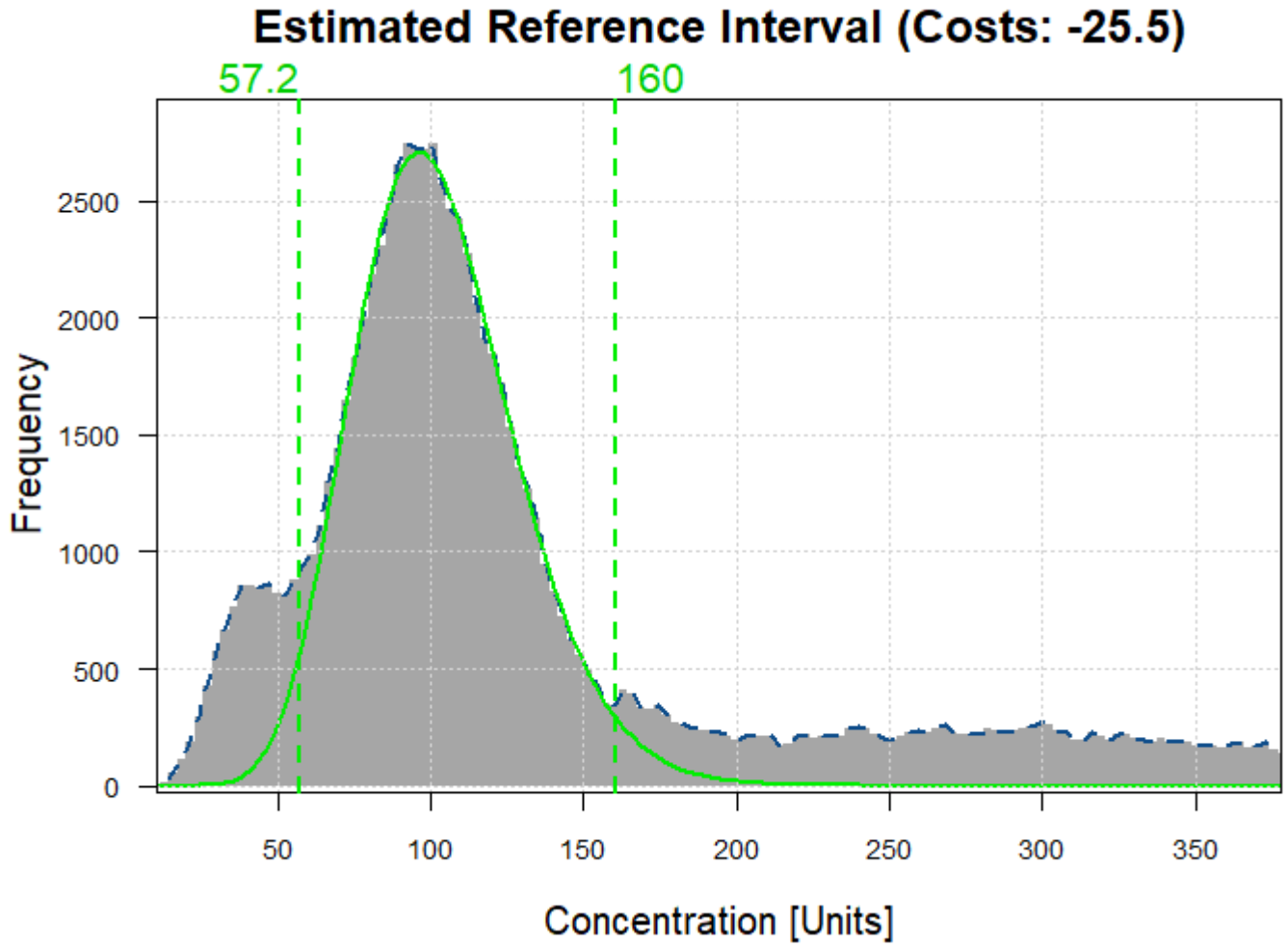
Ammer T, et al. J Appl Lab Med. 2023 Jan 4;8(1):84-91.

refineR Package Vignettes

```
library(refineR)

# first example
data(testcase1)
resRI <- findRI(Data = testcase1)
print(resRI)
plot(resRI, showPathol = FALSE)
```

N = 10,000 simulated measurements
80%/20% non-pathological to pathological



Ammer T et al. Sci Rep. 2021 Aug 6;11(1):16023

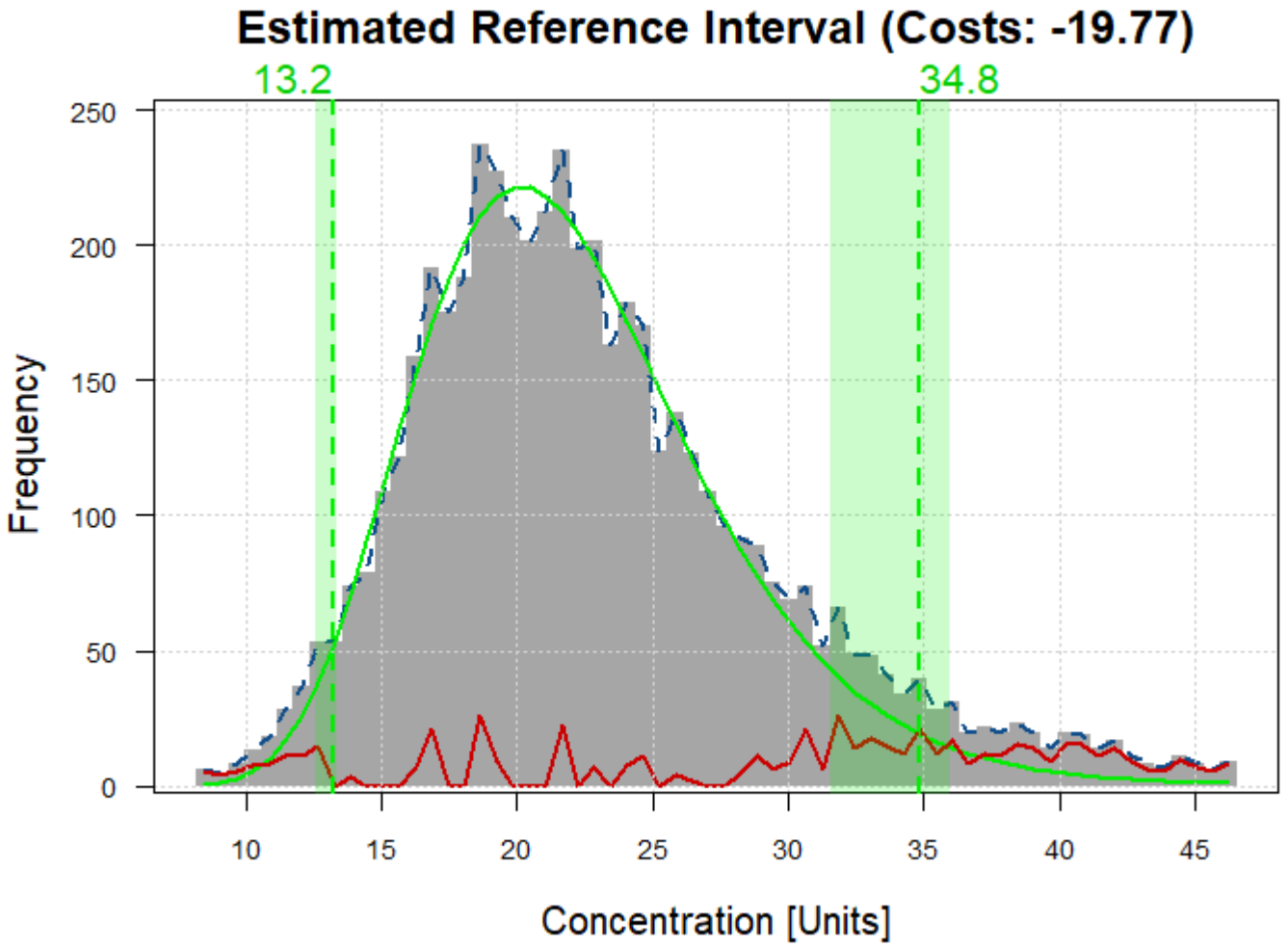
Example: First Attempt

Thyroxine Binding Globulin

Package insert claim: 13 – 31 µg/mL (n = 75)

refineR estimated: 13.2 – 34.8 µg/mL (N = 5,872)

Literature RI: 15 – 34 µg/mL



refineR – Getting StaRted

```
# load refineR package
library(refineR)

 # To open the help page
?refineR

# Load filtered/cleaned/partitioned data
rawData.DF <- read.csv("andro_all.csv")
Data.DF<- rawData.DF %>% filter(AGE.DECIMAL >17.99,
           AGE.DECIMAL < 40.00, SEX == "F")

# Run refineR estimation using findRI
fit <- findRI(Data=Data.DF)

# Print summary of estimated model
Print(fit)

# Run refineR findRI plus bootstrapping
fit.bs <- findRI(Data=Data.DF, NBootstrap=200)

# Print summary of estimated model
print(fit.bs)
```

```
Reference Intervals
-------------------------------
lower limit [ 2.5% perc]: 0.366
upper limit [97.5% perc]: 2.82

Model Parameters
-------------------------------
     method: refineR (v1.6.0)
      model: BoxCox
     N data: 25101
    rounded: yes (base: 0.001)
  point est: fullDataEst
     lambda: 0.103
         mu: 0.0693
      sigma: 0.523
      shift: 0
       cost: -29.9
NP fraction: 0.988
```

```
Reference Intervals
-------------------------------------------------
lower limit [ 2.5% perc]: 0.366 (0.335; 0.384)
upper limit [97.5% perc]: 2.82 (2.16; 2.88)

Model Parameters
-------------------------------------------------
     method: refineR (v1.6.0)
      model: BoxCox
     N data: 25101
N bootstrap: 200
    rounded: yes (base: 0.001)
  point est: fullDataEst
     lambda: 0.103
         mu: 0.0693
      sigma: 0.523
      shift: 0
       cost: -29.9
NP fraction: 0.988
```


Ammer T, et al. J Appl Lab Med. 2023 Jan 4;8(1):84-91.

refineR – Getting StaRted

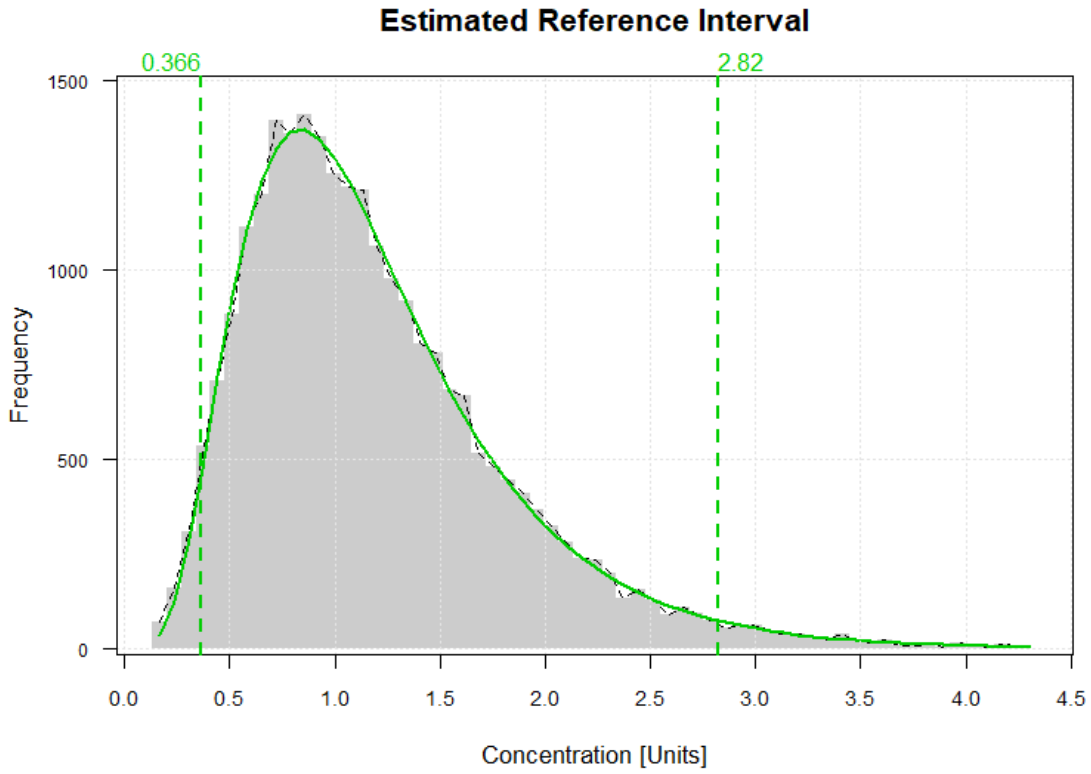
```
# Run getRI to compute estimates for specified
percentiles, confidence region, and point estimate
position
ri_fit.bs<- getRI(fit.bs, RIperc = c(0.01, 0.025,
0.975, 0.99), CIprop = 0.95,
pointEst ="fullDataEst"))
```

	Percentile	PointEst	CILow	CIHigh
1	0.010	0.2953126	0.2585747	0.3165687
2	0.025	0.3660094	0.3350618	0.3841925
3	0.975	2.8189462	2.1591106	2.8829025
4	0.990	3.3434405	2.4504120	3.4453127

Ammer T, et al. J Appl Lab Med. 2023 Jan 4;8(1):84-91.

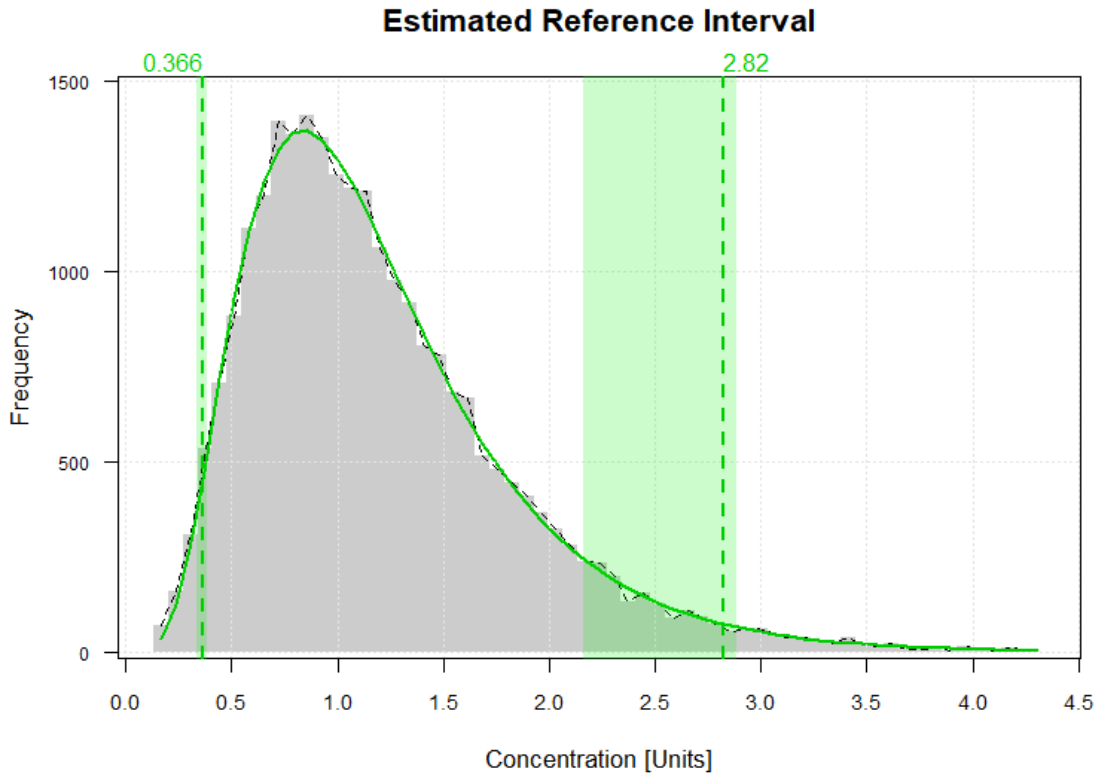
refineR – Androstenedione Example

```
# Default plot function
plot(fit)
```



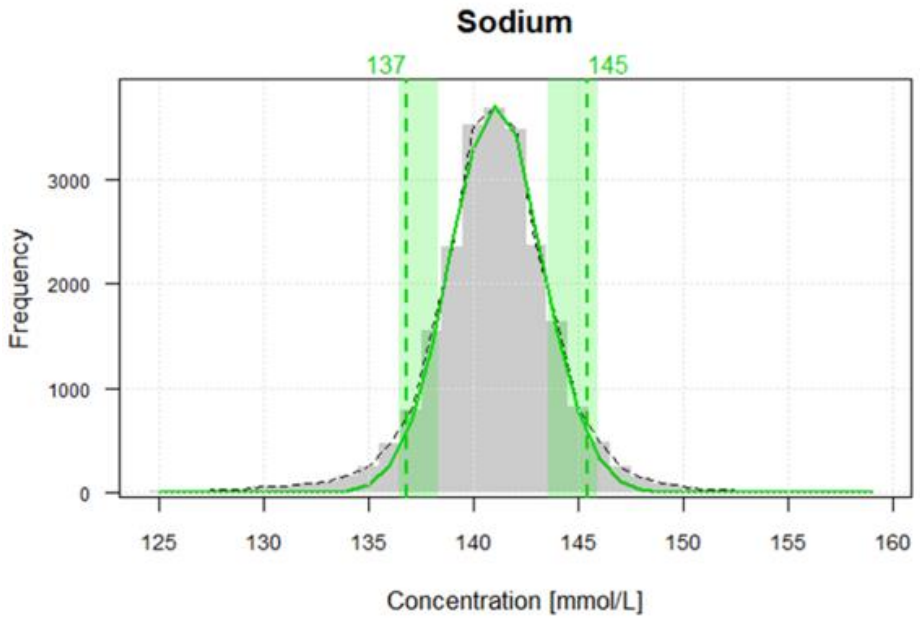

```
Reference Intervals
-------------------------------
lower limit [ 2.5% perc]: 0.366
upper limit [97.5% perc]: 2.82
```

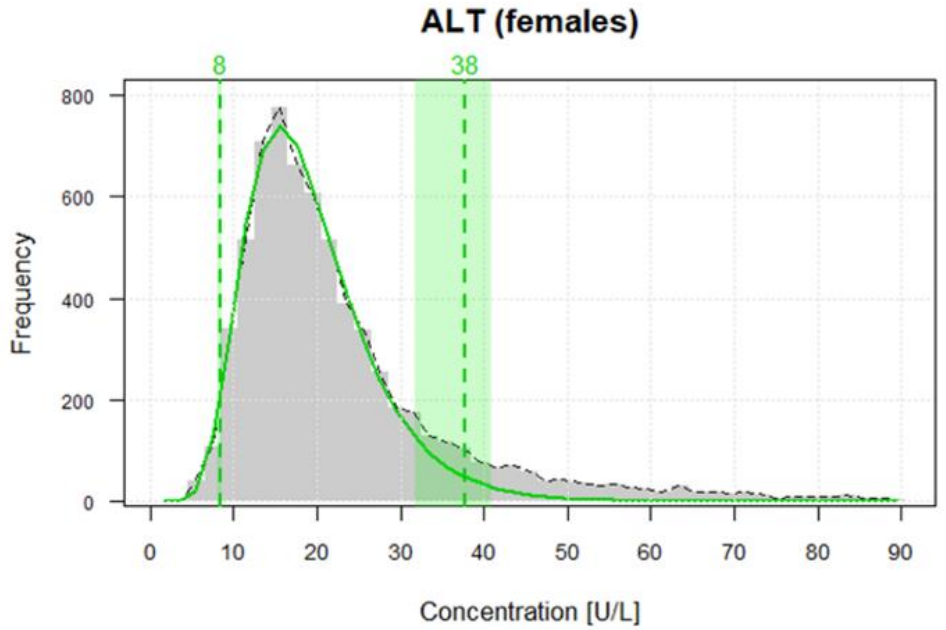
```
# Default plot function
plot(fit.bs)
```




```
Reference Intervals
-----------------------------------------------
lower limit [ 2.5% perc]: 0.366 (0.335; 0.384)
upper limit [97.5% perc]: 2.82 (2.16; 2.88)
```

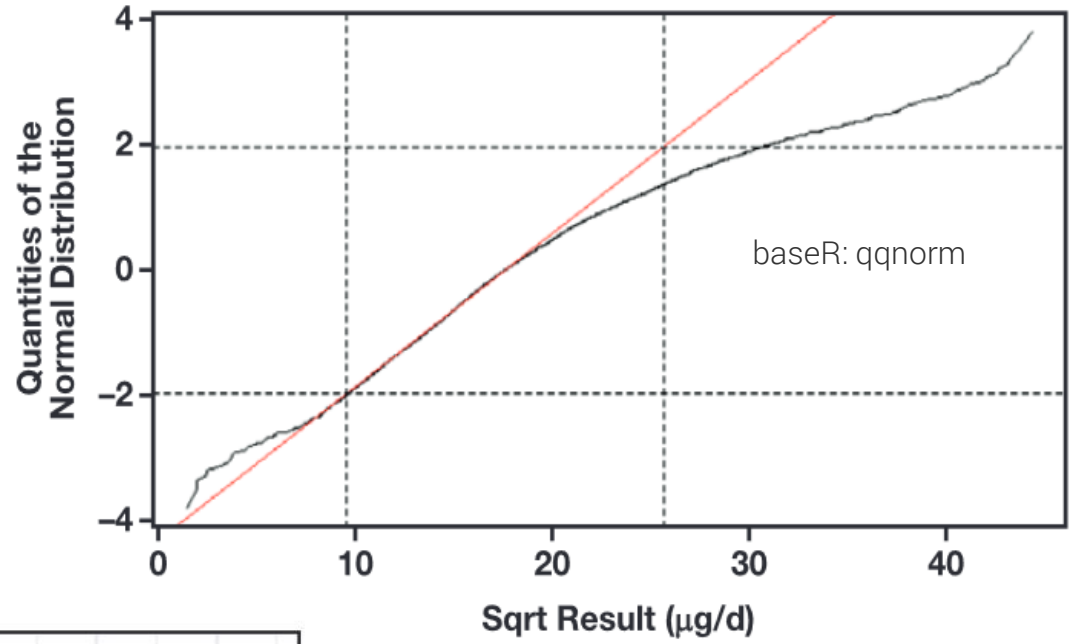
Indirect RI Estimation
Normal and Skewed Data Sets





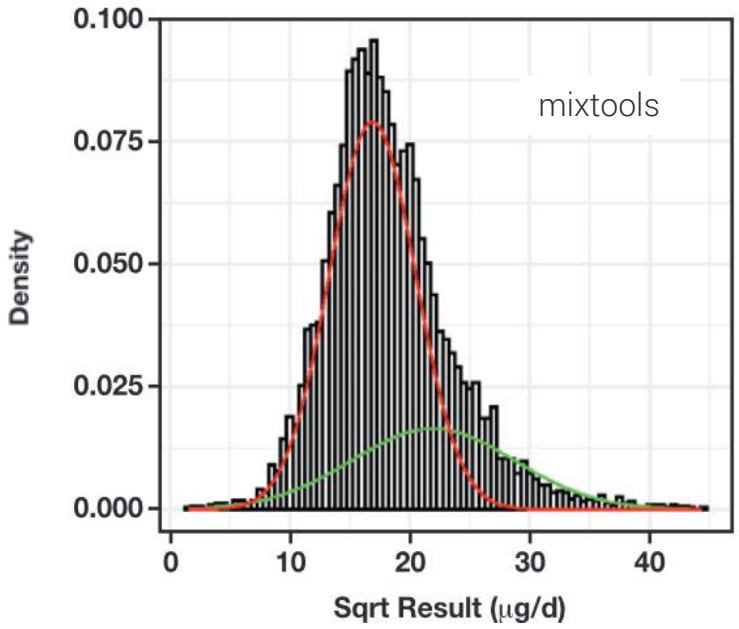
Ammer T, et al. J Appl Lab Med. 2023 Jan 4;8(1):84-91.

Working with Skewed Distributions -- Transformed Normal Approach



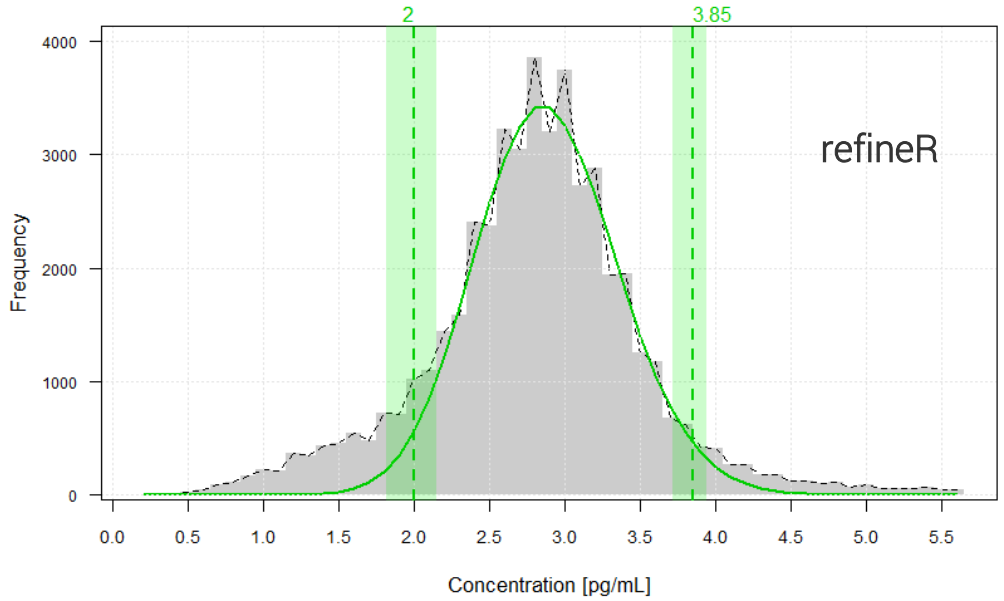
- Manual transformation
- Evaluate normalcy (e.g., QQ-plot)
- Estimation of ranges (e.g., Hoffman, mixtools)

- Not recommended



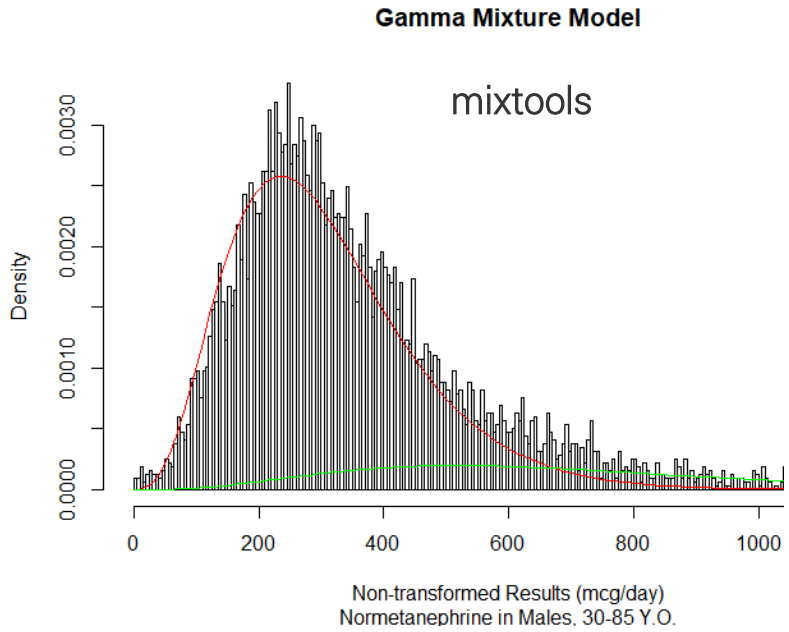
Doyle K, Frank EL. AJCP. 2021. 156(4):691-699. PMID: 33880513

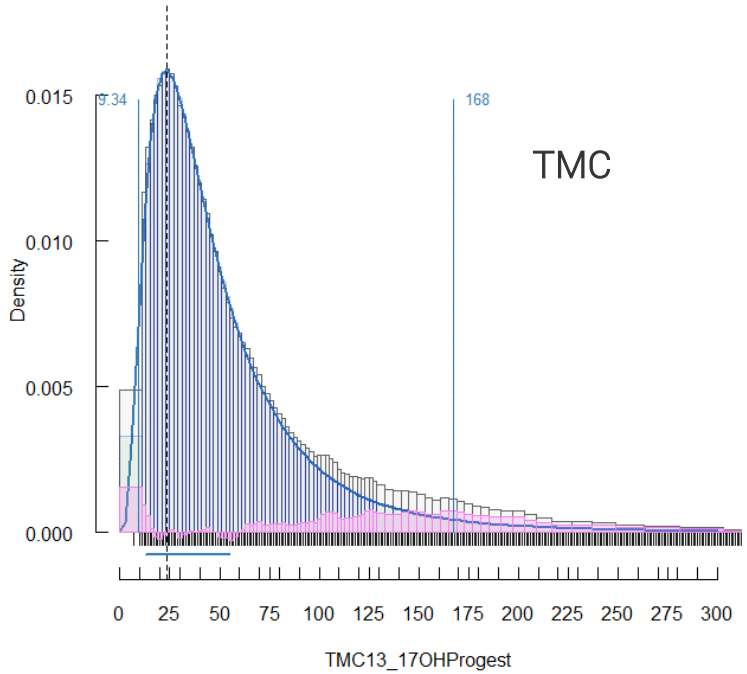
Skewed Distributions: Gamma Model or Iterative Fitting



library(mixtools)
-non-Gaussian gamma mixture model

library(refineR)
TMC program (multiple R packages)

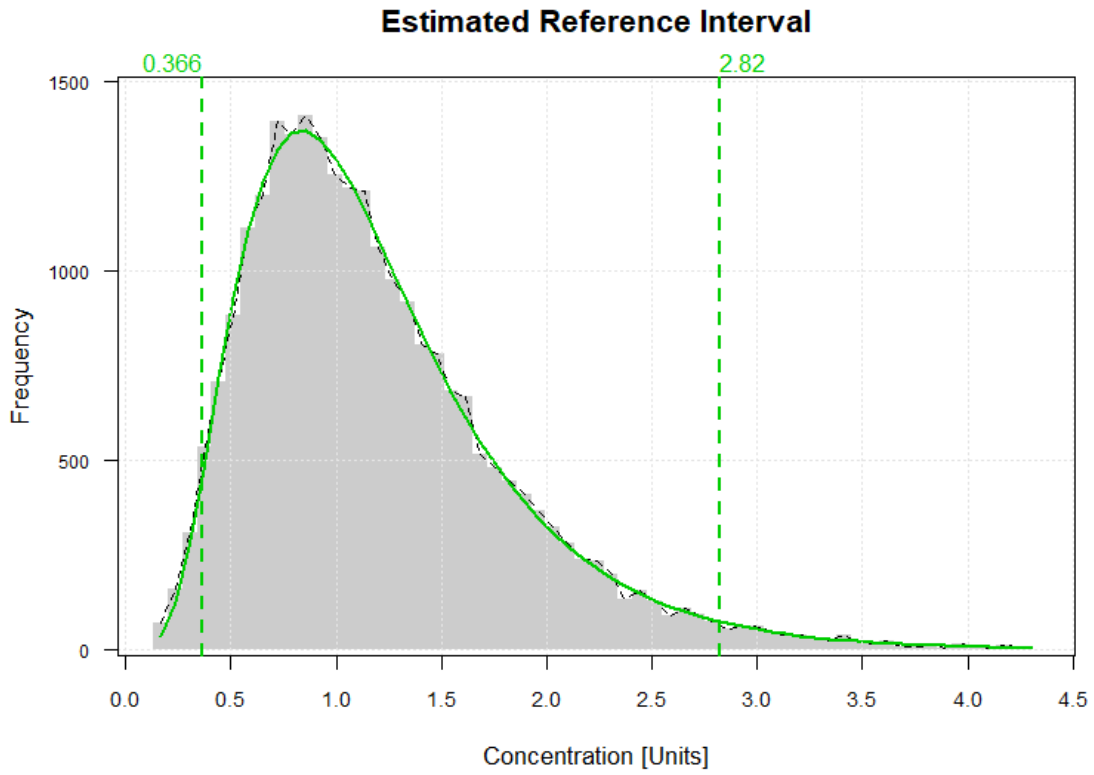


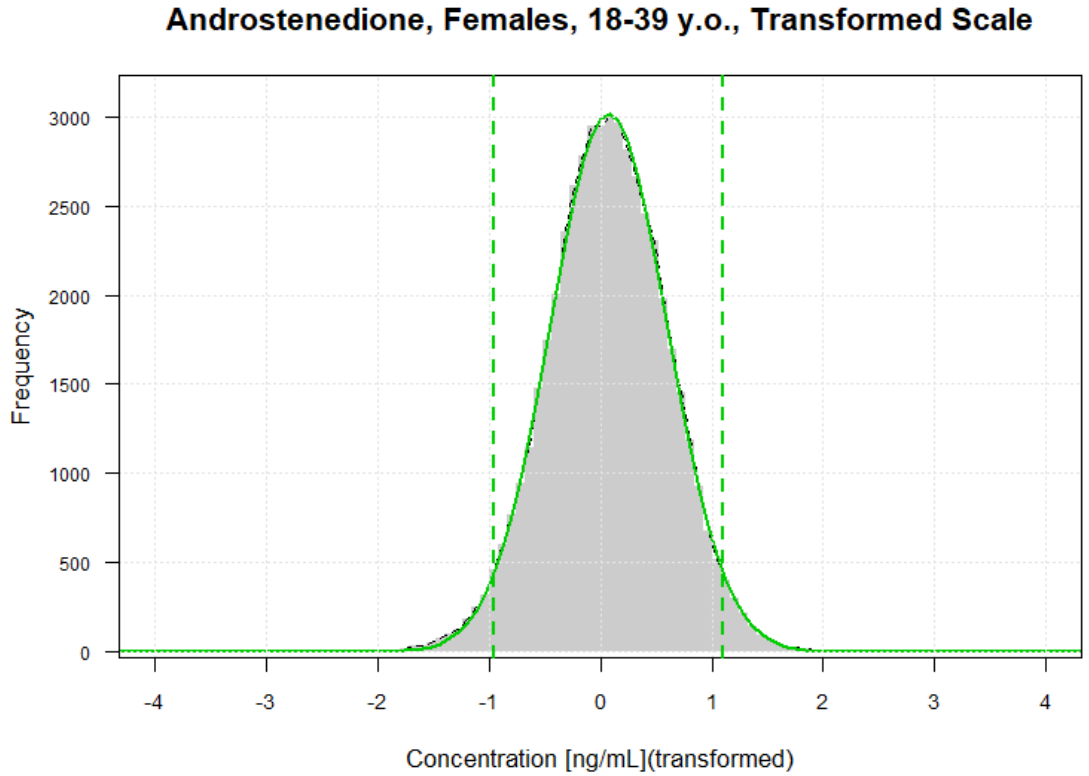


Doyle K, Frank EL. AJCP. 2021. 156(4):691-699. PMID: 33880513
Ammer T, et al. Sci Rep. 2021 Aug 6;11(1):16023. PMID: 34362961
Wosniok W. et al. CCLM. 2019; 57(12):1933-47. PMID: 31271548

Lightly and Heavily Skewed Data - refineR

library(refineR) – 1 parameter Box-Cox (default)



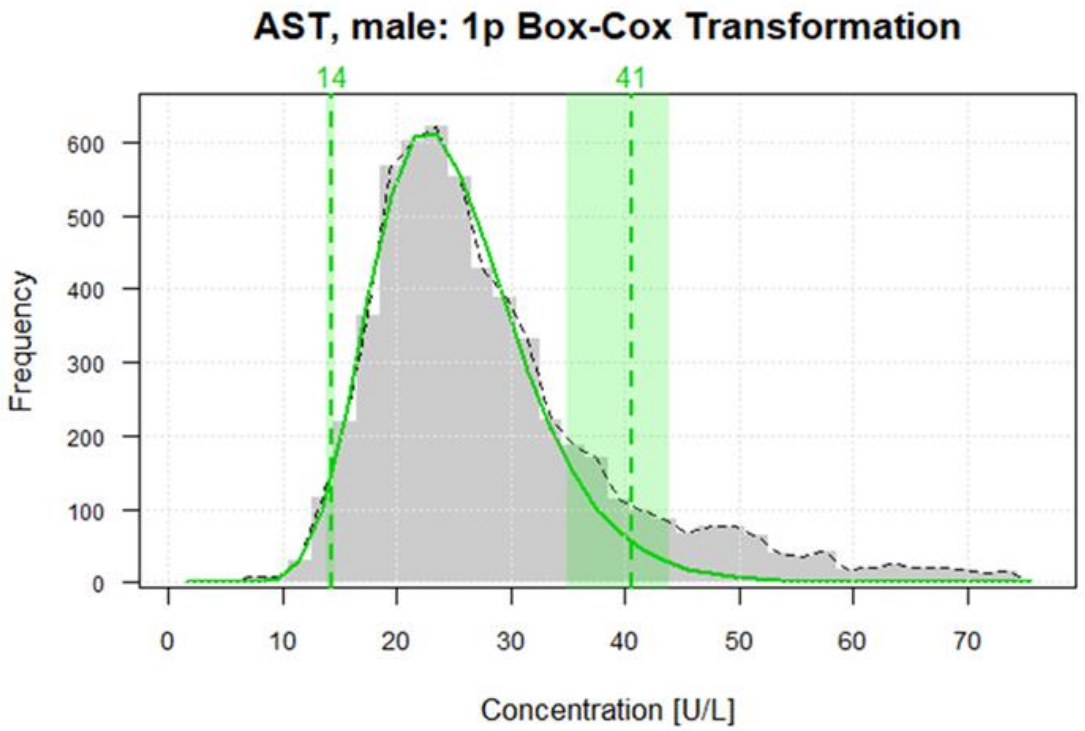


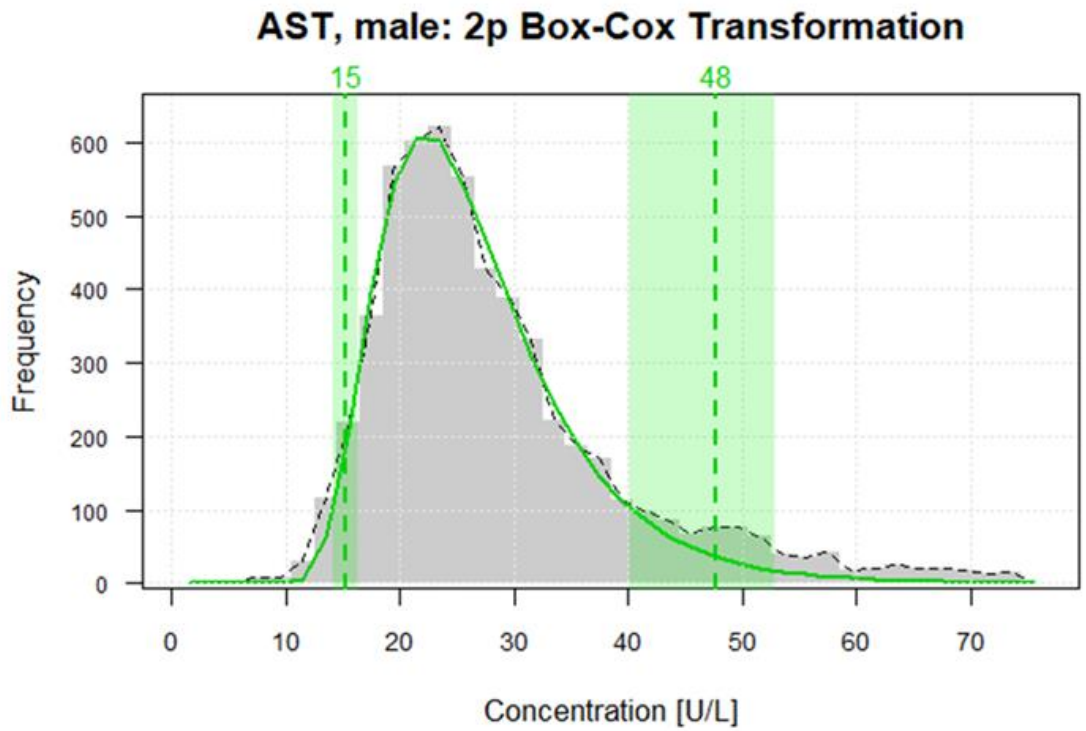
refineR allows for graphing in transformed space.
Shift away from 0 suggests trying 2 –parameter transformation.

Ammer T, et al. J Appl Lab Med. 2023 Jan 4;8(1):84-91.

refineR (1.5) : Two-Parameter Box-Cox

library(refineR) – 2 parameter Box-Cox



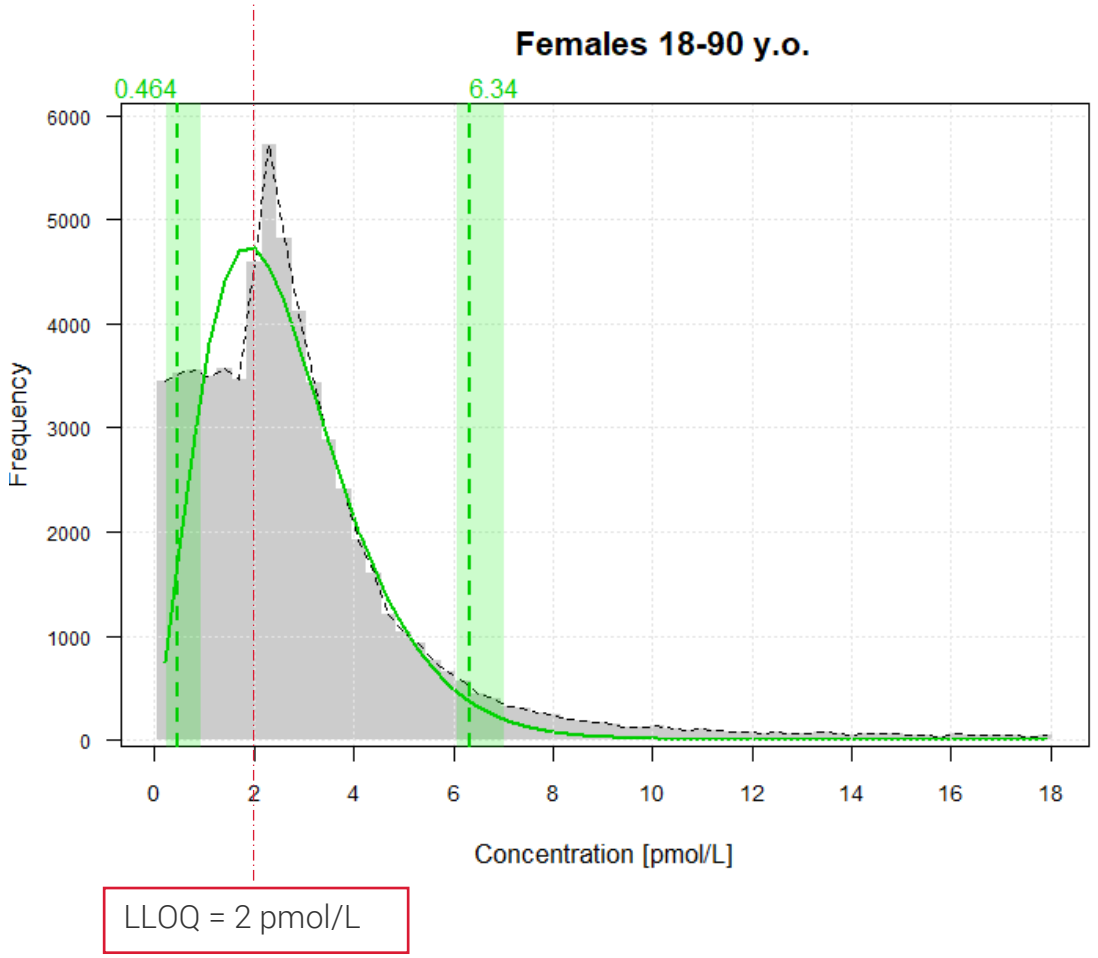


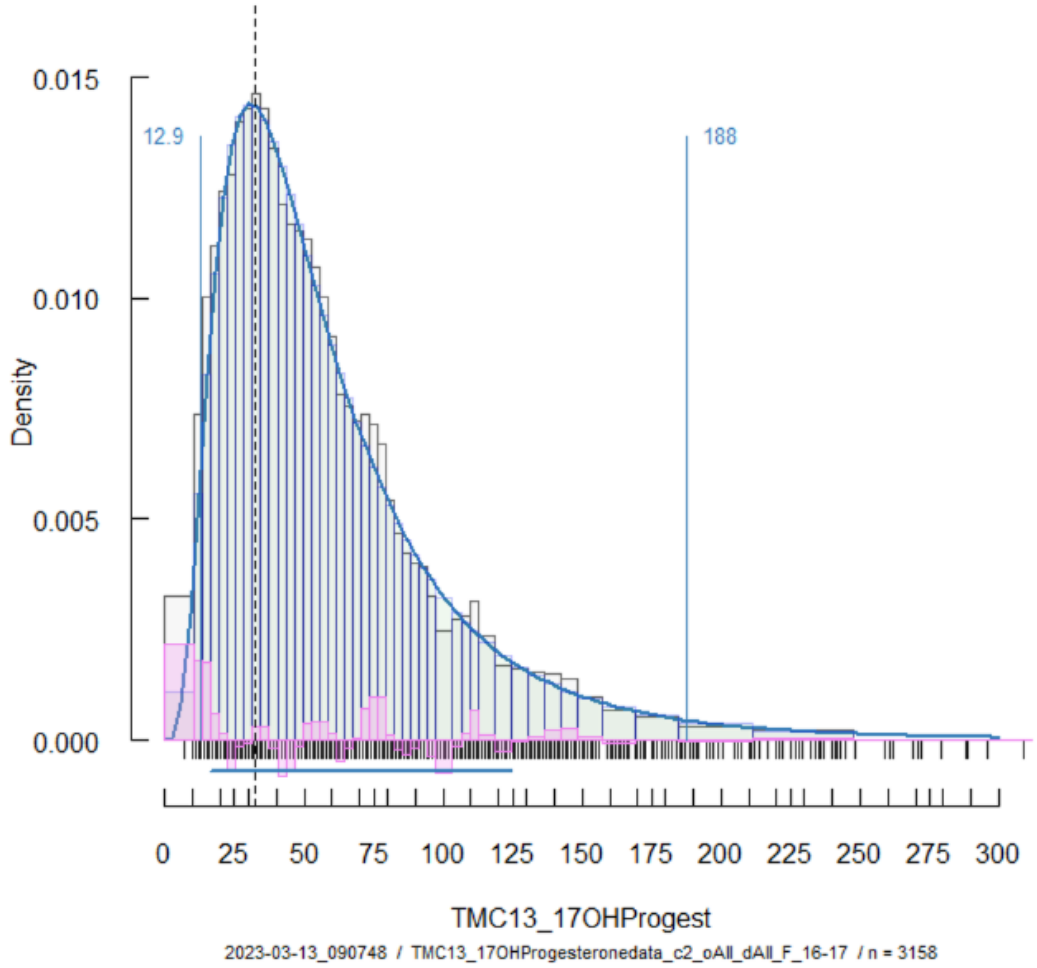

```
fit.bs <- findRI(Data=Data.DF, model = "BoxCox",
NBootstrap=200)
```

```
fit.bs <- findRI(Data=Data.DF, model = "ModBoxCox",
NBootstrap=20)
```


Ammer T, et al. J Appl Lab Med. 2023 Jan 4;8(1):84-91.

Indirect RI Estimation:
Partial Distributions (Limited Assay Sensitivity)



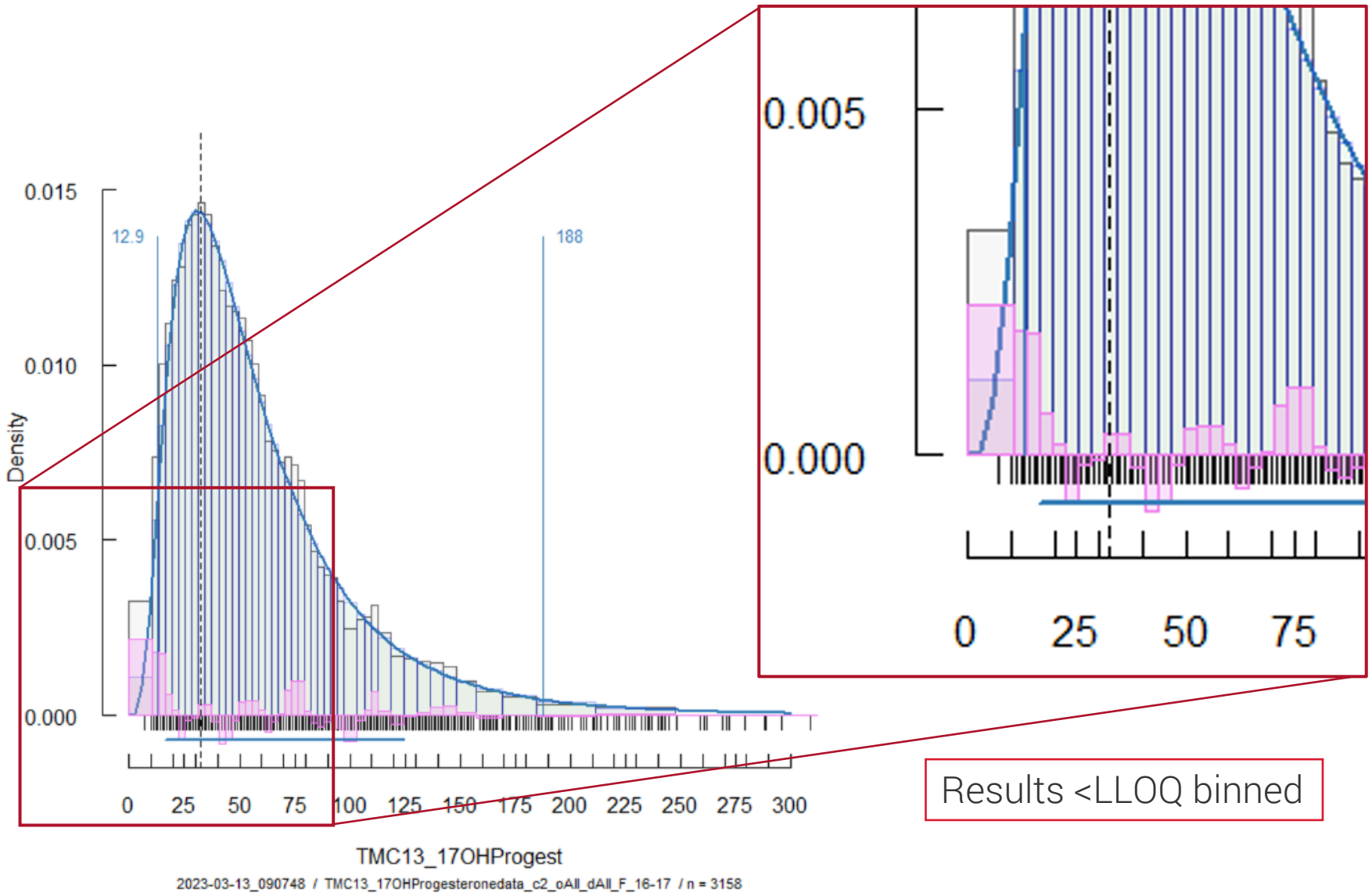


TMC Package in R for Partial Distributions

17-OH Progesterone

<u>5% of results are <LLOQ</u>

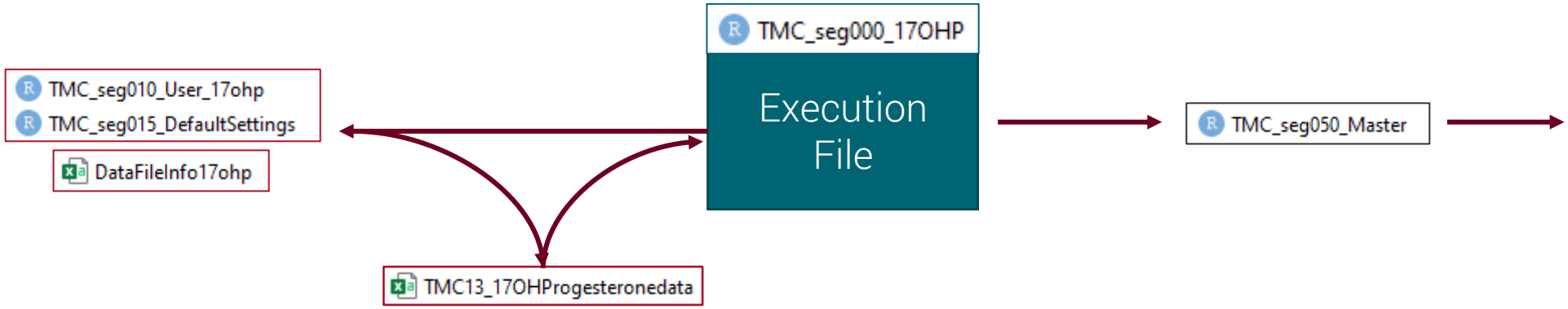
TMC can handle "<" results as its own bin

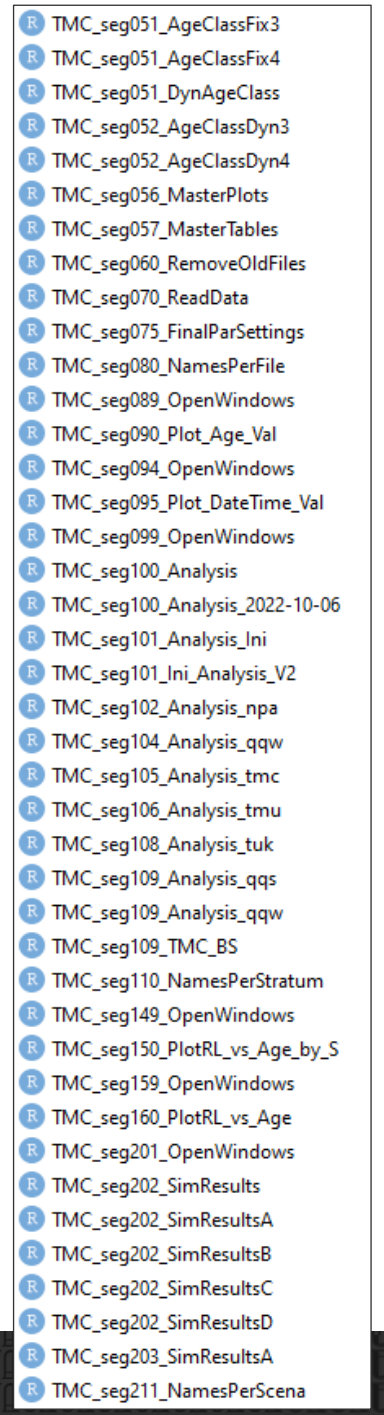


Results <LLOQ binned

Wosniok W. et al. CCLM. 2019; 57(12):1933-47. PMID: 31271548

TMC Package Workflow in R





DataFileInfo17ohp

FileNo;FileName;Path;Label;Value;Rounding;Sex;SexCodeM;SexCodeF;Age;DateTime;Device;DecChar

0001;TMC13_17OHProgesteronedata.csv;U:/Stats math/Reference Intervals/Indirect RI/Tools/TMC/TMC13/data/;TMC13_17OHProgest;2;1;4;M;F;3;5;6;.

	A
1	PatId;Value;Age;Sex;DateTime;Device
2	0001;56;27;F;01.01.2016 03:22;MS1
3	0002;75;15;F;01.01.2016 03:22;MS2

Dataset

Indirect RI Estimation - Many RI Partitions

Example: Endocrine-related analytes often have sex- and age-specific partitions

- Analysis of each partition can lead to repetitive and time-consuming code writing

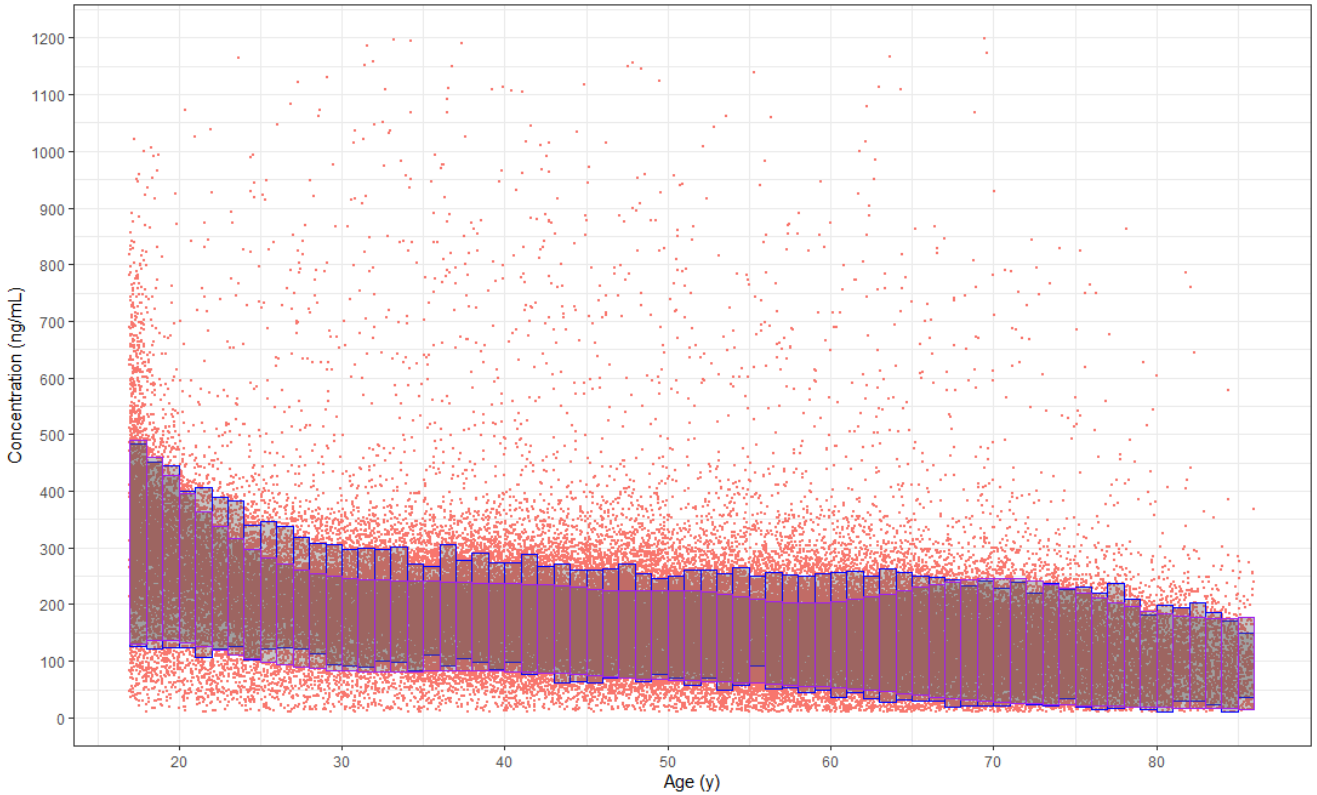
Solution: Code functions that loop over parameters from a table/spreadsheet

```
Functions
  twoparFUN          function (df, mu1, mu2, sd1, sd2, co, sex_sel, age_bin_start, age_bin_end)
```

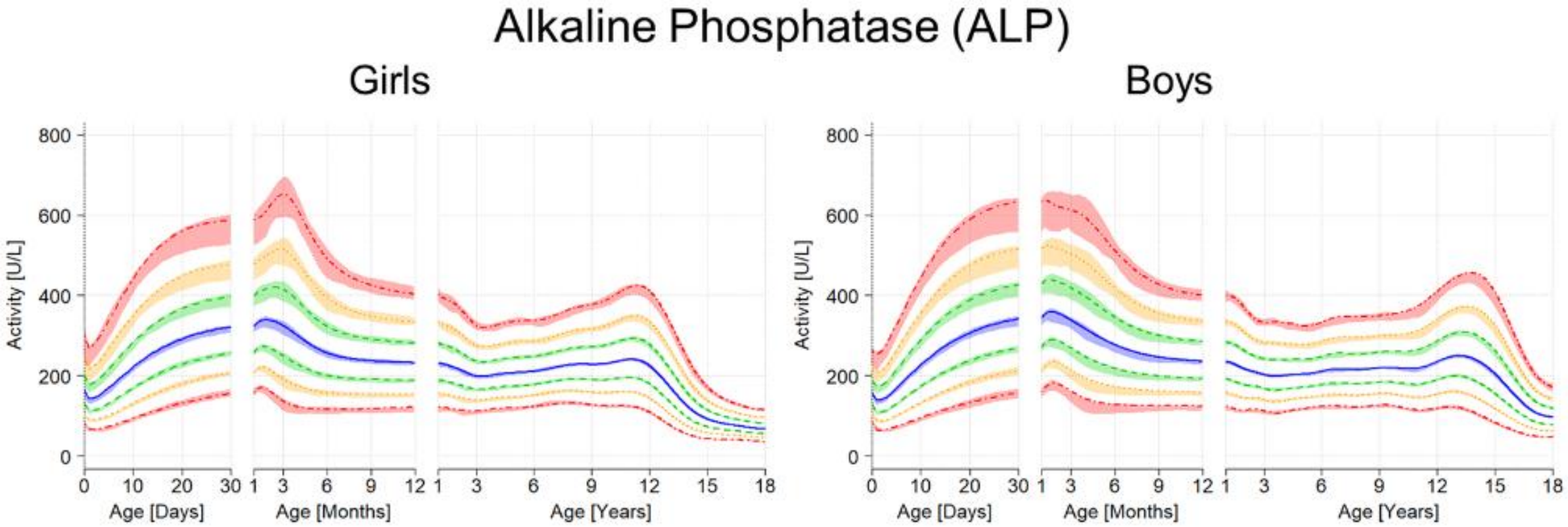
```
params
    $ .df            :
    $ dataset.name   :
    $ .mu1           :
    $ .mu2           :
    $ .sd1           :
    $ .sd2           :
    $ .co...7        :
    $ .data          :
    $ .mu1_val       :
    $ .mu2_val       :
    $ .sd1_val       :
    $ .sd2_val       :
    $ .co            :
    $ age_bin_start  :
    $ age_bin_end    :
    $ sex            :
```

```
df
    $ id             :
    $ sex            :
    $ years_old      :
    $ _result        :
    $ collection     :
    $ verified       :
    $     _result    :
```

Crock pot method
"Set it and forget it!"



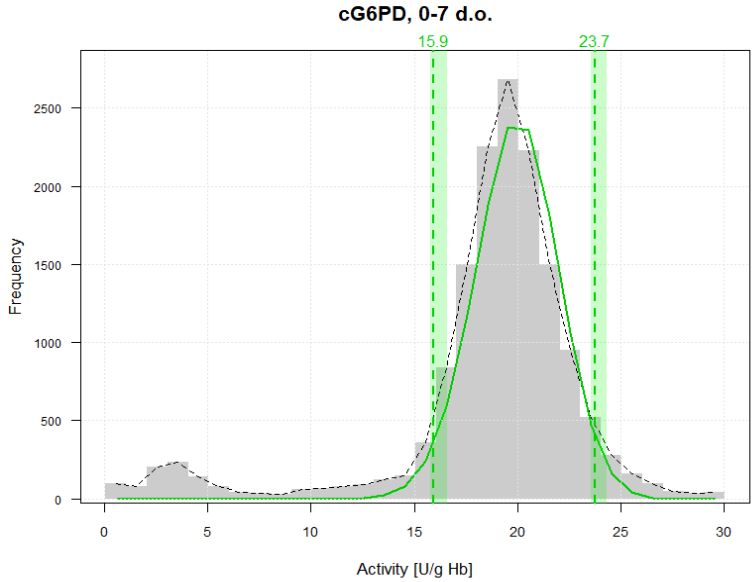
Continuous Indirect Reference Interval Estimation

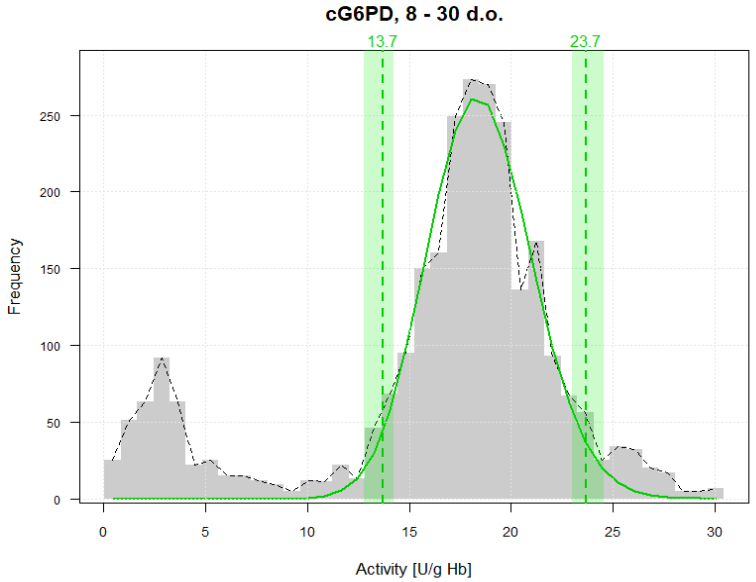


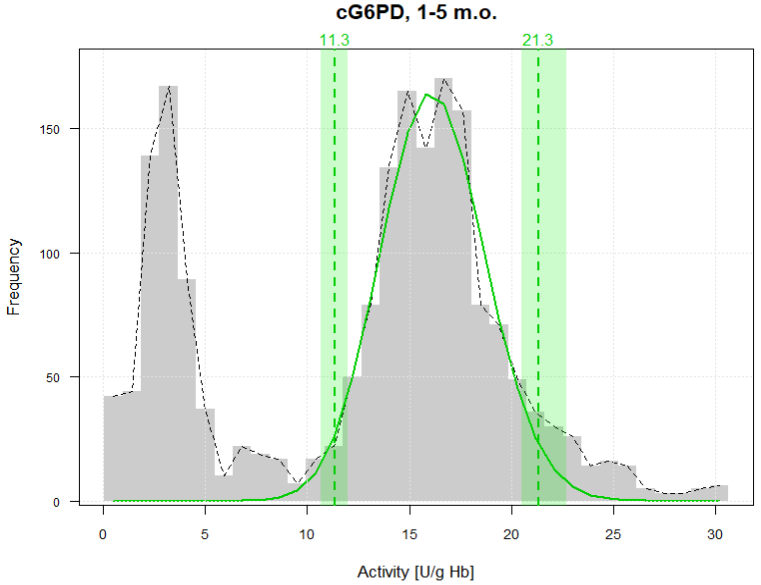
R Packages used: Runner pipeline = gamlss + refineR

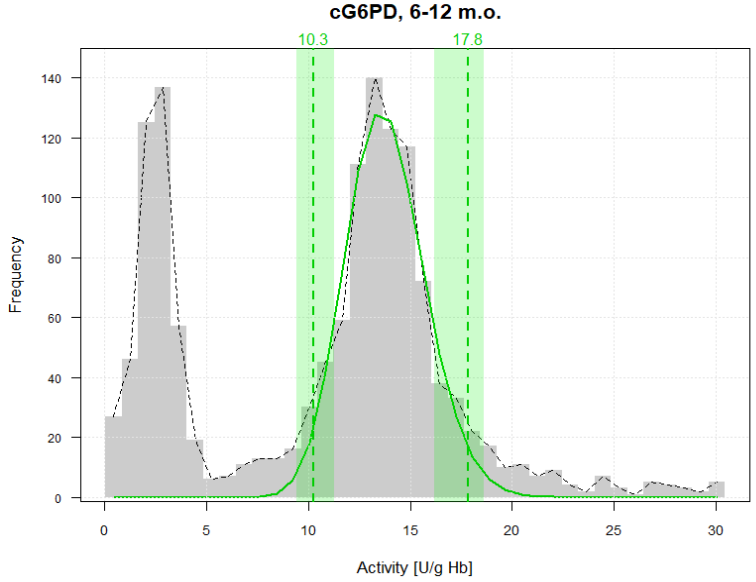
Ammer T et al. Sci Rep. 2023 Aug 18;13(1):13440. PMID: 37596314

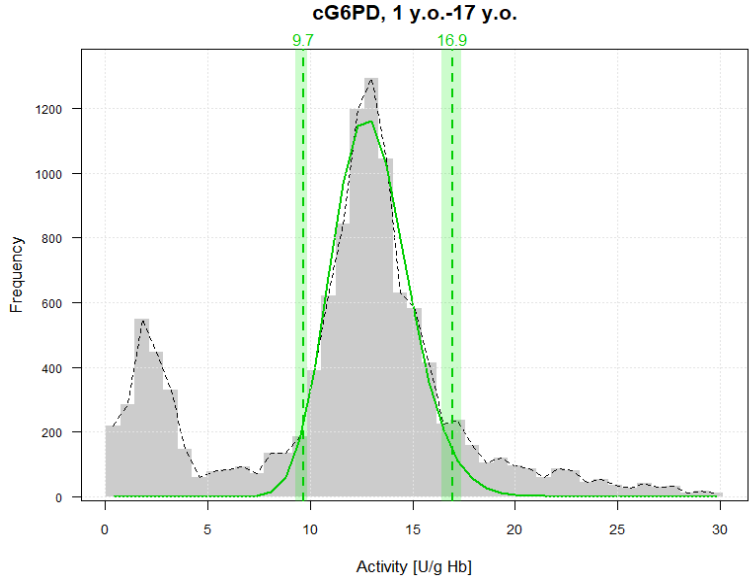
Example of Verifying Reference Intervals – G6PD Activity

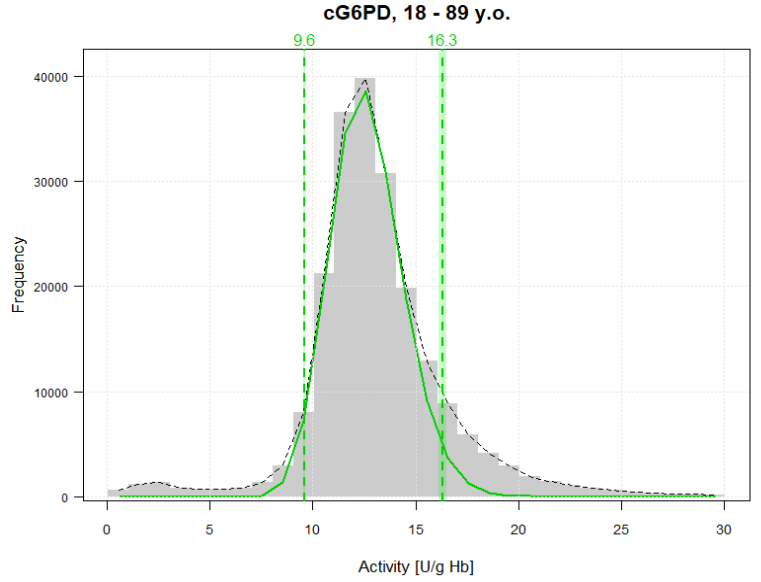




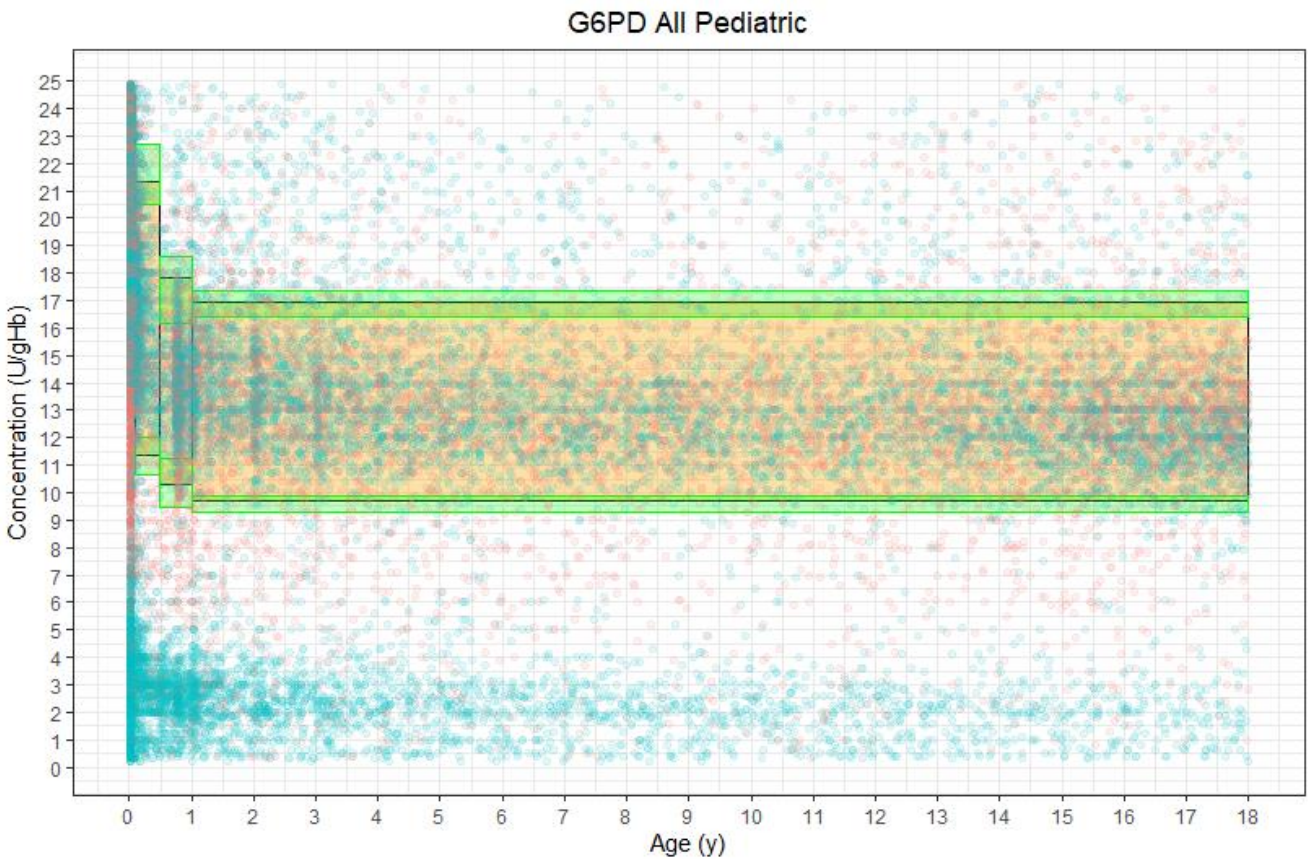


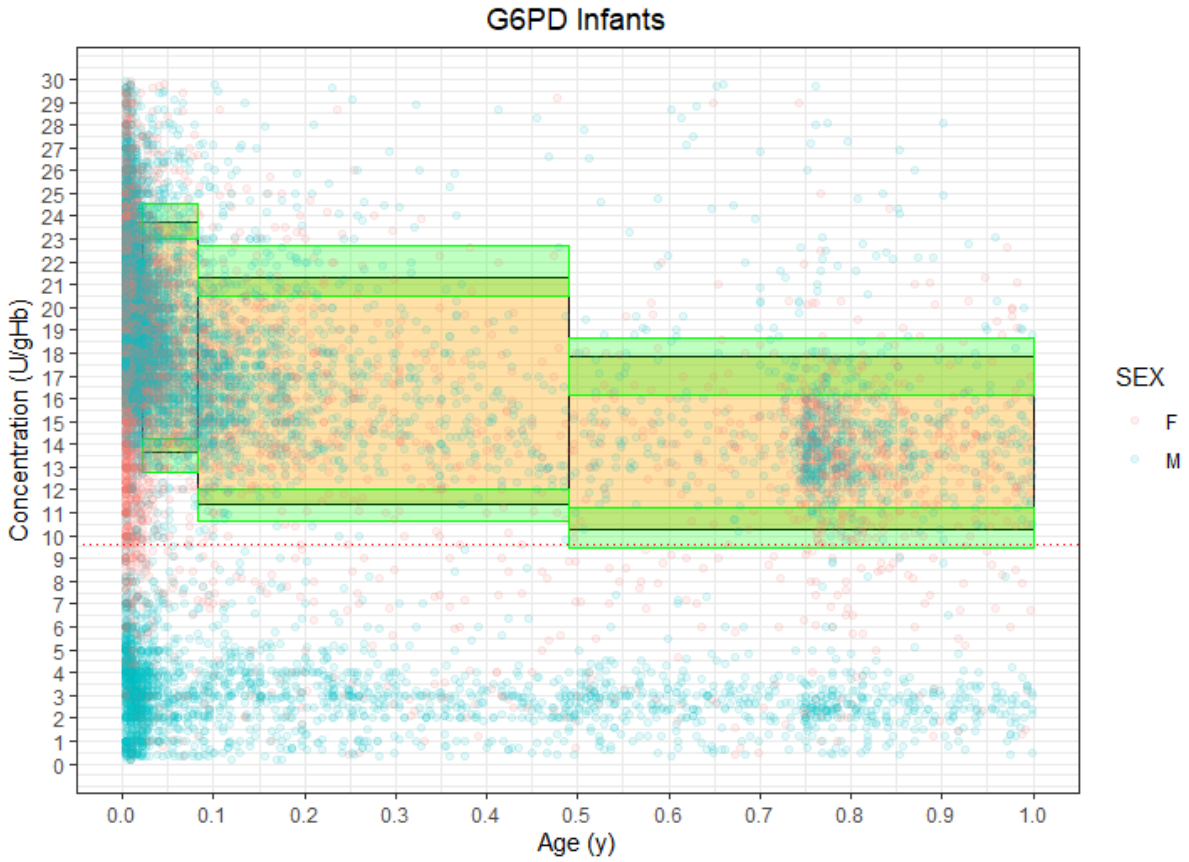






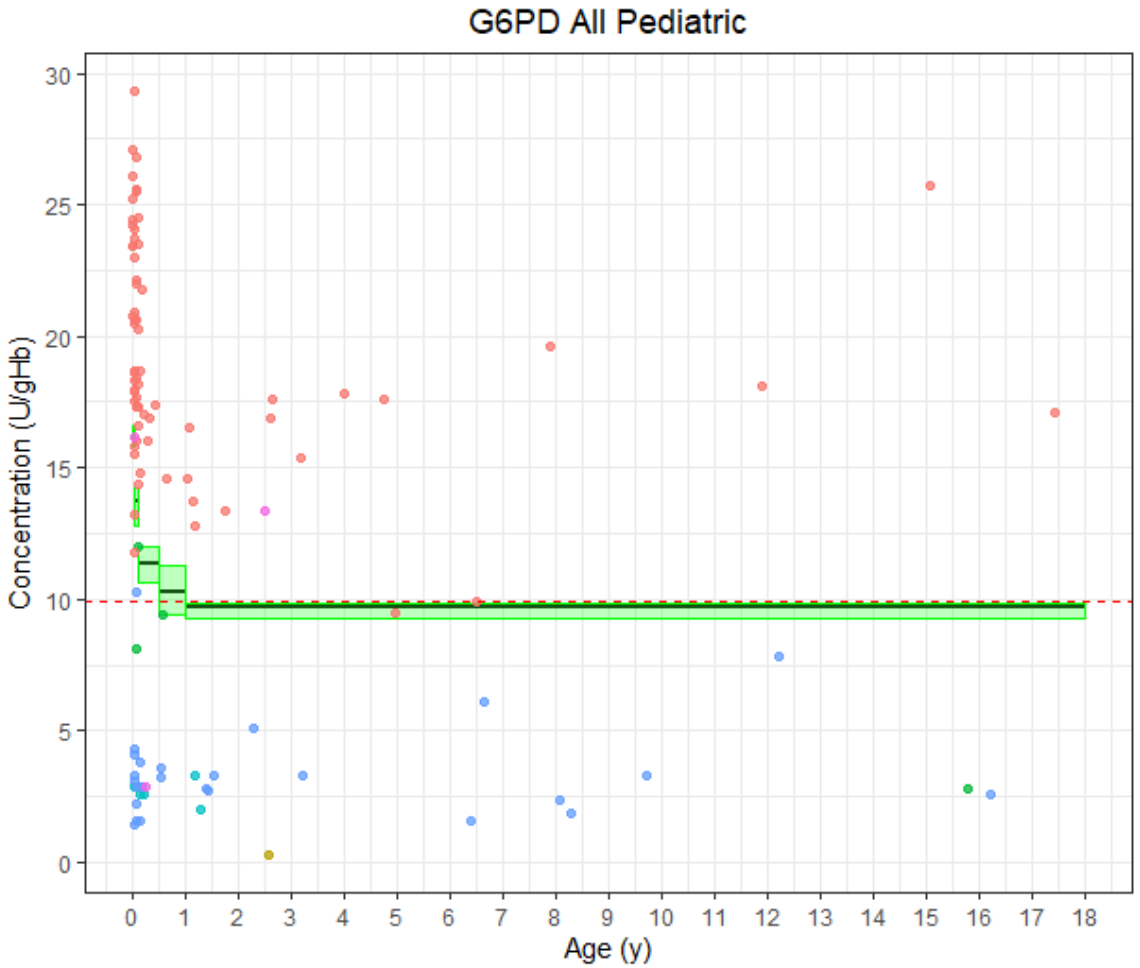
Estimated reference intervals coincide with dot plot trends…

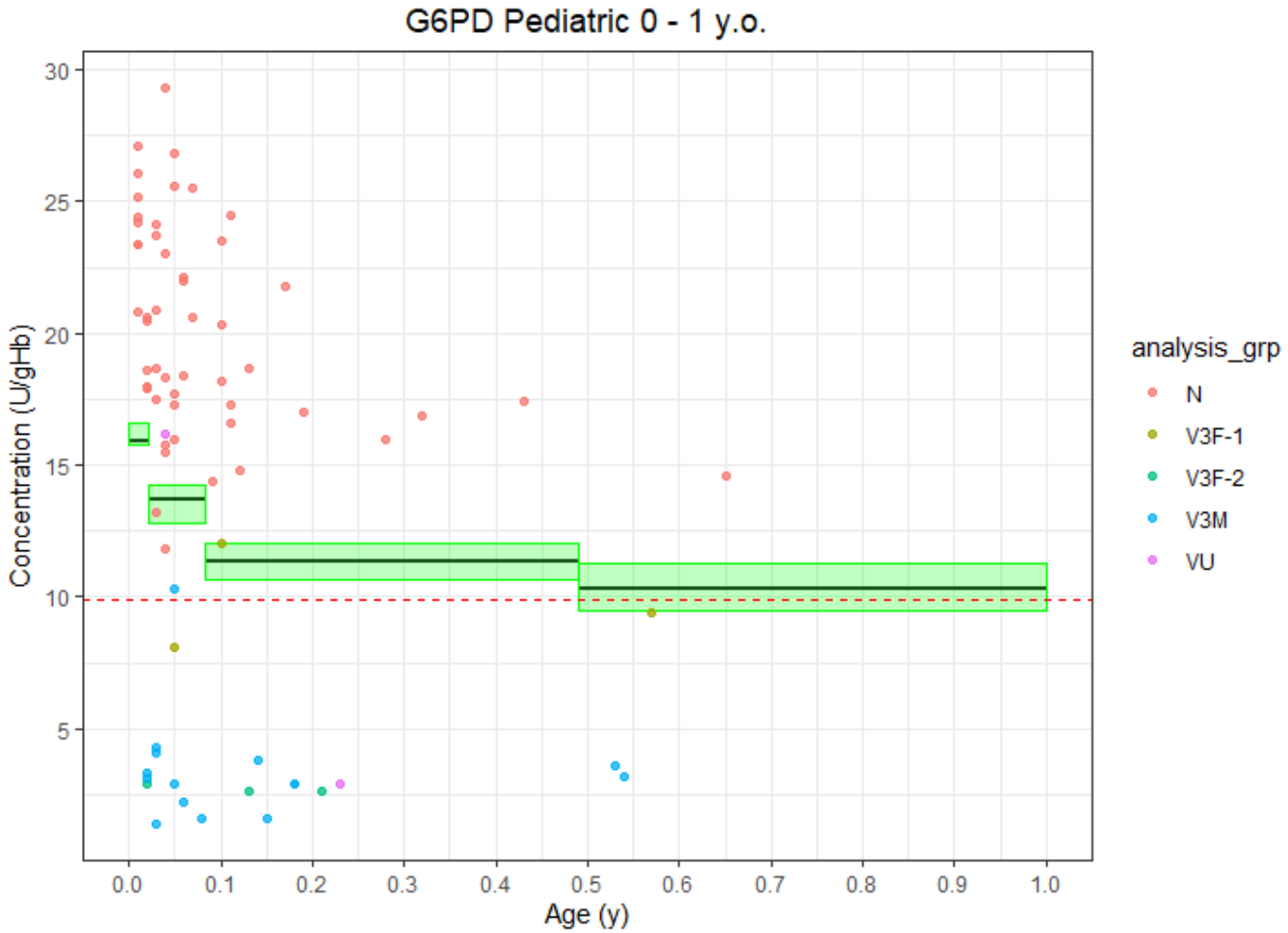




…but is there another way to verify clinical appropriateness?

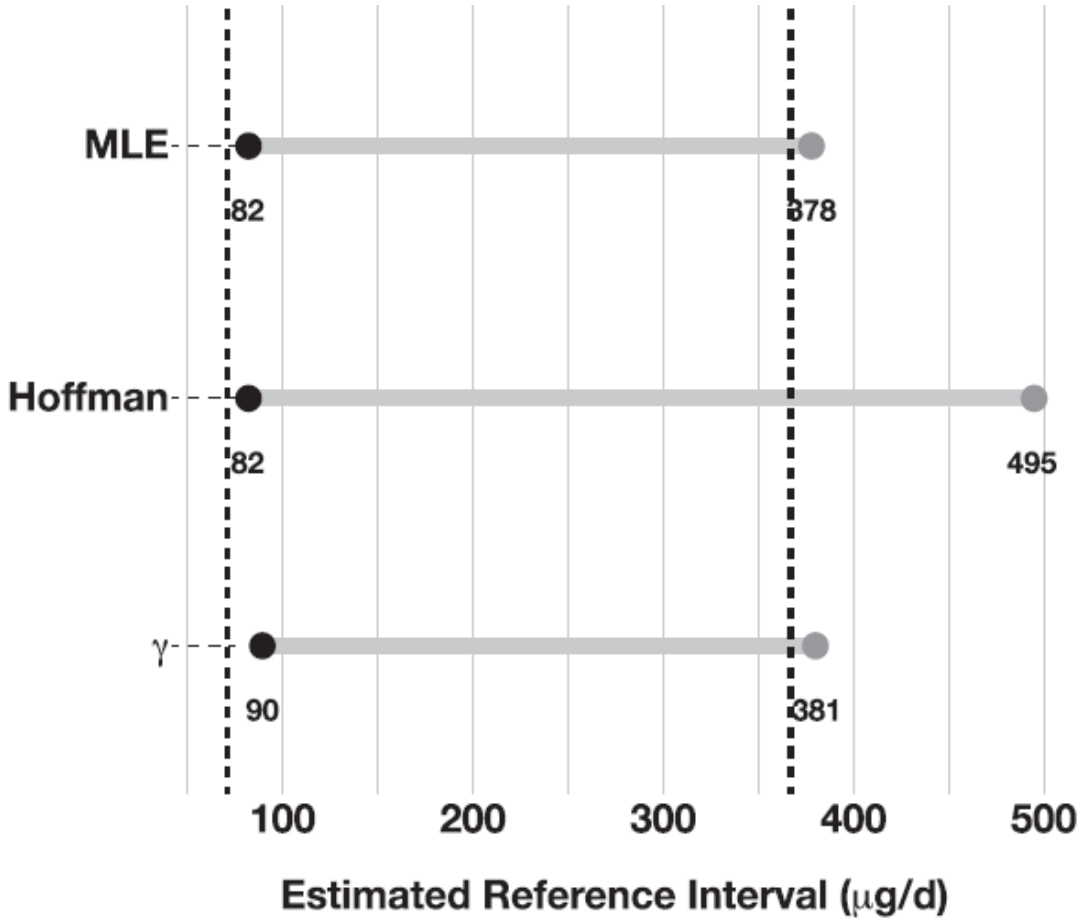
Estimated Phenotype RI With Genotype Data

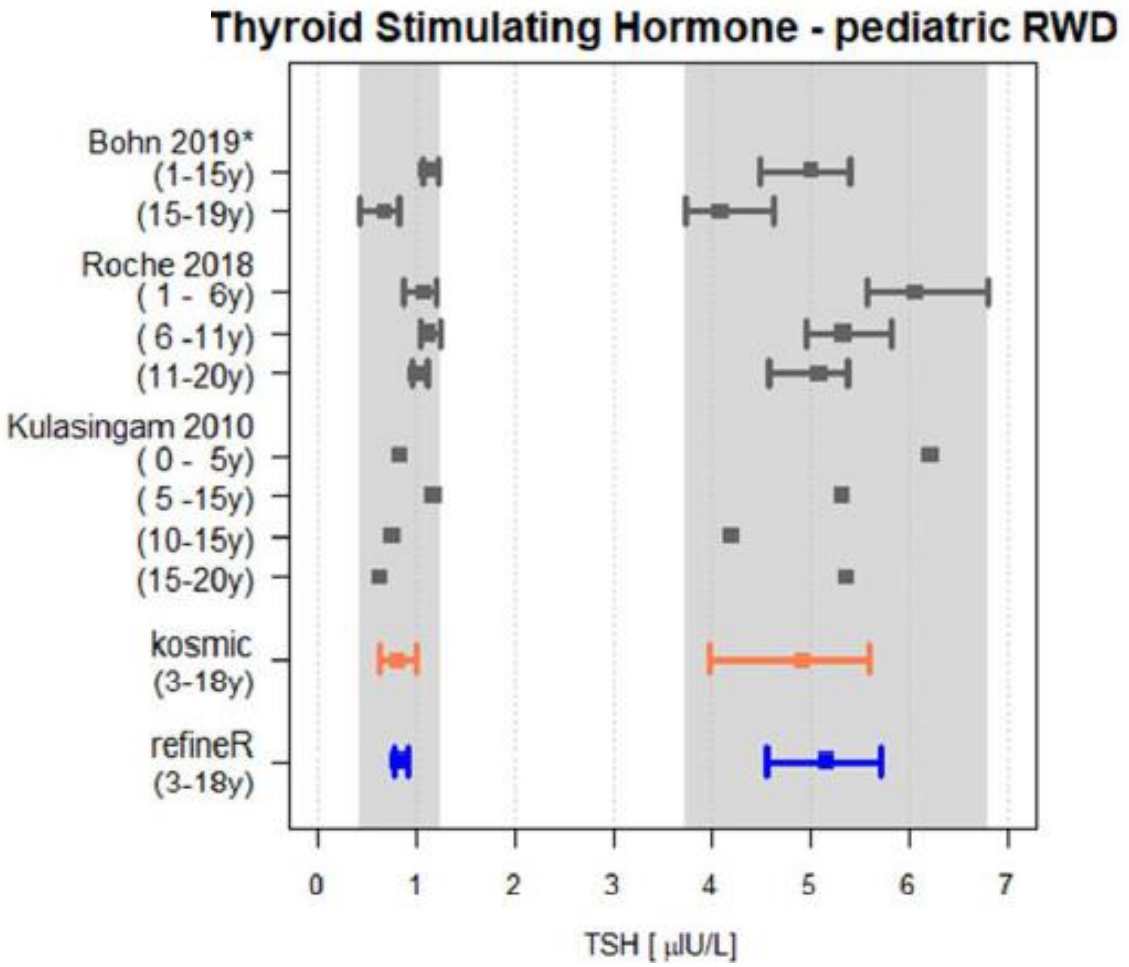




Only the lower estimated RI (CI = 95%) is shown with adult LRI shown as a red dashed line (9.9)

Compare to Other Methods and Published Studies





Words of Caution

- Indirect methods do not work for all analytes
  - » Patient demographic/cohort
    - Pathological data
    - Circadian cycles
    - Inpatient/outpatient
    - Collection techniques
    - Tanner stages

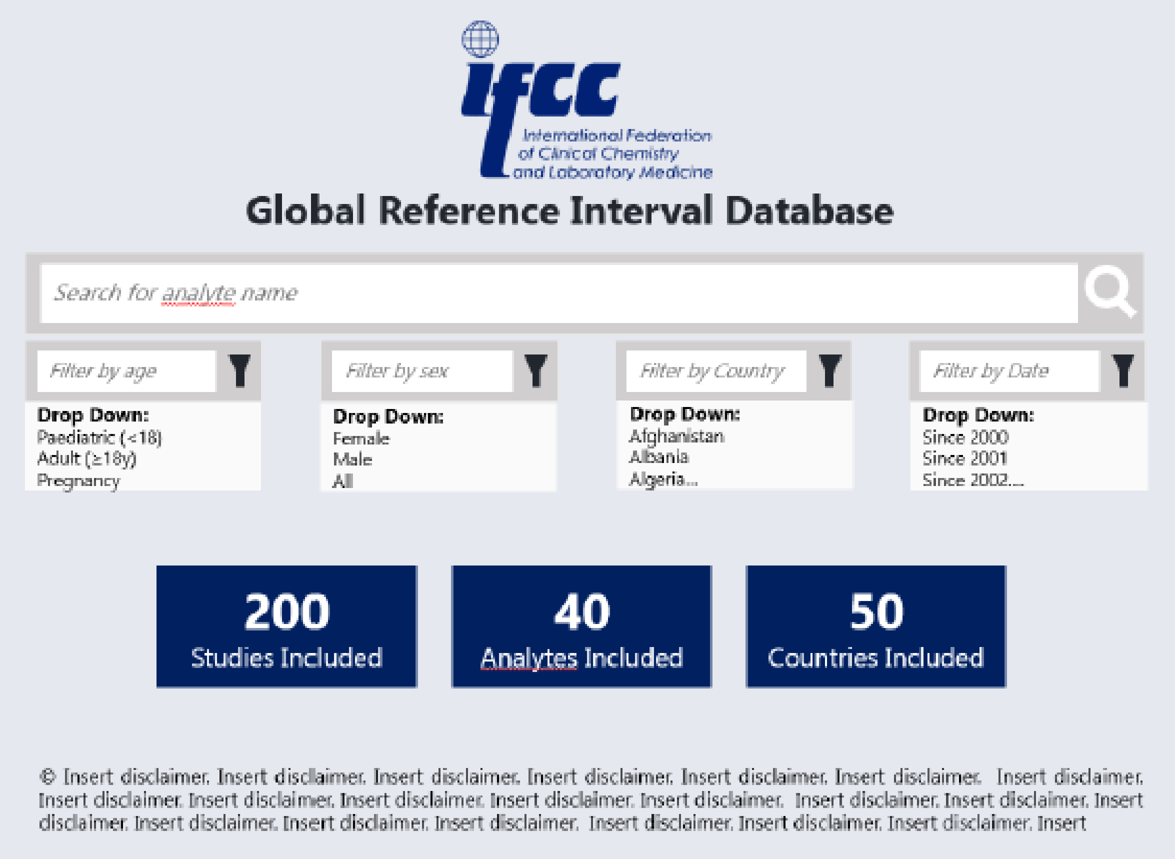
- Do not rely too much on too little data

IFCC Committee Guidance

2018 IFCC C-RIDL recommendations

“encourage the ***use*** of indirect methods to establish and verify reference intervals, to promote ***publication*** of such intervals with clear explanation of the process used, and also to support the ***development*** of improved statistical techniques for these studies.”

» Task Force on Global Reference Interval Database (TF-GRID)



Resources

- CLSI document EP28-A3c. Wayne, PA: Clinical and Laboratory Standards Institute; 2008. Reaffirmed: April 2016
- Jones RD, et al. *Clin Chem Lab Med* 2019;57(1):20-29.
- Ozarda Y. *Biochemia Medica* 2016;26(1):5-16.
- Doyle K, Bunch DR. Crit Rev Clin Lab Sci. 2023 Sep;60(6):466-482.
- Holmes DT, Buhr KA. Am J Clin Pathol. 2019 Feb 4;151(3):328-336. PMID: 30475946.
- IFCC Committee on Reference Intervals and Decision Limits. Clin Chem Lab Med. 2018 Dec 19;57(1):20-29. PMID: 29672266.

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HEALTH
UNIVERSITY OF UTAH

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