Creatinine Reference Ranges and Impact on the Application of the NKF eGFR Clinical Decision Limits in the primary Care Setting

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Outline

- Why we are interested in Creatinine RR
- Data Mining for Clinical & Lab Decision Making
- Some Results from Our Study at GDML
- Impact of Creatinine on the Interpretation of the eGRF
- Recommendation for the Primary Care

Interest in Creatinine RR : Background

- KDOQI Recommendation - report eGFR on all creatinine requests
- Global Move (North America, Australia, Europe, Asia)
- OAML (Ontario) guidelines Private Labs
- Feb & June 2006, the 3 major Private Labs in Ontario began reporting an eGFR
- MDRD (Modification of Diet in Renal Disease) Formula
- What Happened next???

What happened next?

- Some not so happy customers/Docs
- Adjustments had to be made
  - Low Flag - changed from < 90 to < 60 mL/min/1.73 m2
  - Normal - kept at eGFR > or = 90 mL/min/1.73 m2

    (60 - 89 mL/min/1.73 m2 : Normal, if no clinical indication or risk of KD)
  - Reporting – numerical/non-numerical cut-off??
    - 60 or 120??
  - GDML: Normal = or > 90; Numerical cut-off 120.
- Normal Creatinine & Reduced eGFR – "real issue" in primary care setting

Some not so Happy Customers.. What did they say??

- No time to explain to patients, especially those receiving their own results, can I opt out?
- MDRD formula is useless, can we not get a more accurate formula?
- Why create confusion in areas where it is not warranted or appropriate (flagging 60 – 89 as abnormal)
- All my healthy patients in the last 2 weeks had normal creatinine and abnormal eGFR; what do I do with them; which follow-up test should I order?
- Don’t know anything about the test, can I get more information?
- Why some many abnormal eGFR with normal creatinine; Are your normal ranges correct?

The Right Information at the wrong time

"I NOTE MANY ABNORMAL SERUM CREATININE RESULTS PAST 4 MONTHS BY YOUR LAB. REPEATED IN OGH OR OTHER LAB NORMAL ALSO YOU ALL ARE CREATING A LOT OF STRESS TO PATIENTS BY PRINTING THE e GFR THIS e GFR IS NOT ACCURATE AND VERY MISLEADING PARTICULARLY OVER AGE 70 . PLEASE WARN YOUR LAB BIOCHEMIST AND MANAGERS."

Is Between Lab Differences in Measured Serum Creatinine the only Problem?

- ***Standardization***
  - All methods/analyzers calibrated with same primary standard or calibration traceable to a primary reference method
  - "Calibration Traceable"
  - Difficult, less practical, resource intensive; long
  - Does not remove significant method Biases

- ***Harmonization***
  - Diff methods calibrated to give same results as a "candidate" reference method
  - Split sample comparisons; calibrator value assignments
  - "Results Traceable"
  - Less difficult/More practical
  - Does not remove method Bias, but comparability of results between Lab achieved

Serum Creatinine Reference Range – Part of the Problem?

- Google Search - ***serum plasma creatinine reference range* – 610,000 Hits**
- Ontario Private Labs
  - GDML Adult (>18yrs) : 60 – 110 (M); 50 – 100 (F)
  - MDS 10Yrs - Adult : 60 – 125 (M) ; 50 - 110 (F)
  - CML 10Yrs - Adult : 60 – 127 (M); 60 – 115 (F)
  - NORIP (Proposed) 18 – 59Yrs: 60 – 100 (M); 50 – 90 (F)
    - ULR 17 – 27 & 5 – 25 umol/L higher in ON than NORIP
- High index of individuality; Population RR is not useful
- Subject RR or RCV is preferred; not well understood & rarely used
- RR from actual patients data (Data Mining) has great potential

Health Record Data, Healthy Male, Non-Caucasian

Year (age)	Method	Lab	Creat umol/L	Ref Range	Interp
1985 (39)	SMA II jaffe	UH, Lon	120	62 - 124	N
1986 (40)	SMA II jaffe	UH, Lon	122	62 - 124	N
1987 (42)	EktachmJ&J, Enz	UH, Lon	124	71 - 168	N
1999 (53)	Vitros, OCD, Enz	MDS, TO	***129***	60 - 125	H
2004 (57)	Advia, Bayer, Jaffe	TWH TO	123	60 - 110	H
2005 (58)	ModR,Roche, Jaffe	GDML, Lon	125	60 - 110	H

Reference Intervals/Ranges

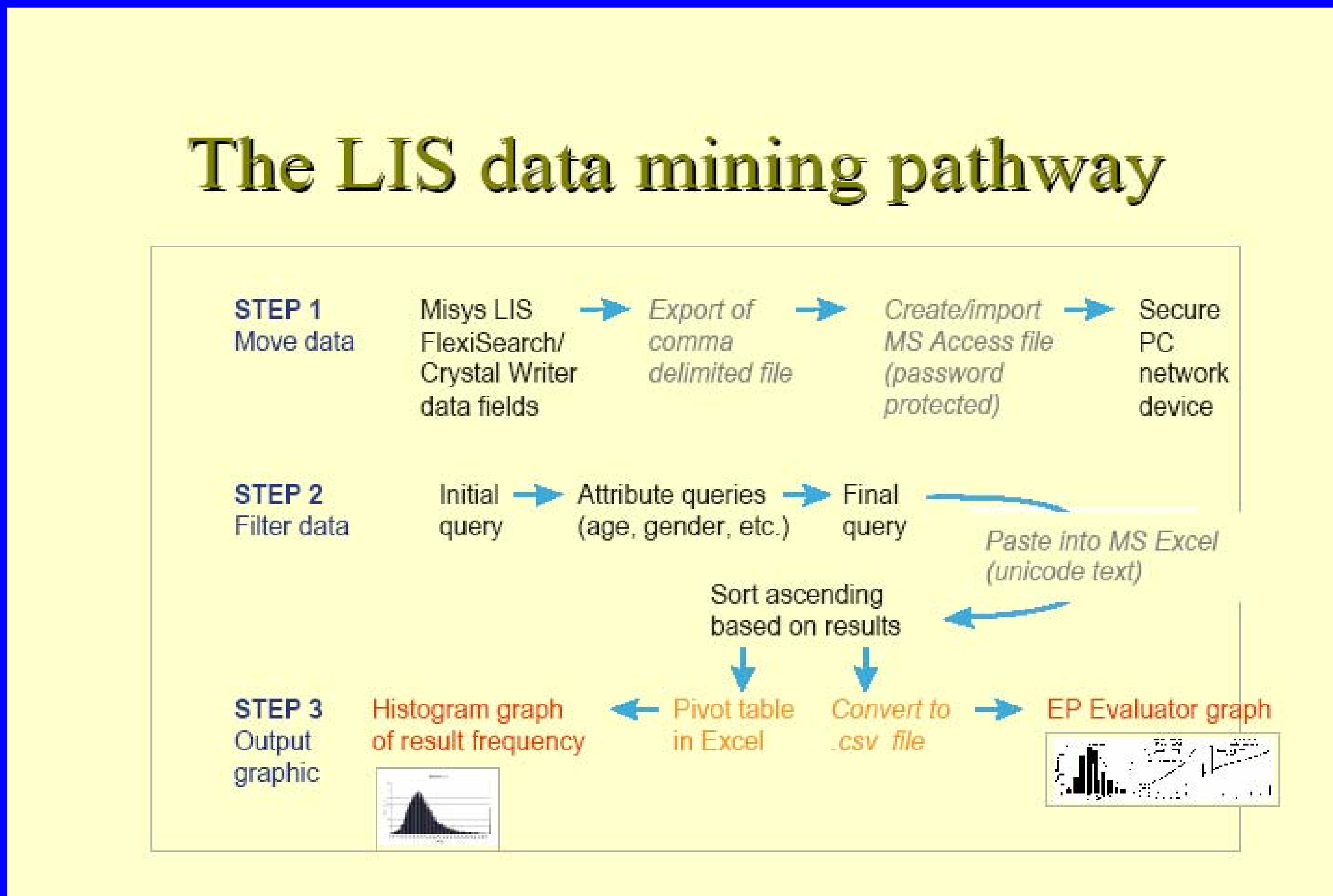
- Gold Standard for Establishing New RI
  - IFCC (EPTRV); CLSI (NCCLS)
  - Resource intensive/ Difficult to do
- Transference of well-established RI
  - Recipient accept donor RI as is (same conditions)
  - Recipient analyses 20 samples (reference individuals)
    - 2 or less outliers
  - Recipient analyses 60 samples (reference individuals
    - Diff between means (Z value)
      - Z-crit = $3\{[(n_1+n_2)/2]/120\}^{1/2}$
      - Inadequate donor info or different method
      - More complicated and SD_R < or = 1.5 SD_D
- Data Mining (LIS, EMR, EHR).
  - Various Stats Tools (New,Validate,Verify & Compare RI's)

Data Mining – Usefulness

- Productivity, Utilization & Clinical Outcomes (Dr. Mc Neely)
- Common Reference Intervals (Dr. G Jones)
- Validating reporting criteria for new tests (eGFR; Dr. J Jones)
  - Peer Comparison Program for Data-Mined Information
- Identifying individuals with a reduced GFR using Ambulatory Lab Database Surveillance (Dr. A Garg)
    - 17 Independent Outpatients Labs; 1.09 Mil people, 18 yrs and older; 32% had at least 1 creatinine done during Sept 1999 – Sept 2000
- Comparing Age-wise Reference Intervals for Serum Creatinine Concentration in a "*Reality Check*" of the Recommended Cut-Off (Dr. Bibhu Ranjan Das; SRL-Ranbaxy Ltd Clin Reference Labs, India)
    - Health Records; 1327 Individuals

Data Mining Pathway

(Dr Jay Jones, AACC Audio-Conference Series)



Data Mining Pathway for Reference Interval Purposes

- MS Excel Spreadsheet Application V1.2 (G Jones, Sydney)

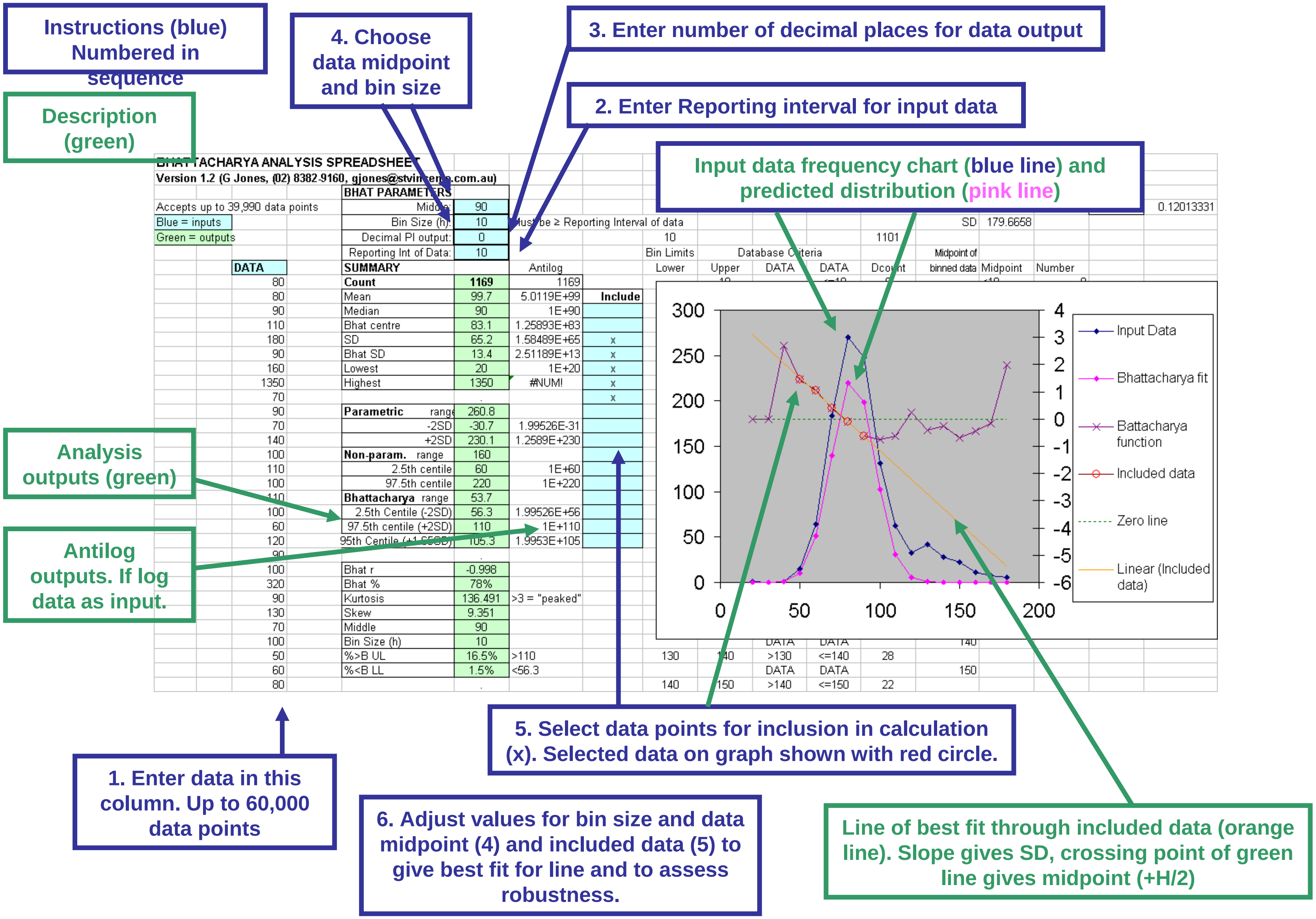
  (Bhattacharya, LG. Journal of the Biometric Society. 1967;23:115-135).
- SPSS for Windows V10.1 (SPSS Inc.)
- EP Evaluator V7.0 (D Rhodes Assoc Inc).

  (RI Estimation plus RR Verification)
- MS Access or Stats Packages in MS Excel

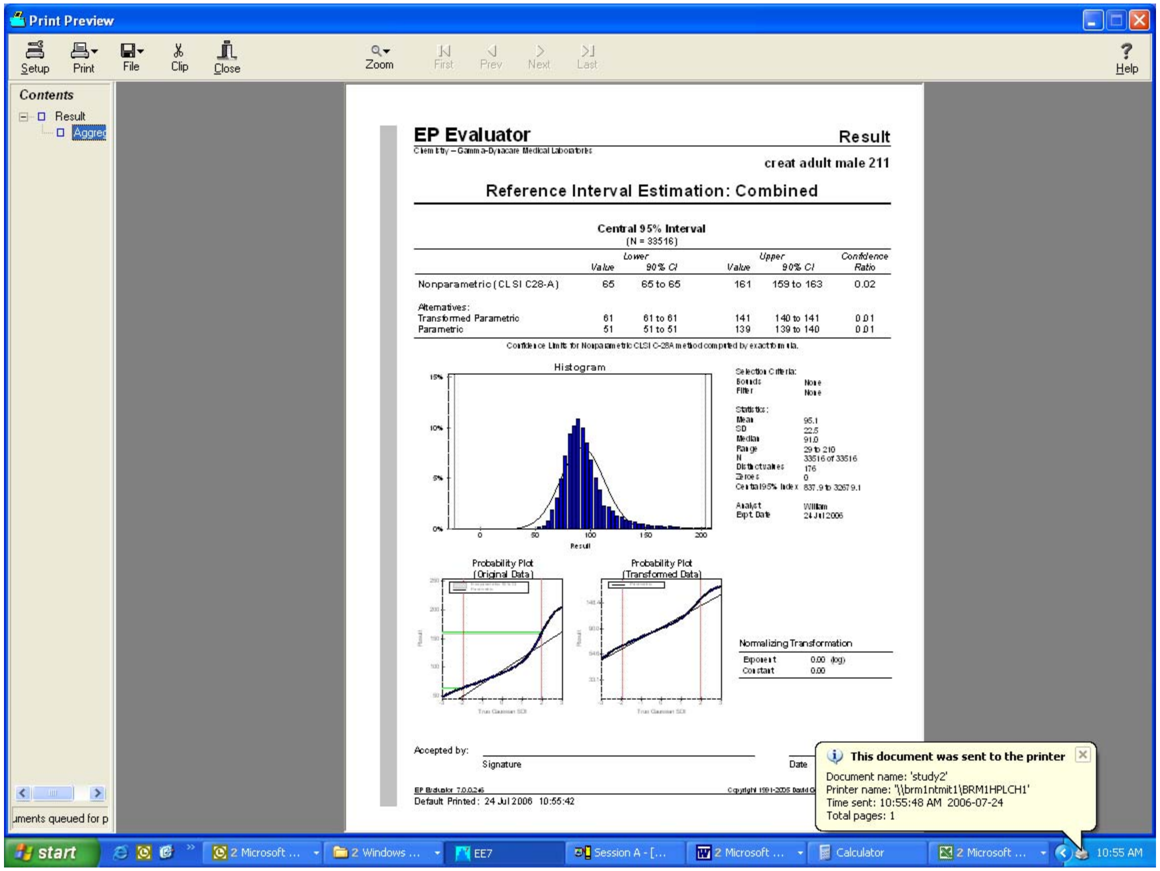
What is Bhattacharya (Bhatt) Analysis

- Bhatt Analysis - a graphical method of identifying a population with a Gaussian distribution in the midst of other data (good for reference interval studies; use untrimmed data without outlier exclusions)
- **Assumptions**
  - Majority of results is unaffected by condition for which patient is seek medical attention.
  - Unaffected population show Gaussian or log Gaussian distribution.
  - Large N size (> 3000; preferred Min: 7000)

Graham Jones - Bhatt spreadsheet



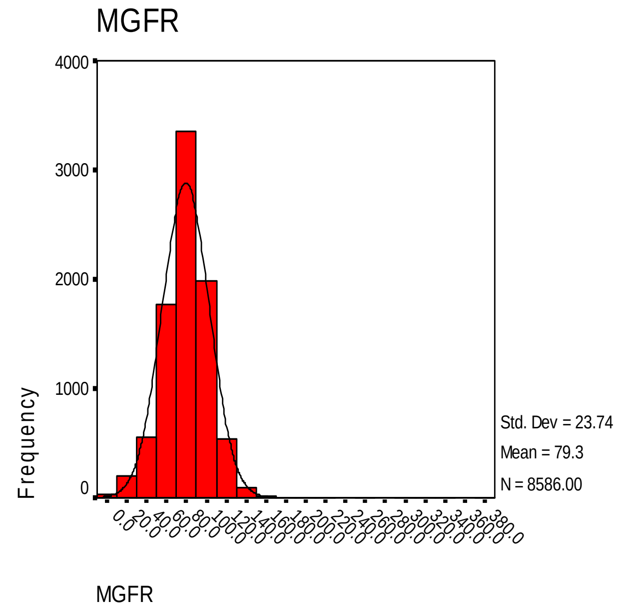
David Rhodes – EP Evaluator



SPSS Inc – Output File

Statistics

		MCR	MGFR	MAGE	FCR	FGFR	FAGE
N	Valid	8586	8586	8627	10747	10747	10819
	Missing	2233	2233	2192	72	72	0
Mean		03.5320	79.2959	56.4458	79.3017	80.3602	55.3170
Median		92.0000	80.0000	57.0000	72.0000	80.0000	55.0000
Std. Deviation		1.57141	3.73753	6.75097	0.41965	4.38228	6.33629
Range		1414.00	367.00	82.00	957.00	246.00	1987.00
Percentiles	2.5	66.0000	28.0000	23.0000	50.0000	30.0000	22.0000
	25	82.0000	66.0000	44.0000	64.0000	66.0000	41.0000
	75	06.0000	93.0000	70.0000	83.0000	95.0000	70.0000
	97.5	12.0000	24.0000	86.0000	55.0000	29.0000	89.0000



Our Results – Post eGFR Implementation Mar 2006

- LIS Data (Private Lab; 3 Divisions)
- 2 sets of data
  - Set I: Represents Single Meas.(N=19,332)
  - Set II: May Incl. Repeat Meas. (N=105,232)
- Determine age by decade and gender stratified RI
  - Bhatt. Analysis
  - EP Evaluator
  - SPSS for Windows
- eGFR: Revised 3 Parameter MDRD (traceable to IDMS ref method)

Methods

1. Creatinine determined by the kinetic Jaffe, Roche Modular System as follows:

Alkaline
Creatinine + Picric acid -------------------→ Creatinine-Picric acid complex
Solution

(The assay is blanked and compensated to minimize effects of interfering substances)

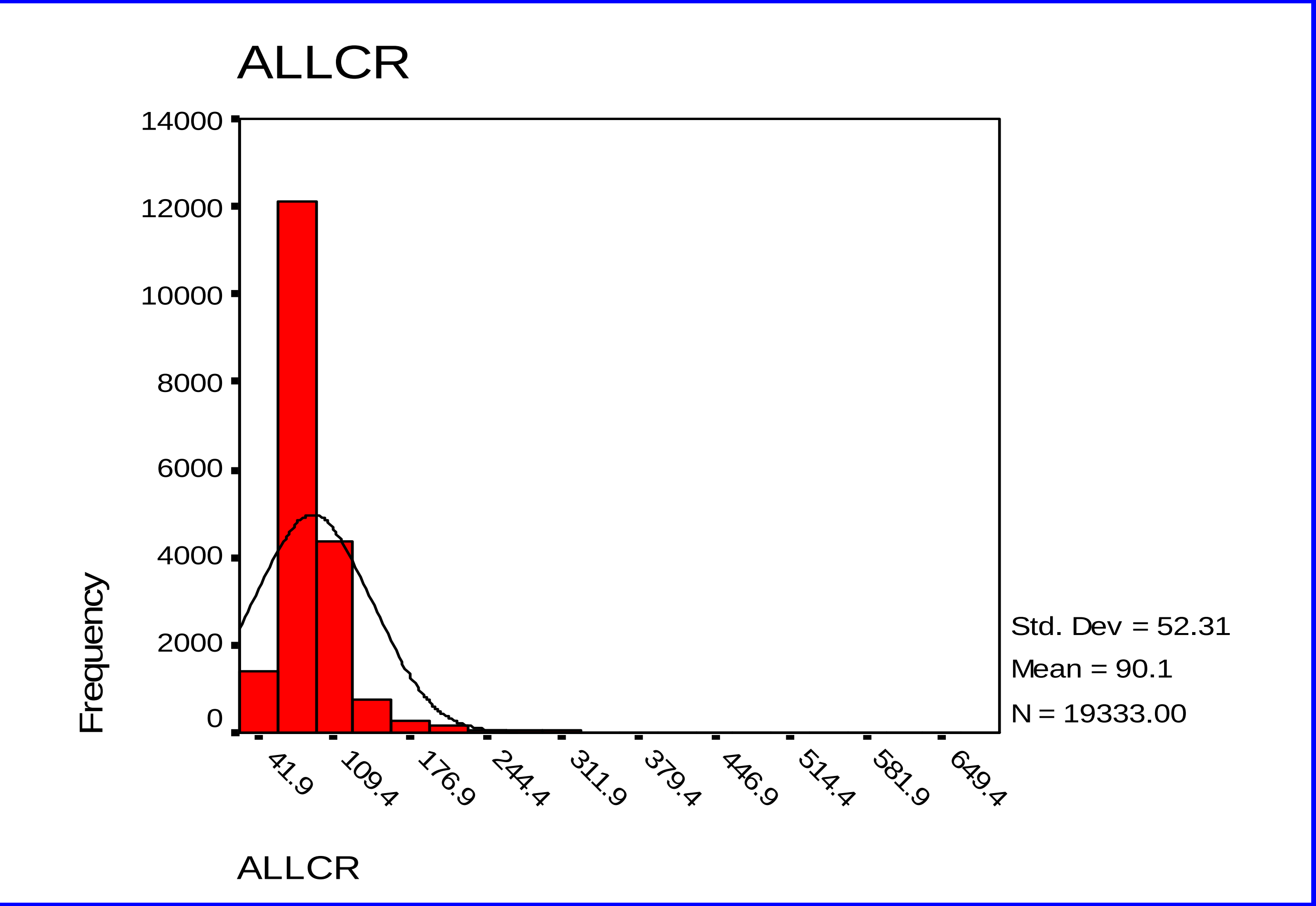
IDMS traceable Creatinine (cCr) was derived from the regression equation:

cCr = 1.043 x Modular Creatinine + 1.695 (DigitalPT, formerly HealthMetrx).

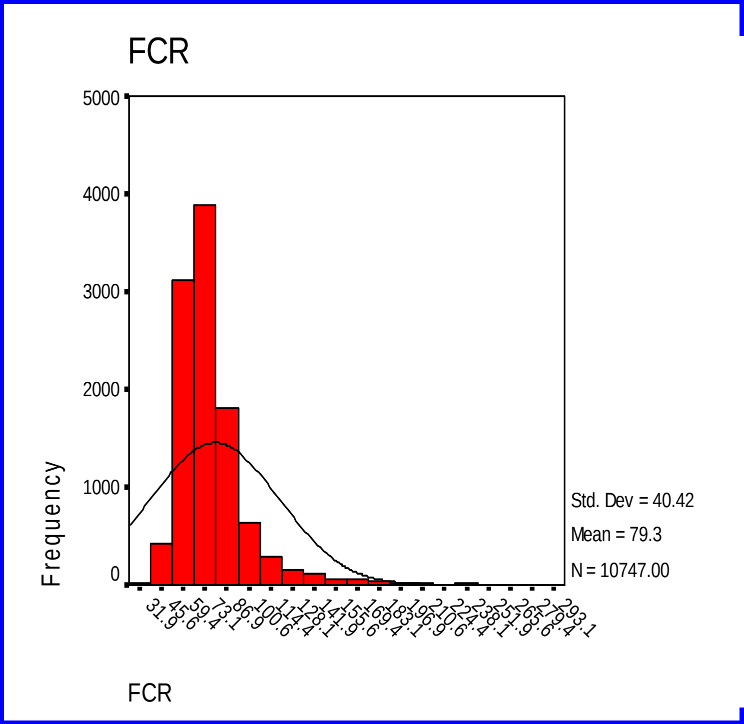
2. The eGFR was calculated using the following equation (MDRD):

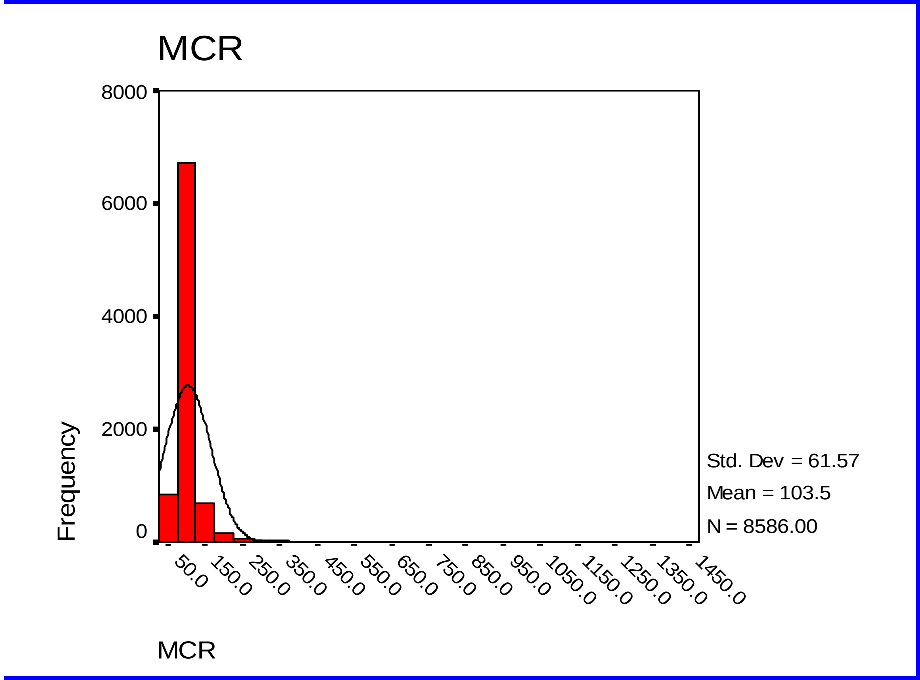
eGFR ($mL/min/m^2$)=175 {[cCr (umol/L)/88.4]$^{-1.154}$ + (Age,Yr)$^{-0.203}$}x 0.742 (if female).

Distribution Curves Creatinine – SPSS Output



Distribution Curves Creatinine – SPSS Output

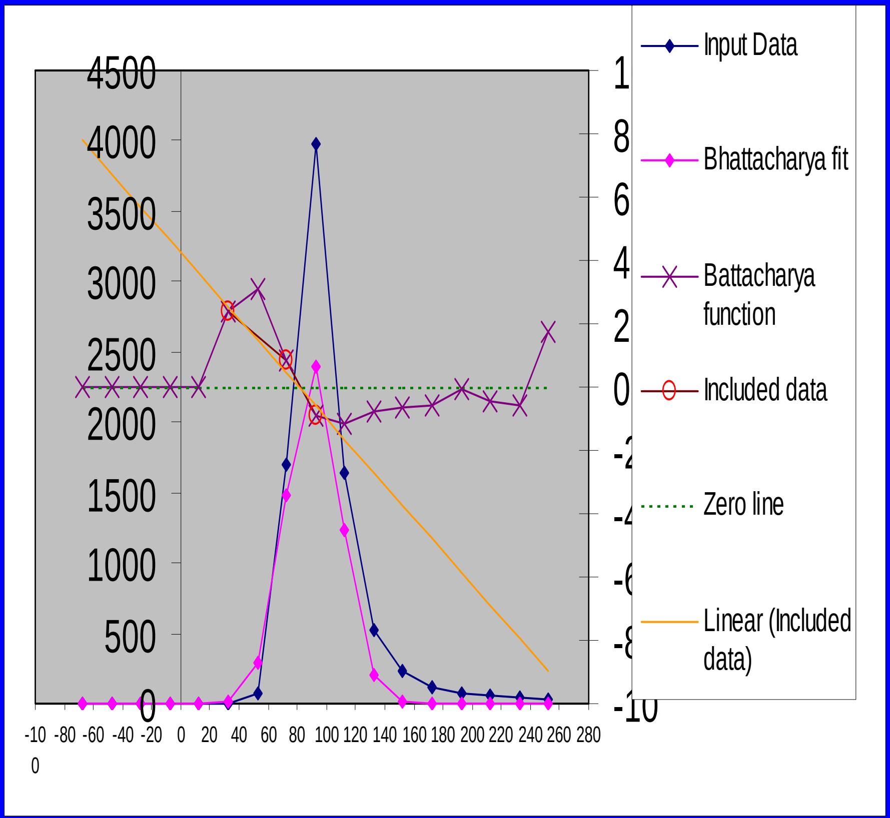


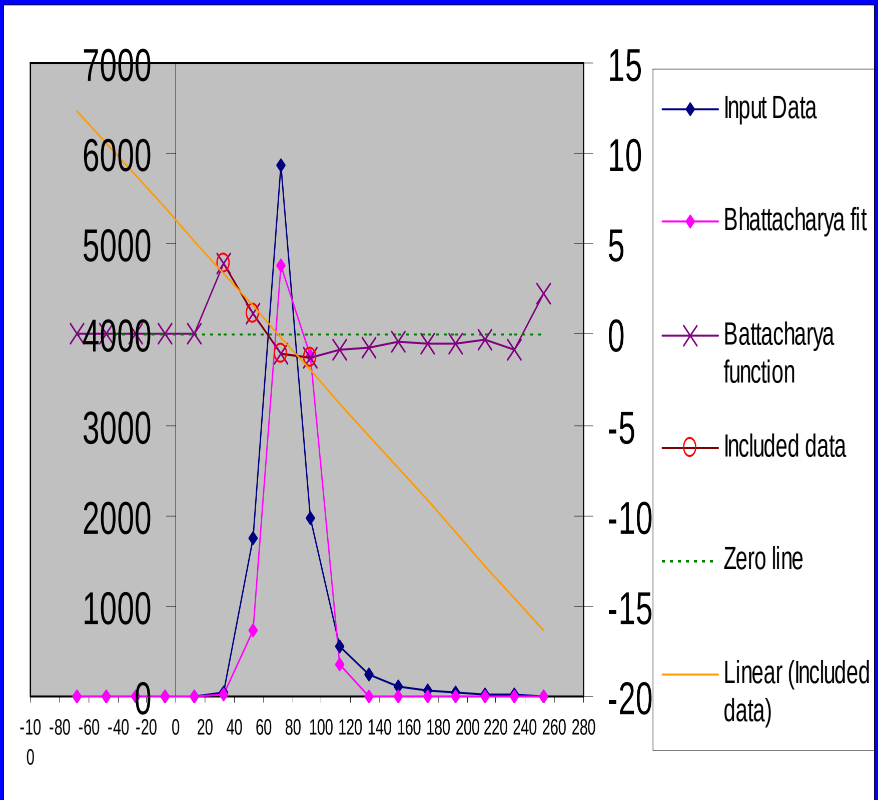


Creatinine – Central 95th Percentile RI – Males

Age (y)	Bhatt (raw)	SPSS (raw)	EP Eval (trim)
19 - 30	68.0 – 111.0	63.6 - 114.4	59 – 105
30 - 39	67.5 – 114.1	66.4 - 125.0	60 - 116
40 - 49	63.4 – 117.0	64.4 - 129.7	60 – 117
50 - 59	66.4 – 118.7	65.0 - 148.0	59 – 123
60 - 69	68.4 – 124.3	66.0 - 198.9	57 – 146
70+	65.9 – 125.7	68.0 - 303.4	55 – 196*
19 – 70+	54.5 – 133.4	66.0 – 212.0	55 - 147

Distribution Curves Creat– Bhatt Analysis: All ages - Left (M); Right (F)





Creatinine – Central 95th Percentile RI - Females

Age (y)	Bhatt(raw)	SPSS (raw)	EP Eval (trim)
19 - 30	50.8 – 88.7	48.0 – 88.2	44 - 82
30 - 39	48.1 – 91.1	47.3 – 91.0	44 – 85
40 - 49	51.0 – 91.1	50.0 – 100.0	46 - 90
50 -59	48.5 – 95.7	51.0 – 113.5	46 - 96
60 - 69	51.7 – 100.6	51.0 – 155.0	45 – 113
70+	53.1 – 103.1	54.0 – 209.9	45 – 150*
19 – 70+	50.0 – 95.6	50.0 – 155.0	43 - 113

Creatinine – Central 95th Percentile RI
EP Evaluator, Trimmed

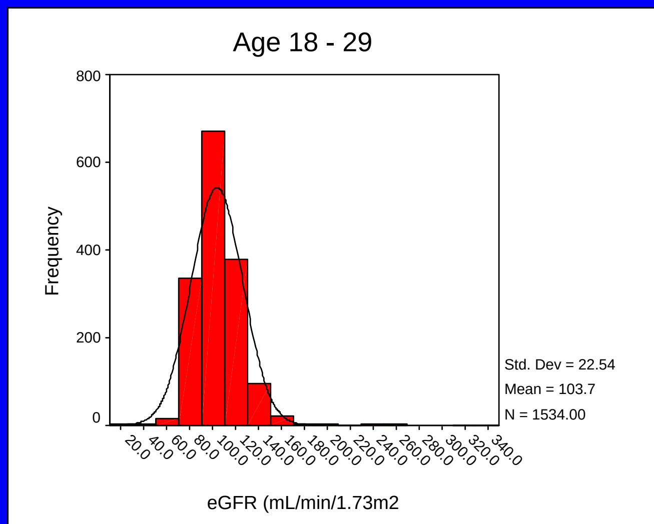
Age (y)	Males	Females
19 - 30	59 – 105	44 - 82
30 - 39	60 - 116	44 – 85
40 - 49	60 – 117	46 - 90
50 -59	59 – 123	46 - 96
60 - 69	57 – 146	45 – 113
70+	55 - 196	45 - 150
19 – 70+	55 - 147	43 – 113 (NP 46 – 133)

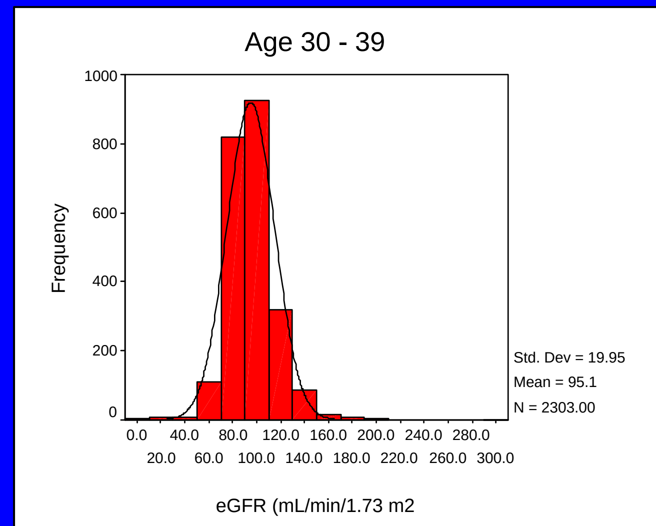
Creatinine – 95 % Range – Scottish Data

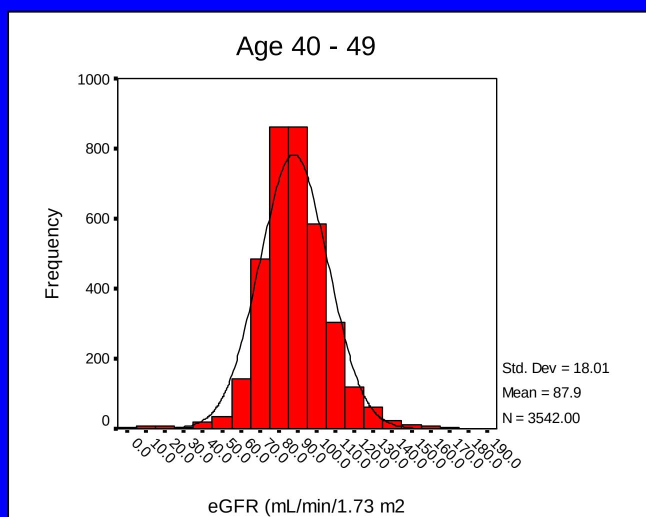
(Gardner & Scott JCP 1980; 33:380 – 385)

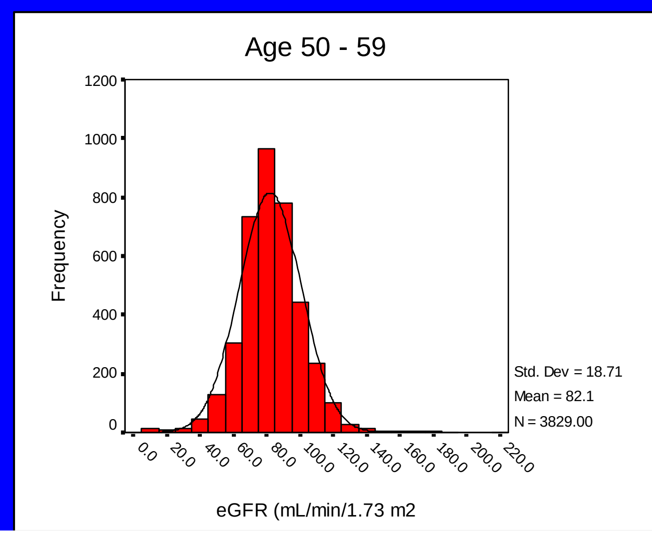
Age (y)	Males	N	Females	N	Our Data Males	EP Eval Females
20 - 30	60 – 110	321	50 – 110	384	59 – 105	44 - 82
30 - 39	60 – 120	537	50 – 110	698	60 - 116	44 – 85
40 - 49	60 –130	476	50 –110	560	60 – 117	46 - 90
50 - 59	60 –140	294	50 –120	279	59 – 123	46 - 96
60 - 69	70 -140	116	50 –120	142	57 – 146	45 – 113
> 69	50 - 160	38	60 -140	50	55 - 196	45 - 150

Distribution Curves eGFR – SPSS Output

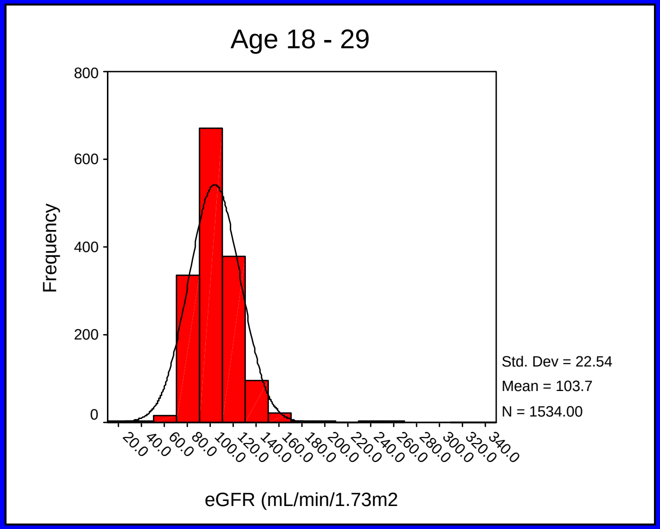


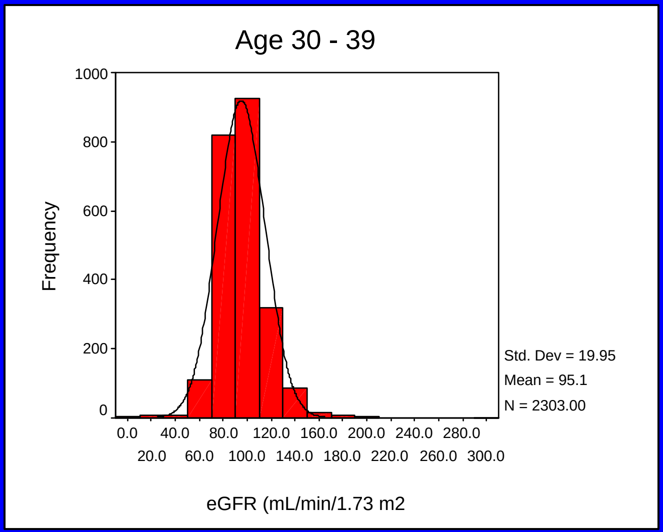


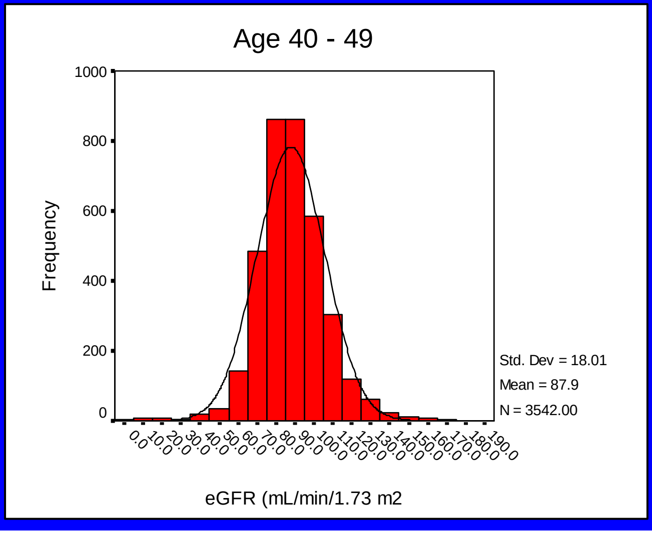


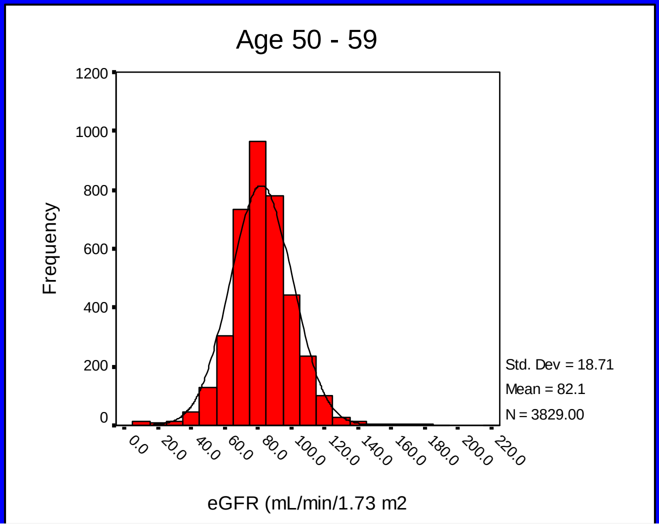


Distribution Curves eGFR – SPSS Output

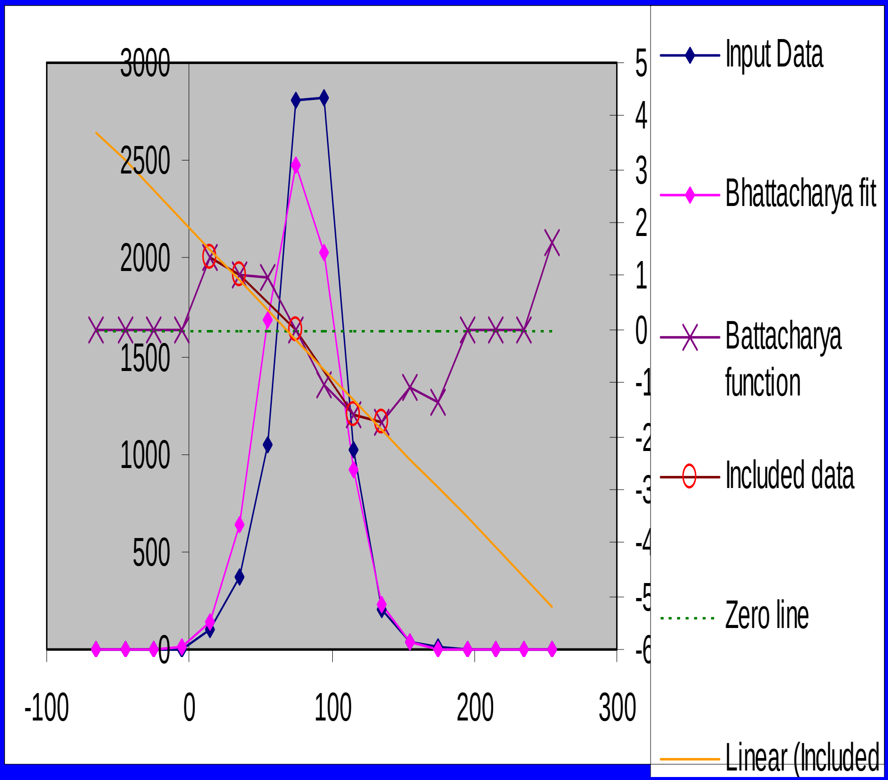


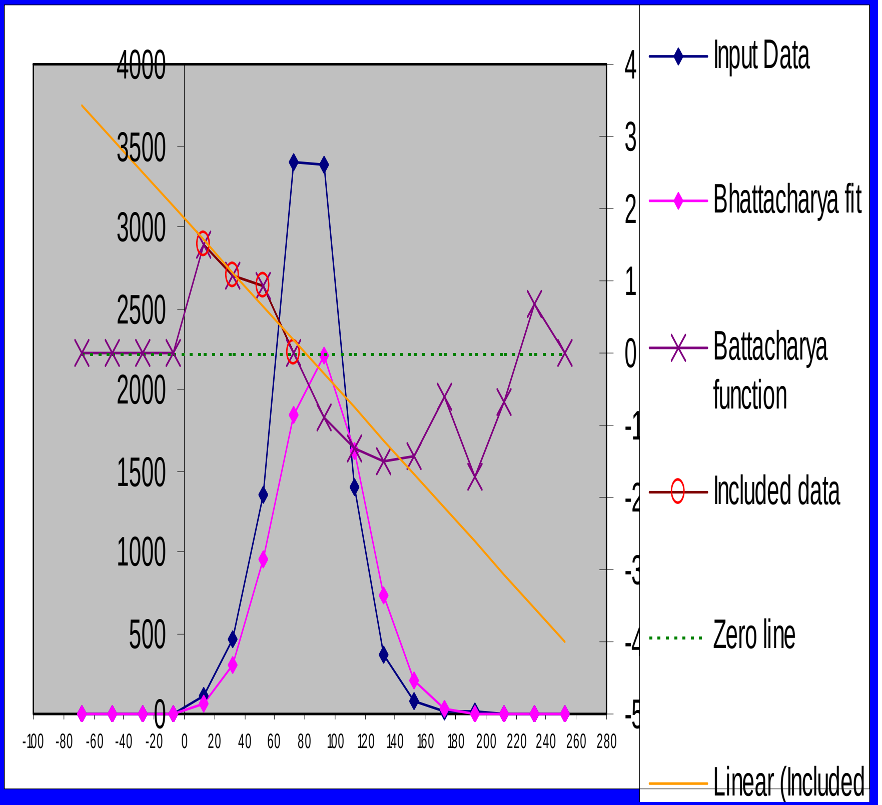






Distribution Curves eGFR – Bhatt Analysis: All ages - Left (M); Right (F)





eGFR - Mean & 95th Percentile RI – Males & Females (combined; raw; SPSS)

Age, years		**eGFR** (mL/min/1.73 m^2	**2.5-97.5th Percentile Range**	**Average Estimated GFR (*)**
	N	**Mean**		
18 – 29	1534	103.7	72.4 – 149.0	116
30 – 39	2303	95.1	63.0 – 138.4	107
40 – 49	3542	87.9	56.0 – 126.0	99
50 – 59	3829	82.1	46.0 – 120.0	93
60 – 69	3207	73.8	31.0 – 114.8	85
70 +	4917	61.9	20.0 – 105.0	75
18–70+	19398	79.9	29.0 – 127	-

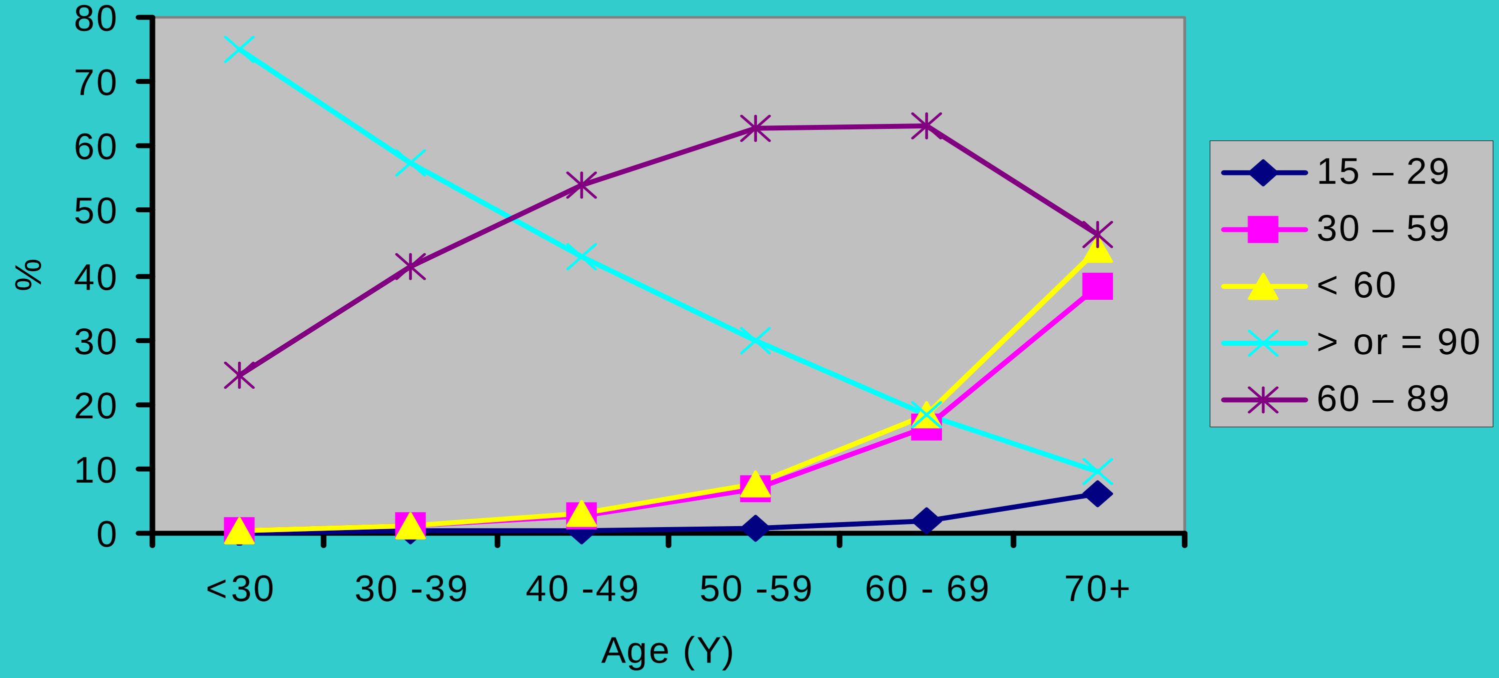
Impact on Interpretation - Health Record Data, Healthy Male, Non-Caucasian

Year (age)	Creat umol/L	eGFR (w/o EF) Orig	eGFR (w/o EF) Revised	eGF (w EF) Orig	eGFR (w EF) Revised	Dep MDRD, Creat RI used,
1985 (39)	120	61.9	58.2	74.9	70.5	1. Delta: 4 –5 umol/l in 20 yrs
1986 (40)	122	60.4	56.9	73.6	68.8	2. All creat high, GDML RI
1987 (42)	124	59.0	55.5	71.4	67.2	3. No CKD, Orig MDRD w EP
1999 (53)	*129*	53.6	***50.4***	64.8	61.0	4. Stage 1or 2 CKD from age 39, orig or revised MDRD w/o EP
2004 (57)	123	55.8	52.5	67.5	63.5	5. RI 65.0 – 148.0 acceptable creat
2005 (58)	125	54.6	51.3	66.0	62.1	

Impact on Interpretation – NKF Staging in the Elderly

- 65 year old male
- Stage 4 CKD, EGFR = 15 to 29
- Stage 5 CKDEGFR = <15
- At EGFR of 29 (stage 4 CKD); Creatinine = 200umol/L
- EGF drops to 15 (48% decr., still Stage 4); Creatinine = 350 umol/L
- 75% Incr. in Creatinine.
- Not uncommon in routine outpatient practice to see creatinine in 200 – 300 umol/L ranges.

Our Study - % Patients with eGFR within Recommended Cut-points (N=105,232)



Summary/Recommendation

- Labs should review existing RI in addition to harmonization & Standardization of creatinine (consider instituting age & sex specific RI)
- For Primary Care Setting: < 20; 20 – 40; 41 – 60 & > 60 yrs; Male & female at each
- eGFR - 60 cut-off for “normal”
- Flag eGFR < 60 as low, but comment on reduced eGFR in healthy older people
- Continuous on-going Education to all users!!!!

References

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Acknowledgements

- Dr Jones, St Vincent Hospital, Sydney
- Dr McNeely, Director Med Informatics, MDS Metro
- Jeff Sumner (CSO), Mike Scime, Dr Joel Goodman, Dr Hilde Vandenberghe & William Hui, Gamma-Dynacare Med Labs, Ontario Division
- Dr Chris Collier, Kingston; Dr. Stuart, Can Med Lab, Onatrio & Dr. Akbari, Ottawa Hospital