

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

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Laboratories, London, ON**

# 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 eGFR
- 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 m<sup>2</sup>
  - Normal - kept at eGFR  $>$  or  $= 90$  mL/min/1.73 m<sup>2</sup>  
(60 - 89 mL/min/1.73 m<sup>2</sup> : 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	<b>129</b>	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)
      - $Z\text{-crit} = 3\{[(n_1+n_2)/2]/120\}^{1/2}$
      - Inadequate donor info or different method
      - More complicated and  $SD_R < \text{or} = 1.5 SD_D$
- Data Mining (LIS, EMR, EHR).
  - Various Stats Tools (New, Validate, Verify & Compare RI's)

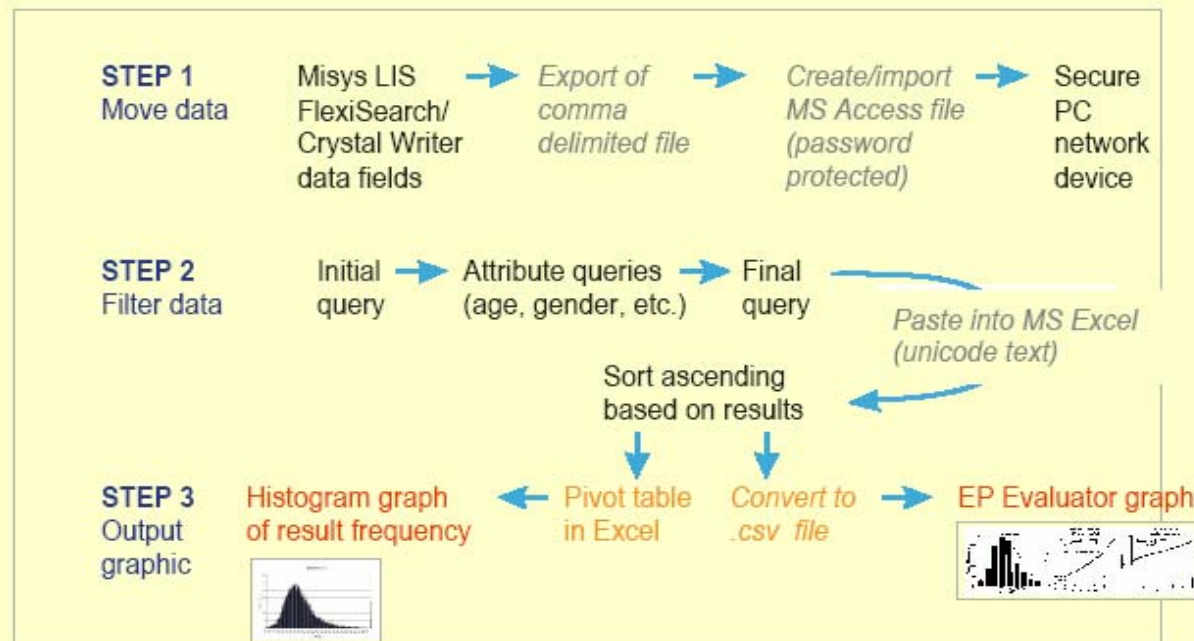
# Data Mining – Usefulness

- 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, AACCC Audio-Conference Series)

## The LIS data mining pathway



# 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

Instructions (blue)  
Numbered in  
sequence

Description  
(green)

4. Choose  
data midpoint  
and bin size

3. Enter number of decimal places for data output

2. Enter Reporting interval for input data

Input data frequency chart (blue line)  
and predicted distribution (pink line)

Analysis  
outputs (green)

Antilog  
outputs. If log  
data as input.

1. Enter data in this  
column. Up to 60,000  
data points

5. Select data points for inclusion in calculation  
(x). Selected data on graph shown with red circle.

6. Adjust values for bin size and data  
midpoint (4) and included data (5) to  
give best fit for line and to assess  
robustness.

Line of best fit through included data (orange  
line). Slope gives SD, crossing point of green  
line gives midpoint (+H/2)

**BHATTACHARYA ANALYSIS SPREADSHEET**  
Version 1.2 (G Jones, (02) 8382-9160, g.jones@stvincemine.com.au)

BHAT PARAMETERS		Database Criteria	
Accepts up to 39,990 data points	Midpoint: 90	Upper: 130	Lower: 140
Blue = inputs	Bin Size (h): 10	DATA: >130	DATA: <=140
Green = outputs	Decimal PI output: 0	DATA: >140	DATA: <=150
	Reporting Int of Data: 10	Dcount: 28	Dcount: 22
		Midpoint of binned data: 150	Midpoint of binned data: 150
		Number: 1101	Number: 1101
		SD: 179.6658	SD: 179.6658

DATA	Count	Antilog	Include
80	1169	1169	
80	99.7	5.0119E+99	
90	90	1E+90	
110	Bhat centre	83.1	1.25893E+83
180	SD	65.2	1.58489E+65
90	Bhat SD	13.4	2.51189E+13
160	Lowest	20	1E+20
1350	Highest	1350	#NUM!
70			x
90			x
70	Parametric range	260.8	
140	-2SD	-30.7	1.99526E-31
100	+2SD	230.1	1.2589E+230
110	Non-param. range	160	
100	2.5th centile	60	1E+60
110	97.5th centile	220	1E+220
110	Bhattacharya range	53.7	
100	2.5th Centile (-2SD)	56.3	1.99526E+56
60	97.5th centile (+2SD)	110	1E+110
120	95th Centile (+1.65SD)	105.3	1.9953E+105
90			
100	Bhat r	-0.998	
320	Bhat %	78%	
90	Kurtosis	136.491	>3 = "peaked"
130	Skew	9.351	
70	Middle	90	
100	Bin Size (h)	10	
50	%>B UL	16.5%	>110
60	%<B LL	1.5%	<56.3
80			

# David Rhodes – EP Evaluator

Print Preview

Contents

- Result
- Aggreg

### EP Evaluator

Client by: Gamma-Dynacare Medical Laboratories

Result  
creat adult male 211

#### Reference Interval Estimation: Combined

Central 95% Interval (N = 33516)					
	Value	Lower 90% CI	Upper 90% CI	Confidence Ratio	
Nonparametric (CLSI C28-A)	65	65 to 65	161	159 to 163	0.02
Alternatives:					
Transformed Parametric	61	61 to 61	141	140 to 141	0.01
Parametric	51	51 to 51	139	139 to 140	0.01

Confidence Limits for Nonparametric CLSI C28-A method computed by exact binomial.

#### Histogram

Selection Criteria:  
Bands: None  
Filter: None

Stats:  
Mean: 85.1  
SD: 23.5  
Median: 91.0  
Range: 29 to 210  
N: 33516 of 33516  
Data strikes: 10  
Discs: 0  
Central 95% Index: 67.9 to 3279.1

Actual: 10/10  
Exp. Date: 23 JUN 2006

#### Probability Plot (Original Data)

From Gaussian 50%

#### Probability Plot (Transformed Data)

From Gaussian 50%

#### Normalizing Transformation

Exponent	0.00
Constant	0.00

Accepted by: \_\_\_\_\_ Date: \_\_\_\_\_  
Signature \_\_\_\_\_

EP Evaluator 2.0.0.24  
Default Printed: 24 Jul 2006 10:55:42  
Copyright 1997-2005 Bentley

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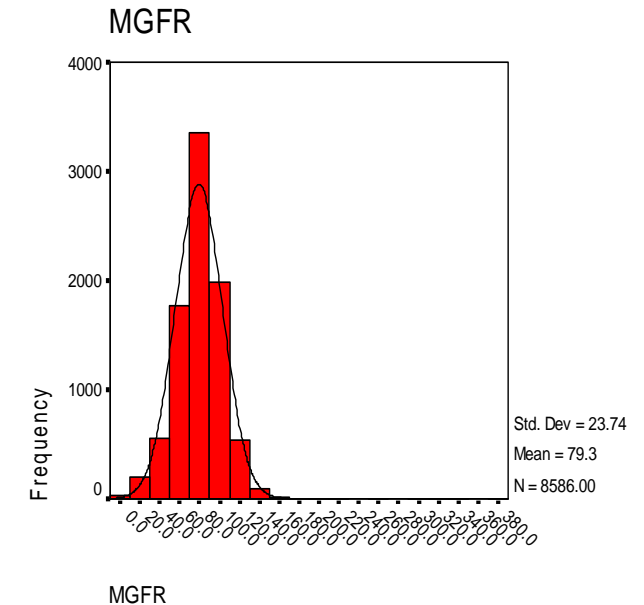
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# SPSS Inc – Output File

## Statistics

		MCR	MGFR	MAGE	FCR	FGFR	FAGE
N	Valid	8586	8586	8627	10747	10747	10819
	Missing	2233	2233	2192	72	72	0
Mean		73.5320	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	96.0000	93.0000	70.0000	83.0000	95.0000	70.0000
	97.5	12.0000	24.0000	86.0000	55.0000	29.0000	89.0000

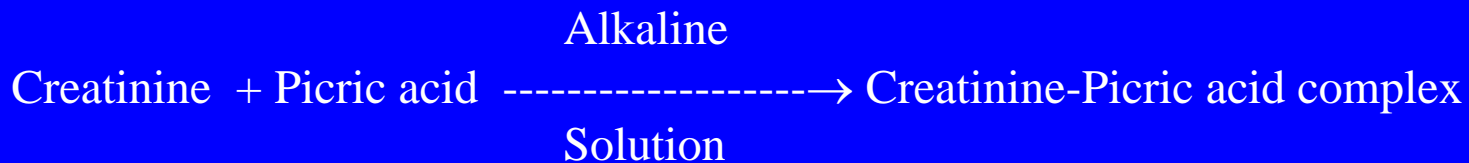


# Our Results – Post eGFR Implementation Mar 2006

- 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:



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

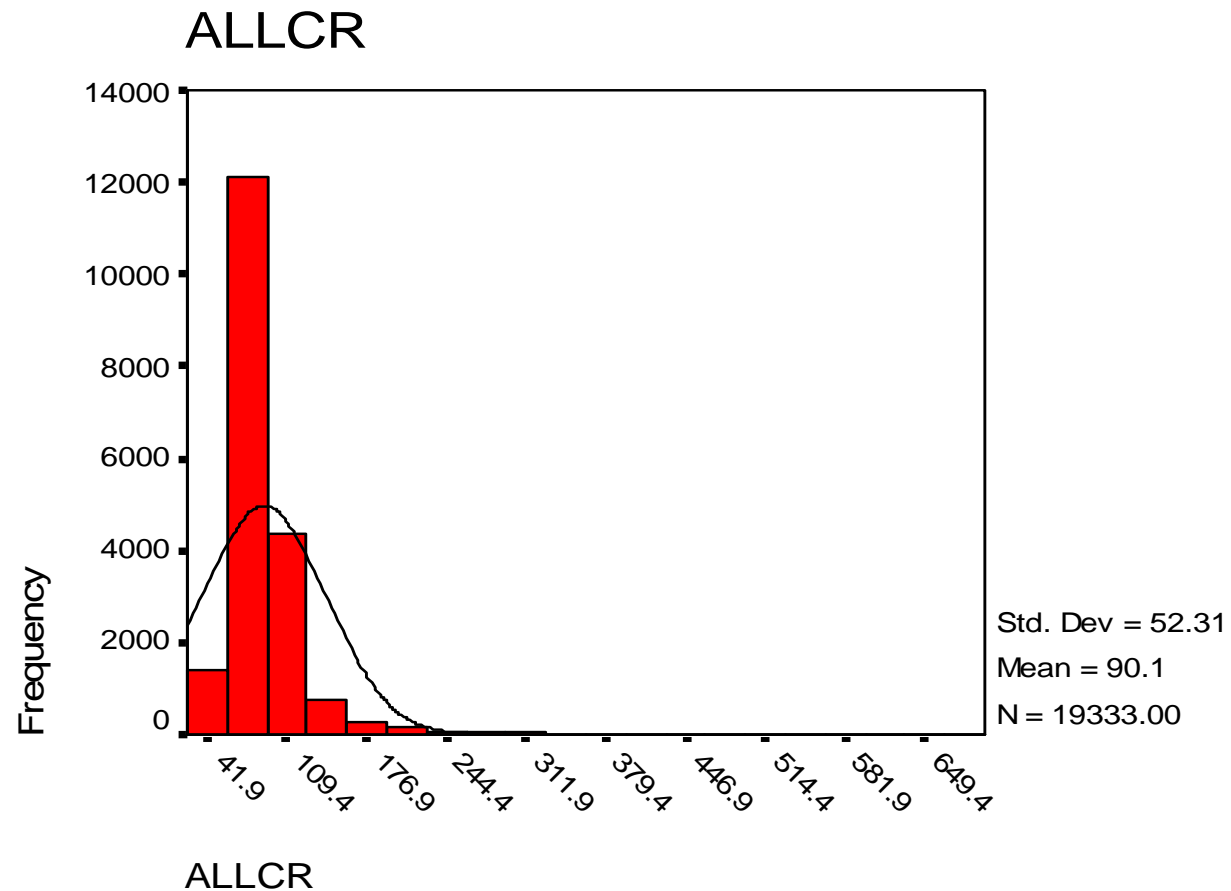
IDMS traceable Creatinine (cCr) was derived from the regression equation:

$$\text{cCr} = 1.043 \times \text{Modular Creatinine} + 1.695 \text{ (DigitalPT, formerly HealthMetrx).}$$

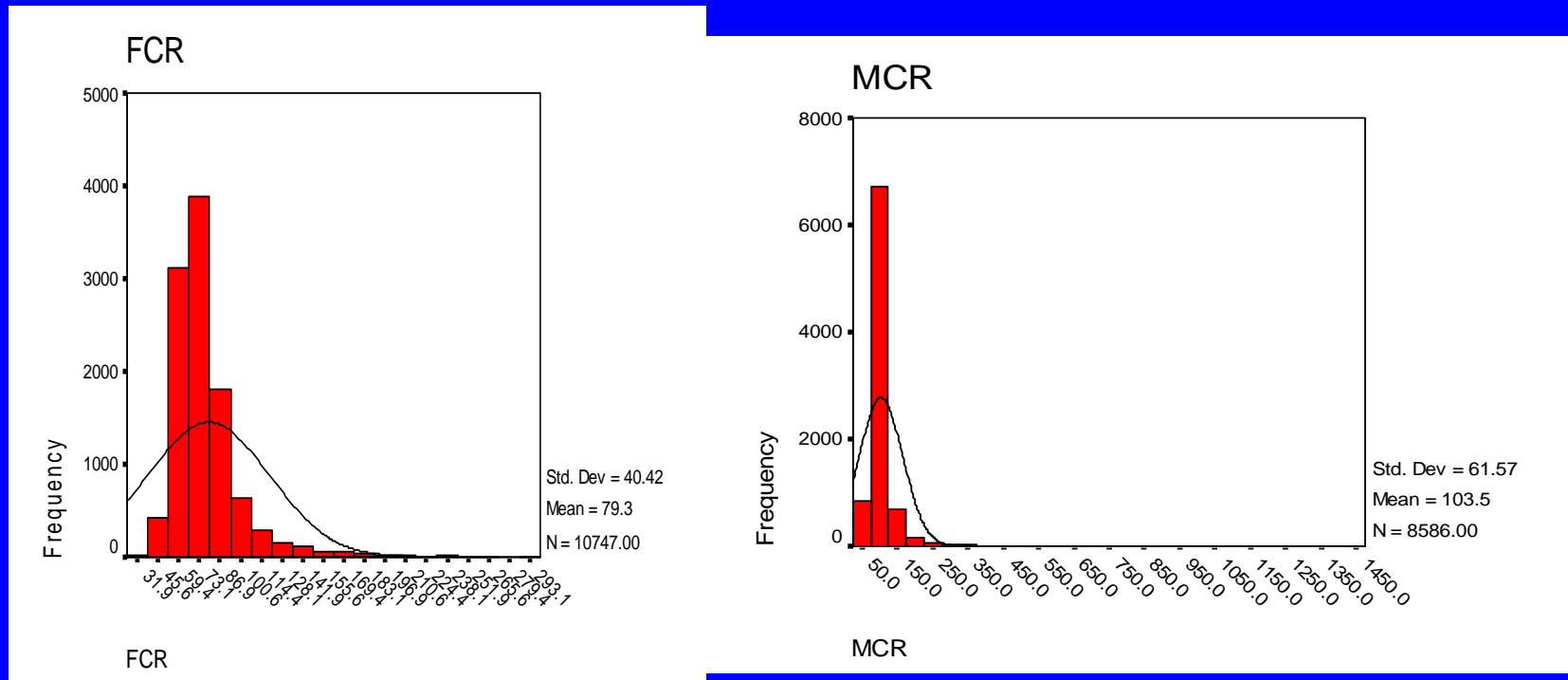
2. The eGFR was calculated using the following equation (MDRD):

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

# Distribution Curves Creatinine – SPSS Output



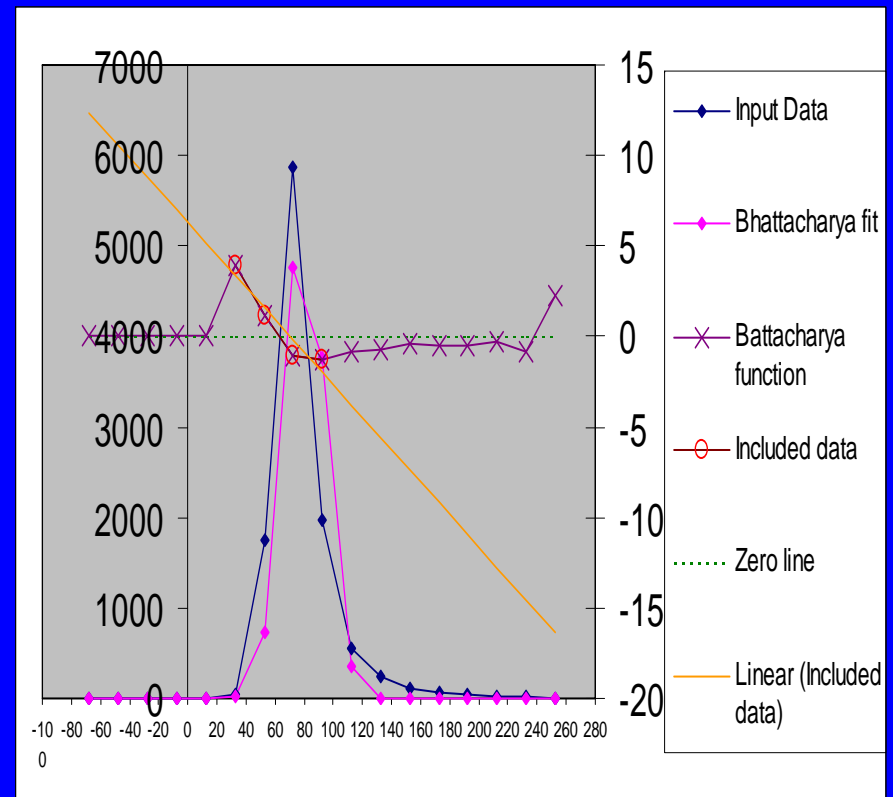
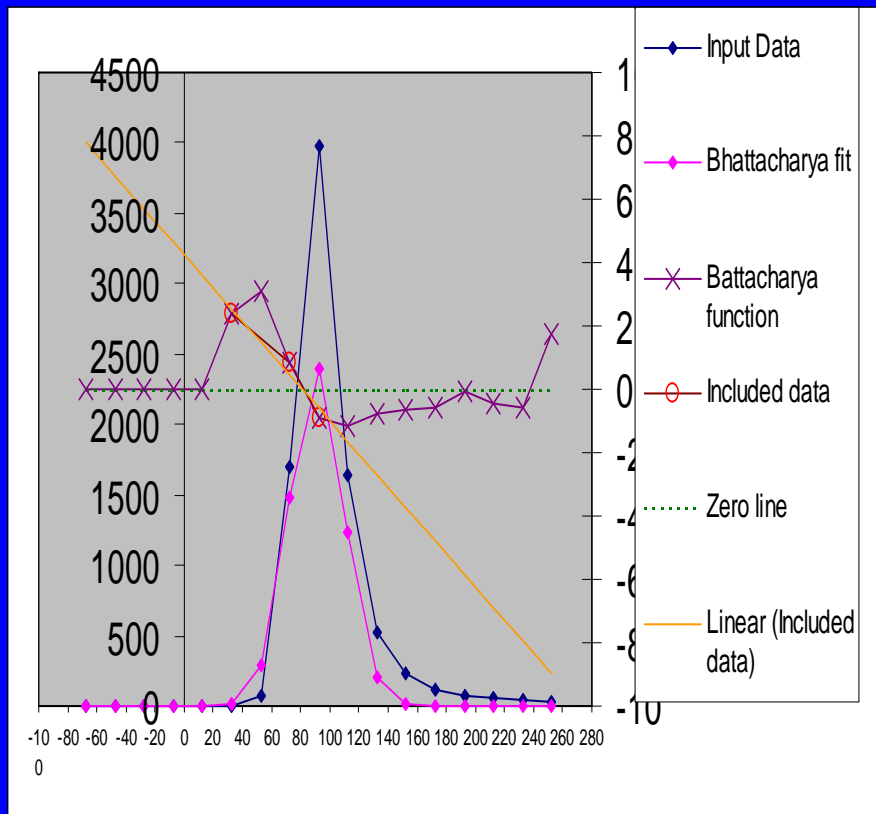
# Distribution Curves Creatinine – SPSS Output



# Creatinine – Central 95<sup>th</sup> 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 95<sup>th</sup> Percentile RI - Females

<b>Age (y)</b>	<b>Bhatt(raw)</b>	<b>SPSS (raw)</b>	<b>EP Eval (trim)</b>
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 95<sup>th</sup> Percentile RI EP Evaluator, Trimmed

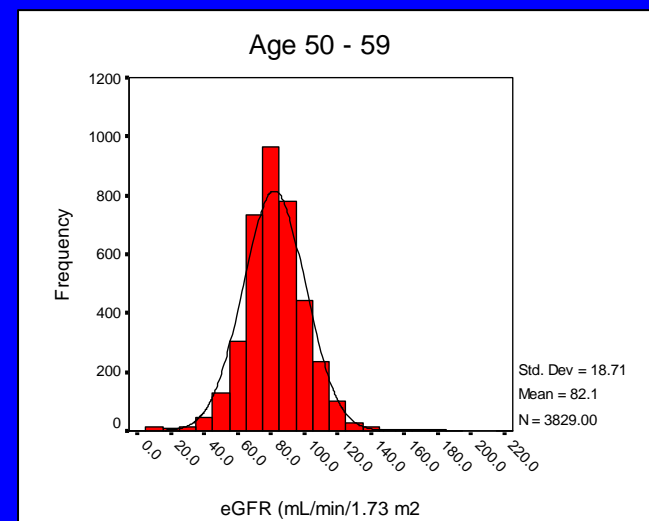
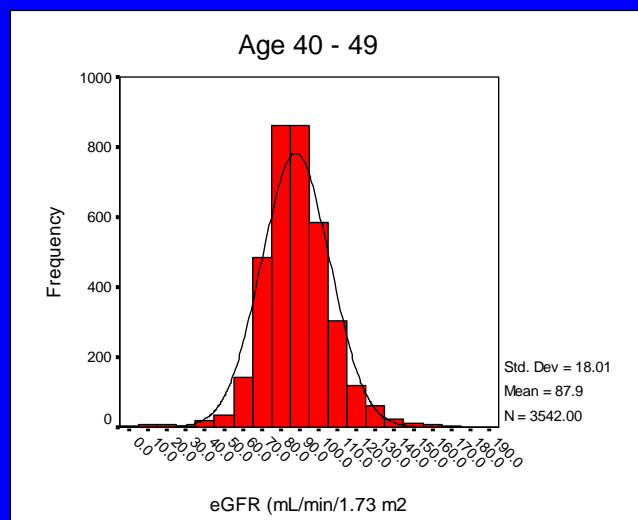
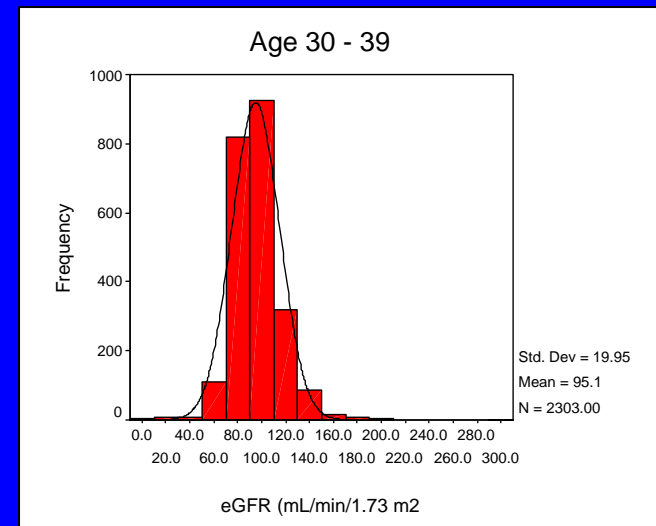
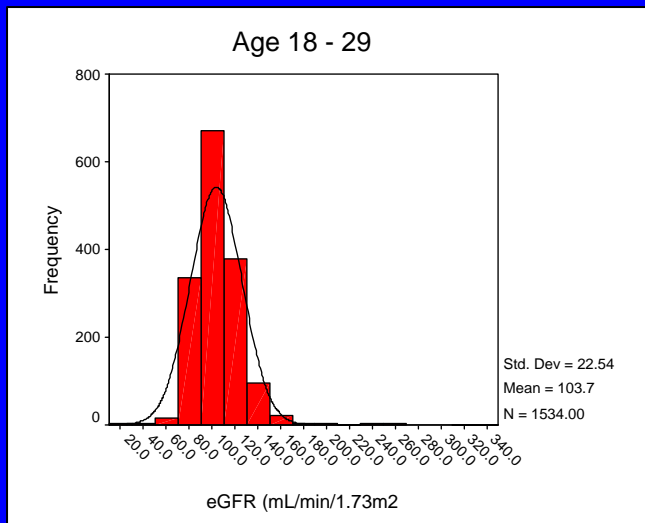
Age (y)	Males	Females
19 - 30	59 – 105	44 - 82
30 - 39	60 - 116	44 – 85
40 - 49	60 – 117	46 - 90
50 -59	59 – 123	46 - 96
60 - 69	57 – 146	45 – 113
70+	55 - 196	45 - 150
19 – 70+	55 - 147	43 – 113 (NP 46 – 133)

# Creatinine – 95 % Range – Scottish Data

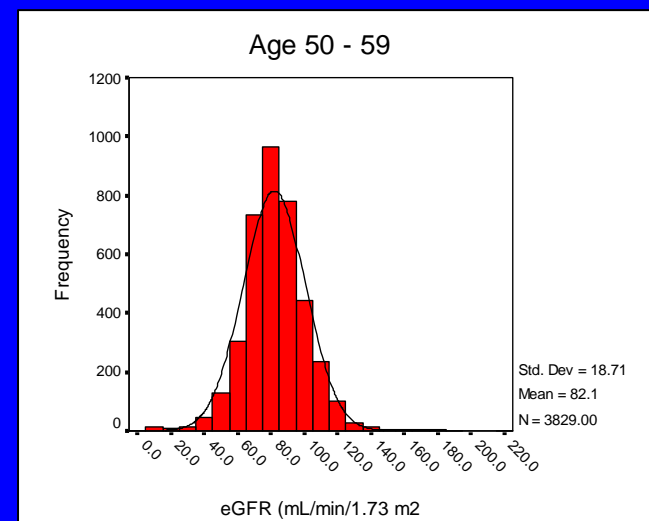
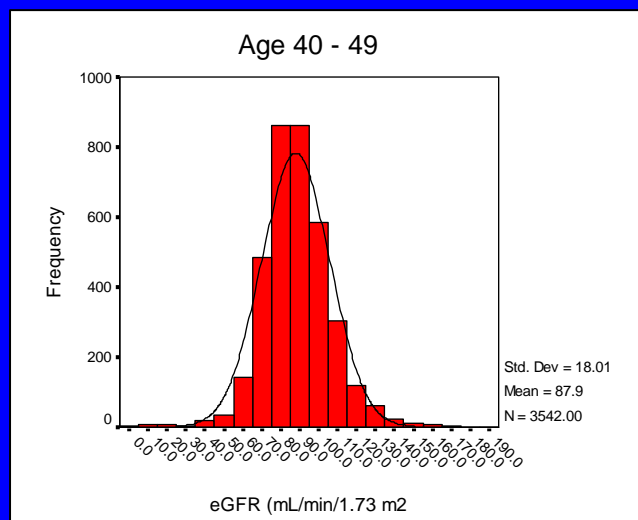
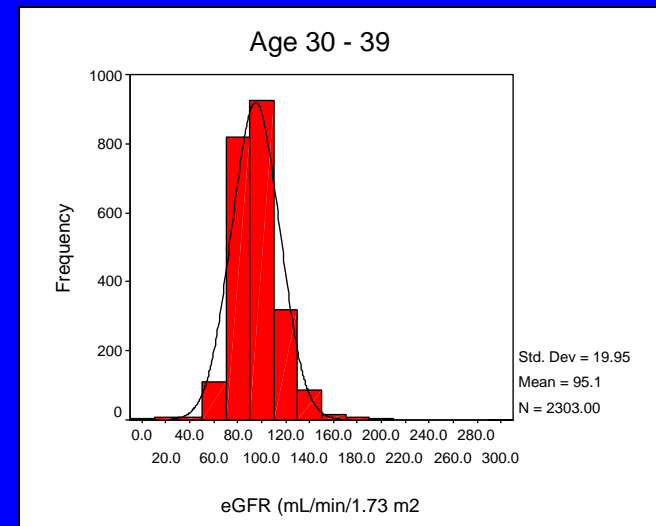
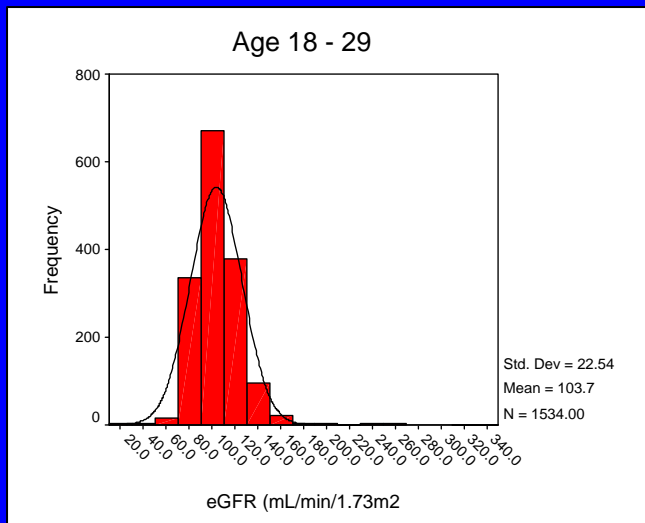
(Gardner & Scott JCP 1980; 33:380 – 385)

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

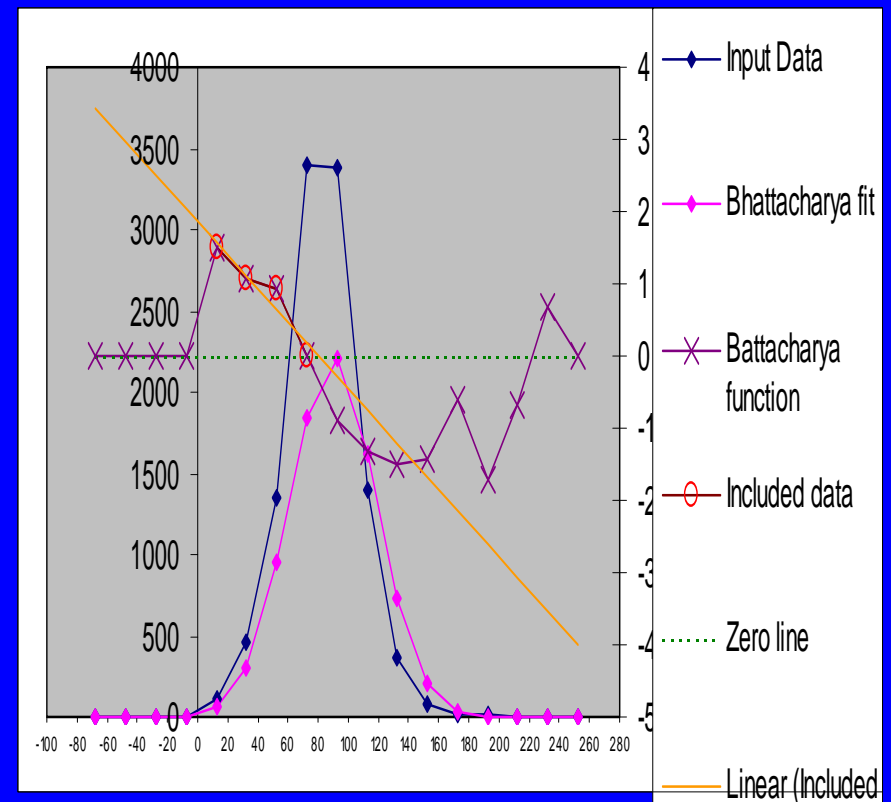
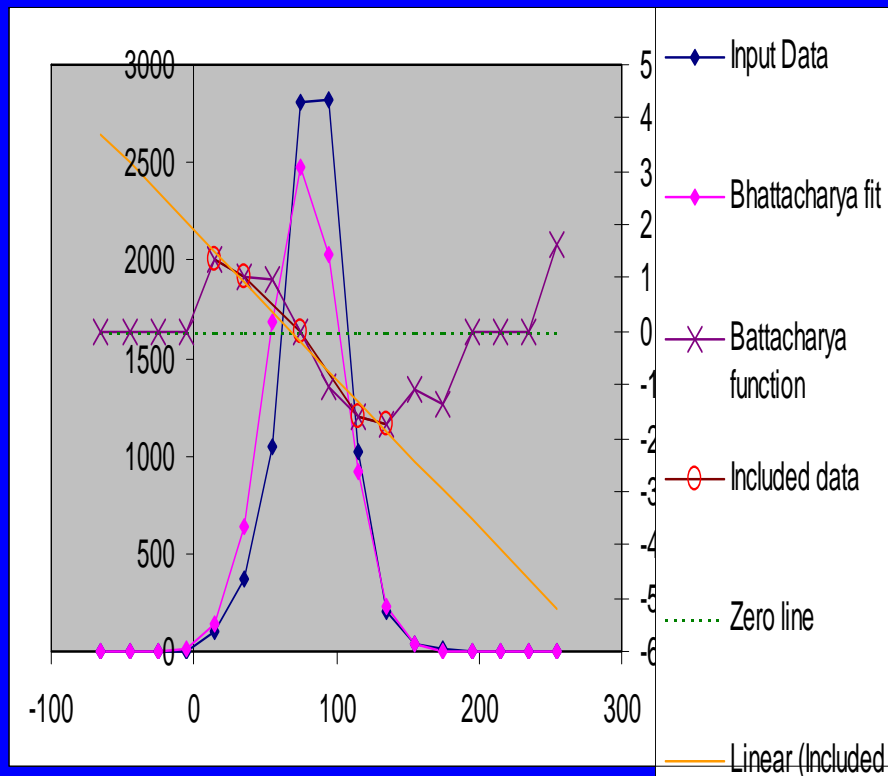
# Distribution Curves eGFR – SPSS Output



# Distribution Curves eGFR – SPSS Output



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



## eGFR - Mean & 95<sup>th</sup> Percentile RI – Males & Females (combined; raw; SPSS)

Age, years		eGFR (mL/min/1.73 m <sup>2</sup> )	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

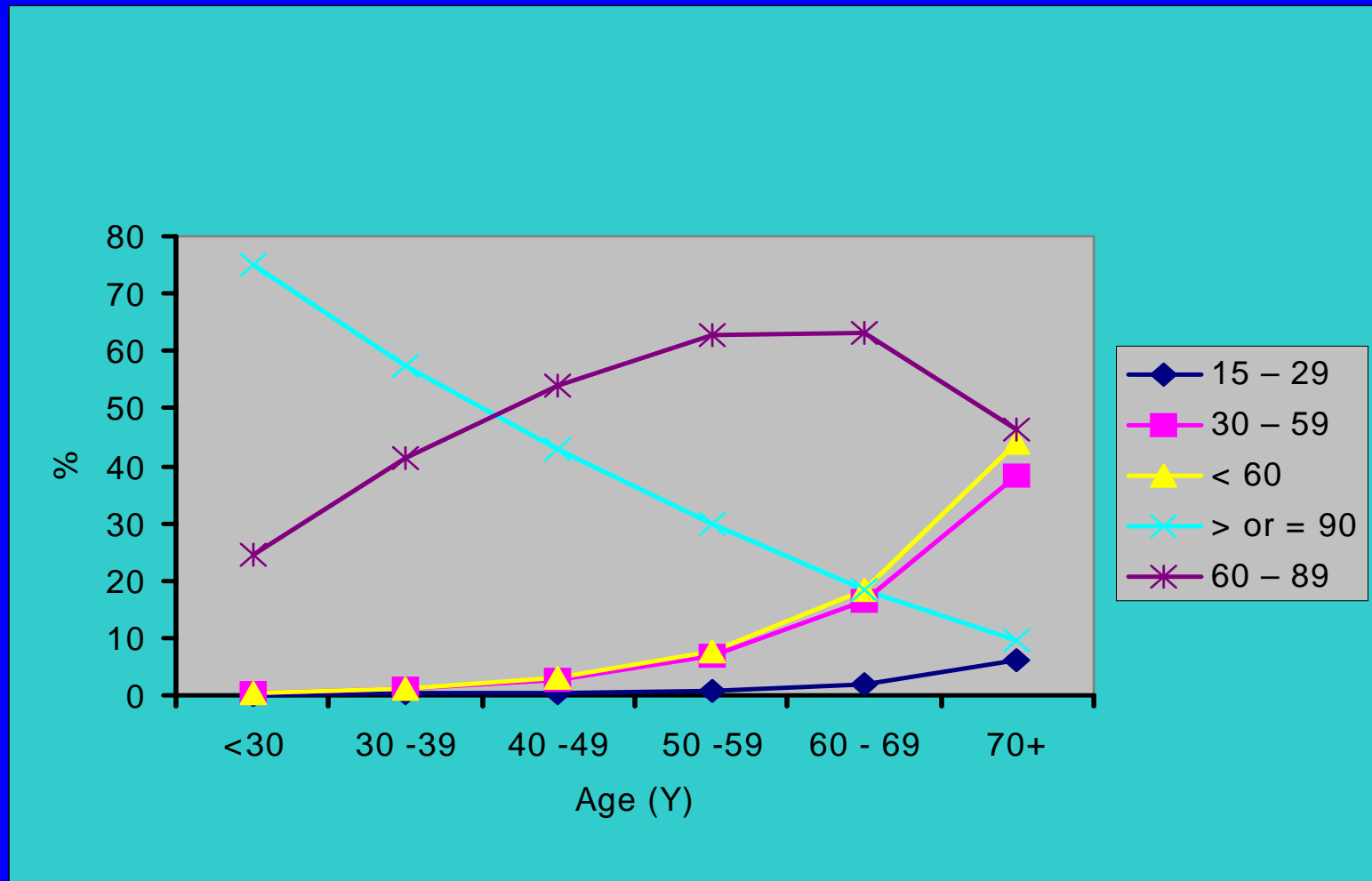
Year (age)	Creat umol/L	eGFR (w/o EF) Orig	eGFR (w/o EF) Revised	eGF (w EF) Orig	eGFR (w EF) Revised	Dep MDRD, Creat RI used,
1985 (39)	120	61.9	58.2	74.9	70.5	1. Delta: 4 –5 umol/l in 20 yrs
1986 (40)	122	60.4	56.9	73.6	68.8	2. All creat high, GDML RI
1987 (42)	124	59.0	55.5	71.4	67.2	3. No CKD, Orig MDRD w EP
1999 (53)	129	53.6	50.4	64.8	61.0	4. Stage 1 or 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

- **Stevens LA** et al., NEJM 2006; 354: 2473 – 83
- **Verma M** et al, Ind J Clin Biochem 2006; 21: 90 - 94
- **Garg AX** et al., J Am Soc Nephrol 2005; 16: 1433 – 1439.
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- **Westgard J**, [www.westgard.com](http://www.westgard.com)

## Acknowledgements

- Dr Jones, St Vincent Hospital, Sydney
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