Implementation of CKD-EPI for calculation of eGFR at S.V.U.H.

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Glomerular Filtration Rate

- Just one of the kidneys functions - decreased GFR sign of kidney disease
- Measured using plasma clearance of exogenous markers
- Estimates (eGFR) based on:
  - Endogenous filtration markers
  - Variables associated with non-GFR determinants of concentration
- eGFR more sensitive and accurate than filtration marker concentration alone
- Inaccuracies between eGFR and GFR
  - Inaccuracies in endogenous filtration marker assays
  - Differences in development datasets vs 'real-life'
- Imprecision in estimates
  - Random variation in surrogates of non-GFR determinants

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Modification of Diet and Renal Disease Study eGFR

- Relationship between creatinine and GFR non-linear
- Multicentre, controlled trial; evaluated the effect of dietary protein restriction & BP control renal disease progression
- Formula based on 1,628 CKD patients
  - GFR <60 mL/min/1.73m^2 (^{125}I-iothalamate clearance)
  - 4 variable equation; age (≥18 years), gender, ethnicity, serum creatinine conc.
  - Modified - differences in creatinine methods
- At SVUH, Roche creatinine enzymatic assay standardised to ID-MS

$$175 \times (\text{SCr } \mu\text{mol/L} \times 0.011312)^{-1.154} \times (\text{Age})^{-0.203} \times 0.742 \text{ (if female)} \left[\times 1.212 \text{ (if black)} \right]$$

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Chronic Kidney Disease Epidemiology Collaboration eGFR formula

- To be as accurate as MDRD at low GFR AND more accurate at higher GFR
- Applies different coefficients to the same 4 MDRD variables
- Developed using 8,254 subjects
  - Wide range of kidney function
  - High number of black participants (32% vs 12% MDRD)
  - GFR measured using ^{125}I-iothalamate clearance
  - Serum creatinine traceable to ID-MS
- Does not overcome the limitations inherent to creatinine based eGFR

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CKD-EPI gender based serum creatinine equations for eGFR

Gender	Serum [creatinine]	>18 years
Male	≤80 µmol/L	$141 \times (\mathbf{SCr}/80)^{-0.411}) \times (0.993)^{\mathbf{Age}}$
	>80 µmol/L	$141 \times (\mathbf{SCr}/80)^{-1.209}) \times (0.993)^{\mathbf{Age}}$
Female	≤62 µmol/L	$144 \times (\mathbf{SCr}/62)^{-0.329}) \times (0.993)^{\mathbf{Age}}$
	>62 µmol/L	$144 \times (\mathbf{SCr}/62)^{-1.209}) \times (0.993)^{\mathbf{Age}}$

[x 1.159, **if black**]

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Kidney Disease Improving Global Outcomes GFR and ACR categories

CKD diagnosed over 3 months

GFR categories (ml/min/ 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90	No CKD without markers of kidney damage		
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Increasing risk

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

Increasing risk

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CKD-EPI versus MDRD eGFR: validation dataset

Variable and Equation	All Patients	Patients with estimated GFR <60 ml/min/1.73 m^2	Patients with estimated GFR ≥60 ml/min/1.73 m^2
Median difference (95% CI), mL/min per 1.73 m2[†]			
CKD-EPI	2.5 (2.1 - 2.9)	2.1 (1.7 - 2.4)	3.5 (2.6 - 4.5)
MDRD Study	5.5 (5.0 - 5.9)	3.4 (2.9 - 4.0)	10.6 (9.8 - 11.3)
Interquartile range for differences (95% CI) - mL/min per 1.73 m^2[‡]			
CKD-EPI	16.6 (15.9 - 17.3)	11.3 (10.7 - 12.1)	24.2 (22.8 - 25.3)
MDRD Study	18.3 (17.4 - 19.3)	12.9 (12.0 - 13.6)	25.7 (24.4 - 27.1)
P_{30} (95% CI) - %[§]			
CKD-EPI	84.1 (83.0 - 85.3)	79.9 (78.1 - 81.7)	88.3 (86.9 - 89.7)
MDRD Study	80.6 (79.5 - 82.0)	77.2 (75.5 - 79.0)	84.7 (83.0 - 86.3)

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; GFR = glomerular filtration rate; MDRD = Modification of Diet in Renal Disease.

[*] To convert GFR from mL/min per 1.73 m2 to mL/s per 1.73 m2, multiply by 0.0167.

[†] Median difference refers to measured GFR minus estimated GFR.

[‡] Interquartile range refers to the 25–75th percentile.

[§] P30 refers to percentage of GFR estimates that are within 30% of measured GFR.

Modified from Levey *et al* Ann Intern Med, 2009 – Vol 50, no. 9 pp 604

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Comparison of eGFR by MDRD versus CKD-EPI

- **Better accuracy**: classification of GFR stage correct more often than classification by MDRD
  - 63% vs 34%, p<0.001

- **Reduced CKD prevalence**: produces higher eGFRs at values >30 mL/min/1.73m^2 vs MDRD
  - Lower CKD prevalence; 11.5 vs 13.1 %
  - Reclassification more evident in <65 years, females and non-blacks
    - Better eGFR and fewer co-morbidities means reclassification = better outcomes

- **CKD prevalence still high in elderly**

- **More targeted healthcare resources**

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CKD-EPI eGFR and the guidelines

- Serum creatinine and eGFR to be reported
- **KDIGO Clinical Practice Guideline (2012)**
  - Report eGFR in adults using the 2009 CKD-EPI creatinine equation
    - An alternative is acceptable if it demonstrates improved accuracy to this equation
- **NICE CKD in adults: assessment and management Clinical Guideline 182 (2014)**
  - CKD-EPI eGFR based on serum creatinine
    - Calibration traceable to SRM; zero bias to ID-MS
- **ACB statement (2016)** supports the NICE recommendations
  - Suggests an implementation date of no later than April 2017

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Setting up CKD-EPI on APEX: Step 1
Derivation of an exponential figure (EEPI) by rule

Gender	Serum [creatinine]	
Male	≤80 µmol/L	$141 \times (\mathbf{SCr}/80)^{-0.411} \times (0.993)^{\mathbf{Age}}$
	>80 µmol/L	$141 \times (\mathbf{SCr}/80)^{-1.209} \times (0.993)^{\mathbf{Age}}$
Female	≤62 µmol/L	$144 \times (\mathbf{SCr}/62)^{-0.329} \times (0.993)^{\mathbf{Age}}$
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Setting up CKD-EPI on APEX: Step 2
Gender specific eGFR using the derived exponential

```
If  NAGE   GT  18        AND  SEX    EQ  M
Formula (a) :
141*((A/79.56)**B)*(0.993**NAGE)
To enter another set of Conditions/Formulae use F12 on Formula field
```

	Test	Low	High	Error		Test	Low	High	Error
A	CRE				G				
B	EEPI				H				

OR

```
If  NAGE   GT  18        AND  SEX    EQ  F
- then use Formula (b) :
144*((A/61.88)**B)*(0.993**NAGE)
or - either use Formula (c) - if one or both conditions fail (default)

   - or Condition Failure Comment : NEGFR
```

```
Description : Patient gender not specified. Unable to calculate EGFR
```

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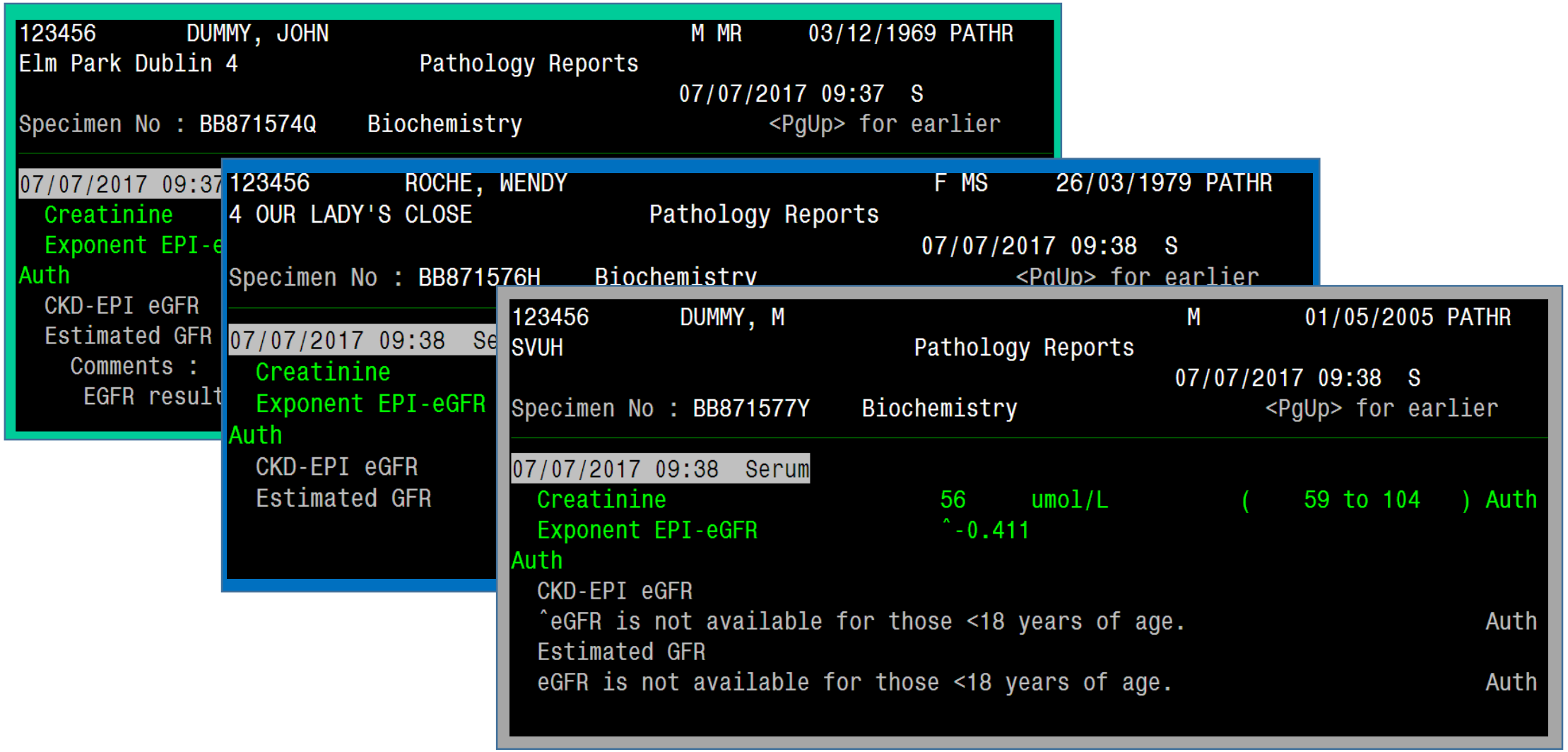
'Dual reporting' of MDRD eGFR and (suppressed) CKD-EPI eGFR



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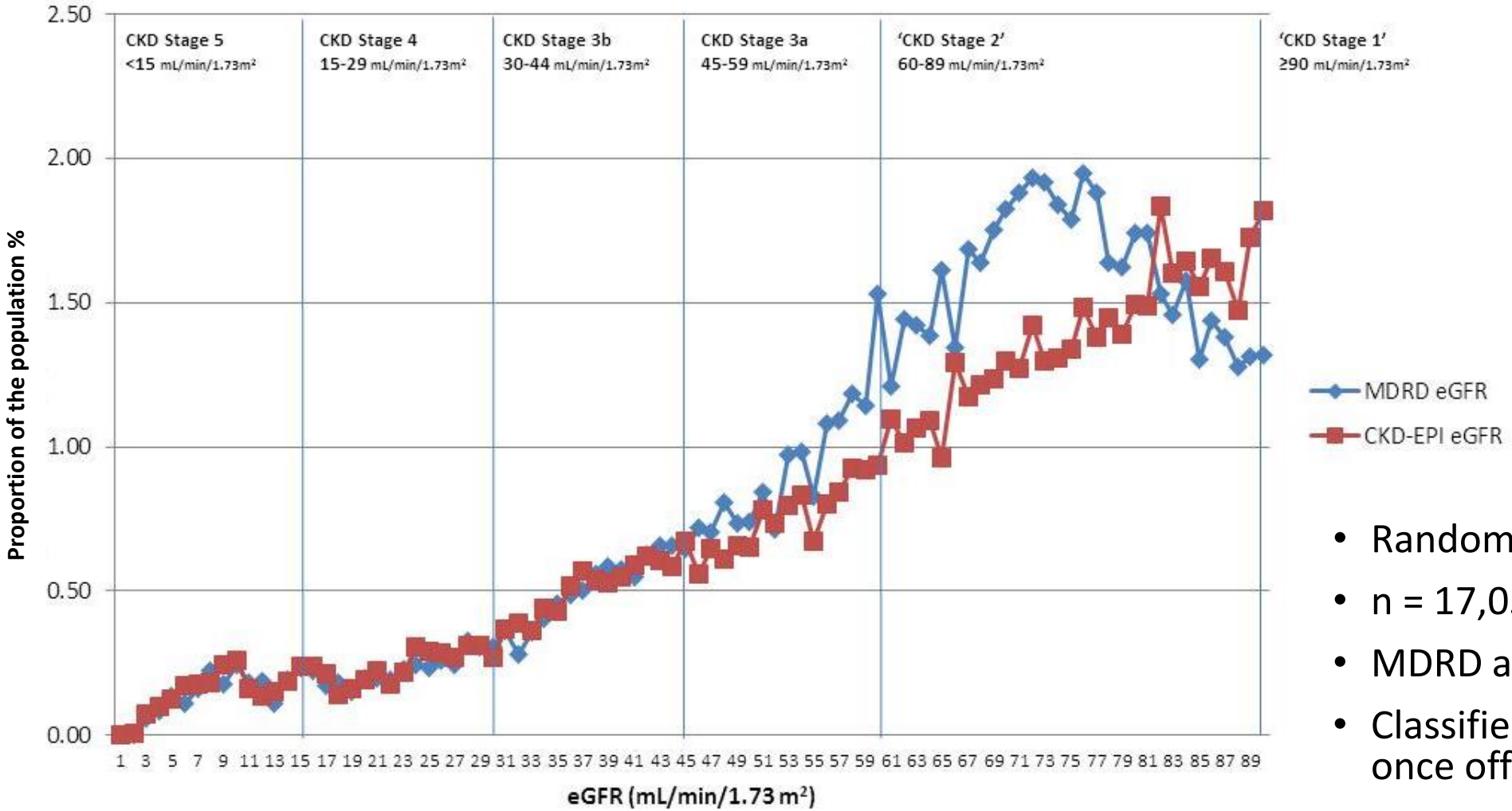
eGFR and CKD stage by MDRD and CKD-EPI equations



- Random 2 weeks examined
- n = 17,055
- MDRD and CKD-EPI paired eGFR
- Classified to CKD stage 1-5 despite once off measure
- eGFR over 90 reported as >90 mL/min/1.73m^2

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Reclassification of eGFR stage: CKD-EPI vs MDRD eGFR

- 'Reclassification' - if CKD stage changed with CKD-EPI eGFR
- 14,150 (**83%**) patients remained in the same CKD stage
- 2,905 (**17%**) patients were reclassified
  - 13.6% had a better eGFR
  - 3.4% had a worse eGFR

	Number (%)	Reclassified by CKD-EPI; Number (%)
All	17,055	2,905 (17%)
<65 years	9,210 (54%)	2,134 (23.2%) ←
≥65 years	7,845 (46%)	771 (9.8%)
Male	8,127	1,200 (14.7%)
<65 years	4,279 (52.7%)	827 (19.3%)
≥65 years	3,848 (47.3%)	373 (9.7%)
Female	8,928	1,705 (19.1%) ←
<65 years	4,931 (55.2%)	1,307 (26.5%) ←
≥65 years	3,997 (44.8%)	398 (10%)

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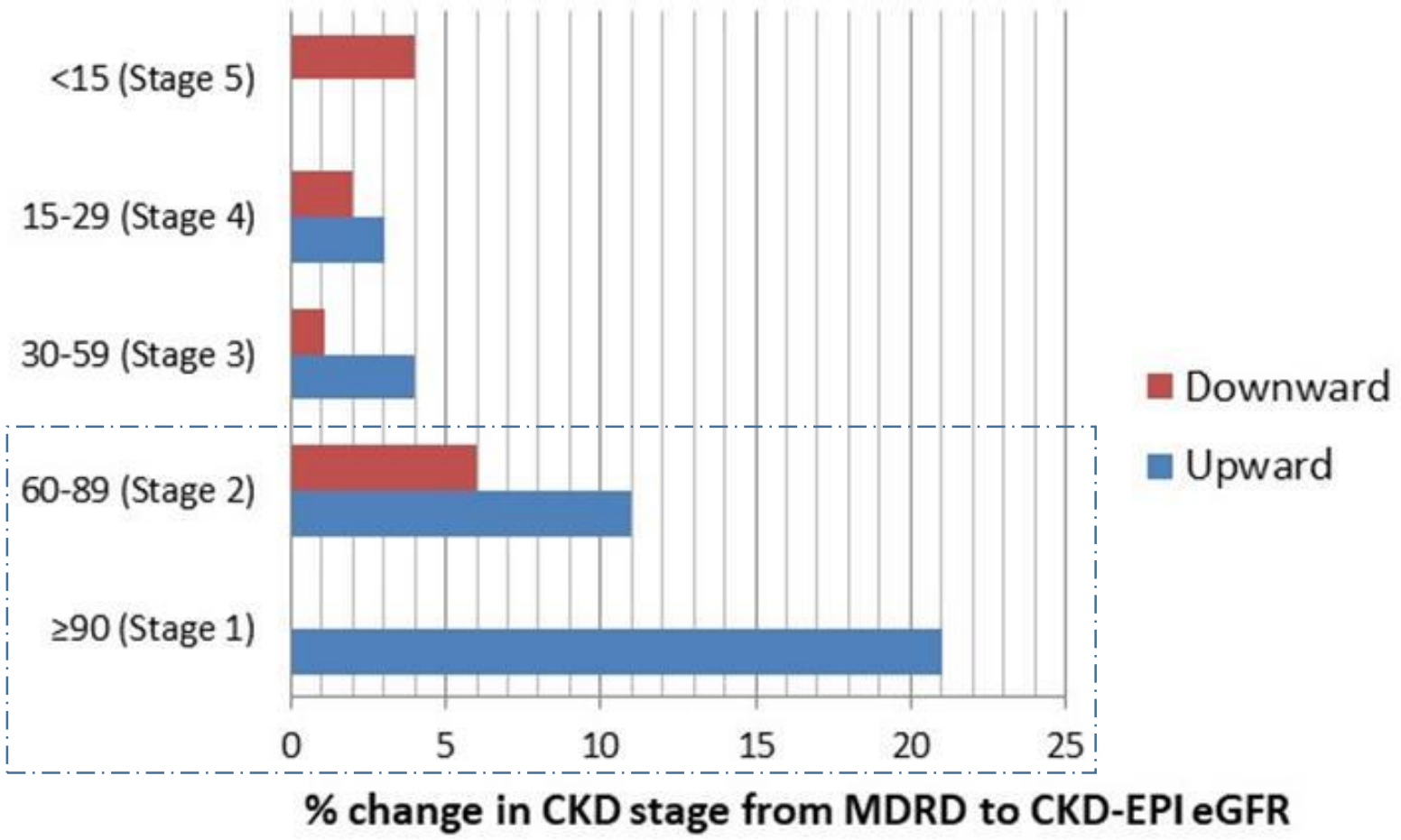
Reclassification of eGFR stage: CKD-EPI vs MDRD eGFR

CKD stages 1&2 need information on albuminuria



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CKD stages 3 to 5: CKD-EPI vs MDRD eGFR

	CKD stage 3-5 classification; % of population			Change in CKD (%) due to CKD-EPI
	MDRD & CKD-EPI	MDRD	CKD-EPI	
All (17,055)	23.4%	25.8%	23.9%	324 (1.9%) ↓
<65 years (9,210)	8.3%	11.5%	8.3%	295 (3.2%) ↓
≥65 years (7,845)	41.2%	42.7%	42.3%	31 (0.4%) ↓
≥75 years (4,394)	50.8%	51.1%	53.1%	88 (2.0%) ↑

- CKD-EPI eGFR resulted in 324 less patients classified with CKD
  - 91% were <65 years
- Of the ≥75 year olds, 2% more patients were classified with CKD using CKD-EPI eGFR
  - These 88 patients would not have been classified by MDRD eGFR
- The increase in CKD diagnosis in the ≥75's - ? compounding risks / faster progression

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APEX reports

```
Creatinine                    96      umol/L          (    59 to 104    )
  Comments :
   Please note:from 07/08/2018 Estimated GFR will be
   calculated using the CKD-EPI formula.
   Please refer to MEMO-EXTCHEM05 EPI dated 30/07/2018
Exponent EPI-eGFR             ^-1.209
Estimated GFR                 67      mL/min/1.73sq.m
```

```
Creatinine                    265     umol/L          (    59 to 104    )
  Comments :
   Please note:from 07/08/2018 Estimated GFR will be
   calculated using the CKD-EPI formula.
   Please refer to MEMO-EXTCHEM05 EPI dated 30/07/2018
Exponent EPI-eGFR             ^-1.209
Estimated GFR                 19      mL/min/1.73sq.m
  Comments :
   EGFR result biochemically consistent with CKD stage 4.
```

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Changing to CKD-EPI eGFR at S.V.U.H.

1. DRIVERS FOR CHANGE

- Guidelines
  - Increased accuracy in individuals with better renal function
  - Reduces prevalence of CKD (focused workload)
- Renal physicians on board
  - Cumulative report requested (same test code)

2. COMMUNICATION

- Discussed in-house; meetings, emails and internal memo
- Memo sent to users with lab contact details
  - Change over date provided
  - Indicated MDRD eGFR was being replaced and why *i.e.* adoption internationally, improved accuracy

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Changing to CKD-EPI eGFR at S.V.U.H.

3. IMPLEMENTATION INTO IT SYSTEM

- Impact on the IT system was minimal
  - Required dialog with CSC/iSOFT
  - Same test code, comments, results autovalidated

4. IMPACT?

- Differences observed by clinicians is equivalent to reporting any analyte using a new assay
- Minimal; no feedback/complaints = seamless success?

5. UNDERSTANDING?

- Assumption made that users understand limitations of creatinine based formulae
- Ideally requires on-going educational effort: strengths versus weaknesses

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