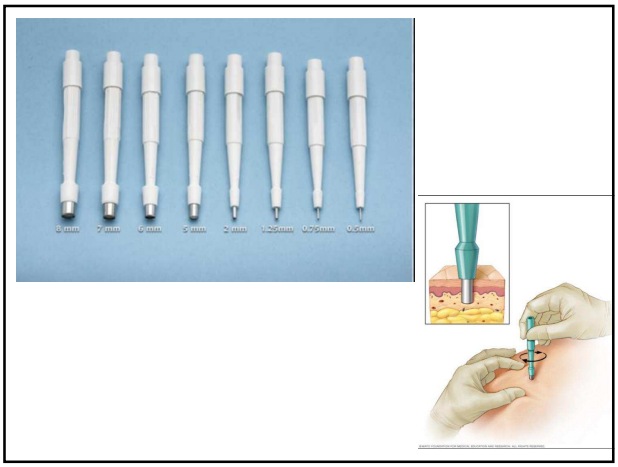
Pathology

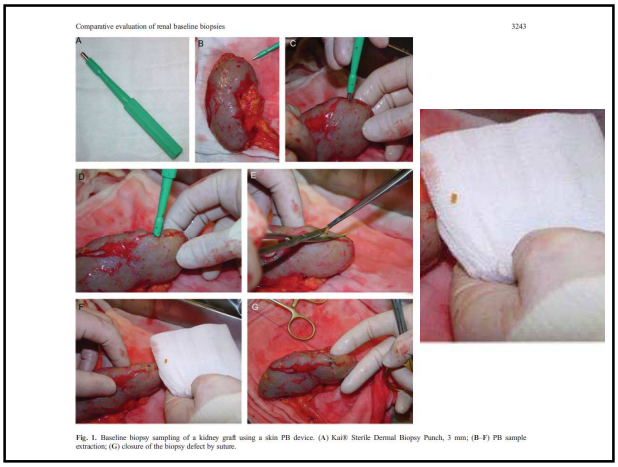
Consortium of 15-17 renal pathologist

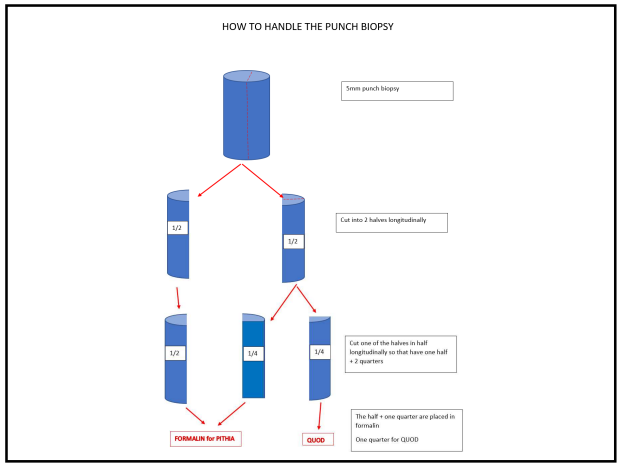
- Had several sessions to discuss
- Following Cambridge modification of Remuzzi
- Discussed each variable to define how to do as uniformly as possible
- 30 Cambridge preimplantation biopsies scanned
- All score and work out the Remuzzi
- Interobserver variability determined
- Outlier cases identified to see why difficult
- Outlier pathologist “retrained”

Pathologists

- 3x Birmingham – Desley Neil, Kassi Skordilis, Bindu Vydianath
- 3x Cambridge – Vicky Bardsley, Sathia Thiru, Meryl Griffiths
- 2 x GSTT– Catherine Horsfield, ?Ran Perera
- 2x Barts - Mike Sheaff , Abigail Lee
- Hammersmith – Candice Roufosse
- Newcastle – Katrina Wood
- Coventry – Kishore Gopolakrishnan
- Bristol – Tasos Chatzitolios
- Portsmouth – Natalie Brearley
- Edinburgh – Chris Bellamy







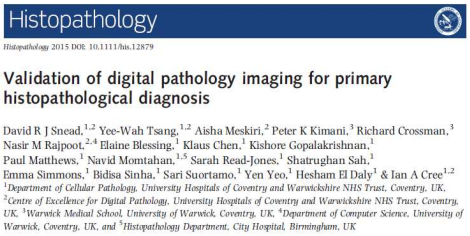
Biopsy sent to scanner centre

- BMS on-call books in biopsy
  - Lab number
- +/- augments fixation
- Process biopsy
- Embedded cut surface down
  - Flat and maximum surface area
- Cut 2 x sections
  - H&E
  - PAS
- Scan and upload WSI to server

Pathology assessment

- BMS contacts Hub (NHSBT duty office) when slides scanning
- Hub contacts on-call pathologist
- Pathologist logs into computer
  - nhs.net email with the request form
    - Identifiers
    - Clinical info
    - Retrieval surgeon and implanting surgeon contact details
  - Login into Slide viewer
    - Downloads reporting proforma
    - Looks at slides
    - Emails report to Hub for distribution
    - +/- phones the implanting surgeon

Scanner


Histopathology

Histopathology 2015 DOI: 10.1111/his.12879

Validation of digital pathology imaging for primary histopathological diagnosis

David R J Snead,[1,2] Yee-Wah Tsang,[1,2] Aisha Meskiri,[2] Peter K Kimani,[3] Richard Crossman,[3] Nasir M Rajpoot,[2,4] Elaine Blessing,[1] Klaus Chen,[1] Kishore Gopalakrishnan,[1] Paul Matthews,[1] Navid Momtahan,[1,5] Sarah Read-Jones,[1] Shatrughan Sah,[1] Emma Simmons,[1] Bidisa Sinha,[1] Sari Suortamo,[1] Yen Yeo,[1] Hesham El Daly[1] & Ian A Cree[1,2]

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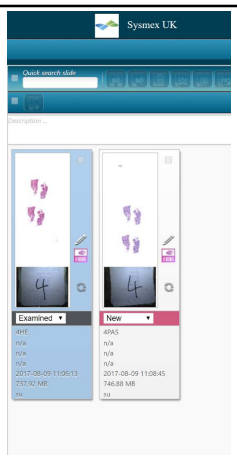
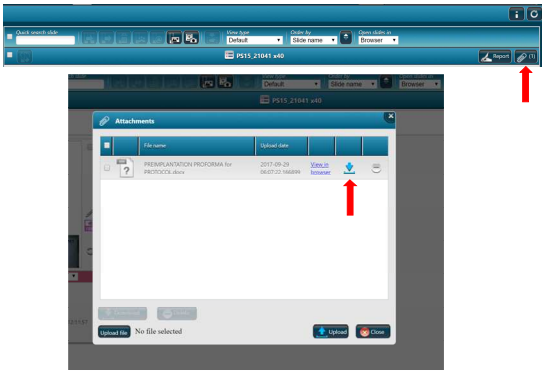
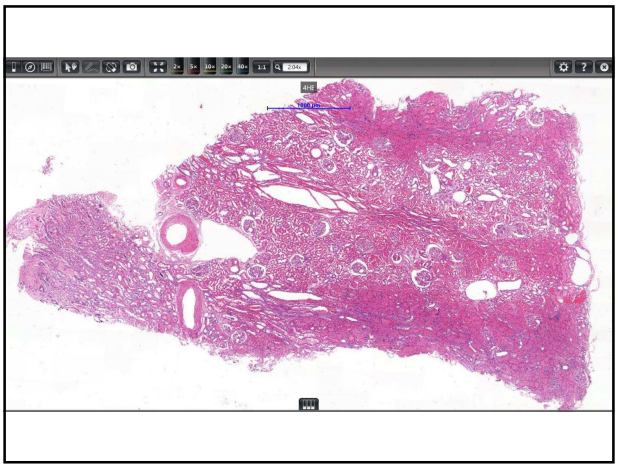
High resolution scanner chosen 0.137µm/pixel (60x)
Best for renal and liver for diagnosis

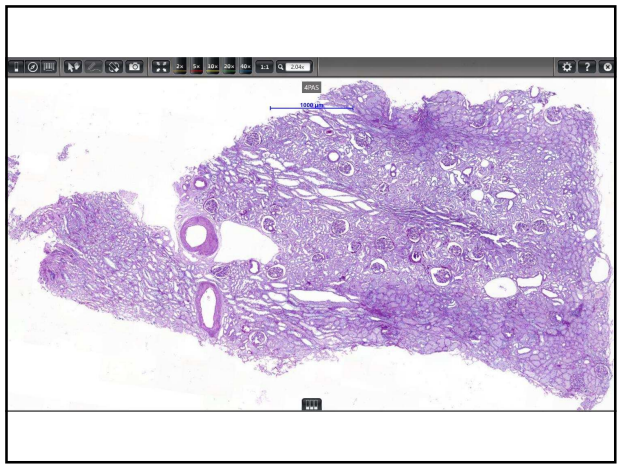
3DHistech scanner

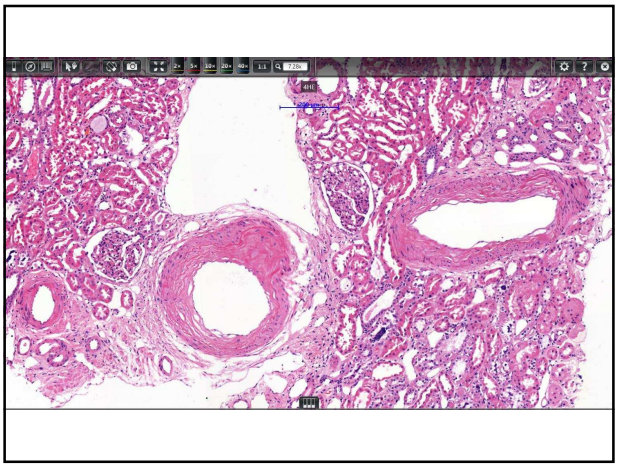
Pannoramic DESK

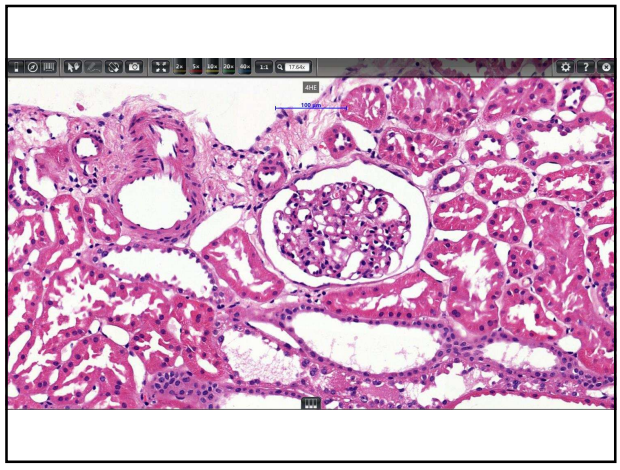












Original Remuzzi variables

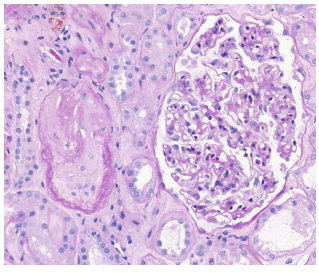
Table 1. Pretransplant biopsy protocol: semiquantitative method of evaluation of slides[a]

Glomerular global sclerosis	
Based on three sections (the first, middle, and last sections, if available); the number of globally sclerosed glomeruli expressed as a percentage.	
0	none globally sclerosed
1+	<20% global glomerulosclerosis
2+	20 to 50% global glomerulosclerosis
3+	>50% global glomerulosclerosis
Tubular atrophy	
0	absent
1+	<20% of tubuli affected
2+	20 to 50% of tubuli affected
3+	>50% of tubuli affected
Interstitial fibrosis	
0	absent
1+	<20% of renal tissue replaced by fibrous connective tissue
2+	20 to 50% of renal tissue replaced by fibrous connective tissue
3+	>50% of renal tissue replaced by fibrous connective tissue
Arterial and arteriolar narrowing	
For the vascular lesions, if the changes are focal, the most severe lesion present gives the final grade.	
0	absent
1+	increased wall thickness but to a degree that is less than the diameter of the lumen
2+	wall thickness that is equal or slightly greater to the diameter of the lumen
3+	wall thickness that far exceeds the diameter of the lumen with extreme luminal narrowing or occlusion
Final grade	
The final grade can range from 0 to a total of 12.	
0 to 3	mild OK for single transplant
4 to 6	moderate OK for double transplant
7 to 12	severe should not be transplanted

[a] Only biopsies with at least 25 glomeruli are considered for slide evaluation. Kidneys with evidence of acute tubular necrosis are not considered for the double transplant. Biopsies are graded as mild if they have 0 to 3 points in total provided they are less than 3 in any one category. Biopsies are graded as moderate if they have 4 to 6 points in total provided they do not have 3 points in more than one category.

Glomerular sclerosis

- >25 gloms (Karpinski >20) – should be 50-75
- G0 no sclerosed gloms
- G1 1% - <20%
- G2 20% - 50%
- G3 >50%
- If 100 gloms
- G1 1GS to 19GS

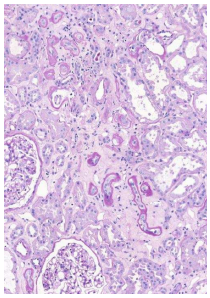


Tubular atrophy

- We are defining tubular atrophy as < 50% diameter of normal tubule (Banff)
- Percent of cortex involved

- TA0 no atrophic tubules
- TA1 >0 - <20%
- TA2 20%-50%
- TA3 >50%

Banff cut off 25%



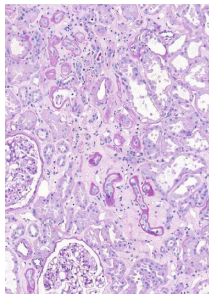
Interstitial fibrosis

- % cortex scarred

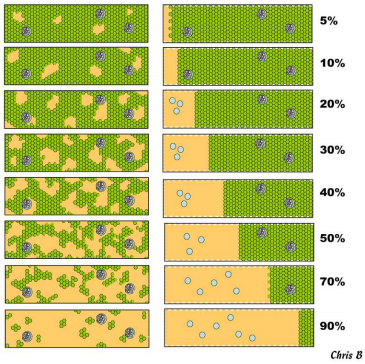
- IF0 no fibrosis
- IF1 >0 - <20%
- IF2 20%-50%
- IF3 >50%

Banff IF0 (ci0) up to 5%

Banff cut off 25%



Tubular atrophy & interstitial fibrosis



TA & IF

- Essentially scoring the same thing twice
- A tiny patchy of atrophic tubules with associated fibrous replacement
- = TA1 + IF1 so starting with a Remuzzi of 2

- Through in 1 GS glom of 100 → Remuzzi of 3 before get to vessels
- For what is minimal CD

Vessels

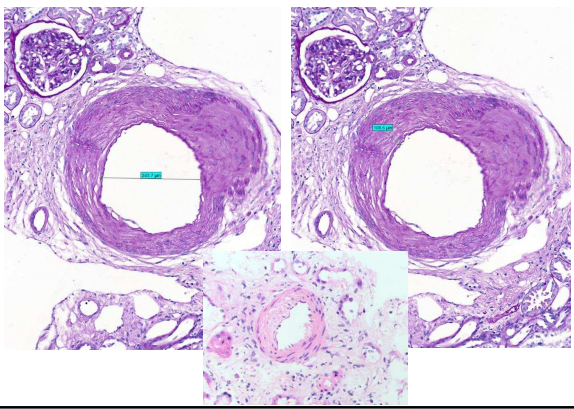
- Cambridge modification
- Do not score arterioles
- Original Remuzzi – worst of artery and arteriole
- If arterioles bad – they will mention in comments and discuss with the surgeon – but not is score.
- WORST ARTERY IN BIOPSY SCORED

- A0 normal artery
- A1 wall thickness < lumen diameter
- A2 wall thickness = ~~or slightly >~~ lumen diameter
- A3 wall thickness >~~>~~ lumen diameter

Cambridge modification

Remuzzi – wall thickness far exceeds with severe luminal narrowing

REMUZZI VASCULAR 1: wall thickness < lumen diameter
wall thickness 108.6 & lumen diameter 243.7



Histopathology scoring proforma

PREIMPLANTATION RENAL BIOPSY

Donor number_____**LAB NUMBER**_____ **SCAN CENTRE**_____

GLOMERULI

No. Glomeruli	100
No. Globally sclerosed	10
% globally sclerosed	10%

Remuzzi grade (G)

Nil	0
<20%	1
20-50%	2
>50%	3

Tubular atrophy

<5%
5-15%
15-25%
<20
>20
25-35%
35-45
45-55
55-65
65-75
>75

TUBULAR ATROPHY

Remuzzi grade (TA)

Nil	0
<20%	1
20-50%	2
>50%	3

Interstitial Fibrosis

<5%
5-15%
15-25%
<20
>20
25-35%
35-45
45-55
55-65
65-75
>75

INTERSTITIAL FIBROSIS

Remuzzi grade (IF)

Nil	0
<20%	1
20-50%	2
>50%	3

ARTERIES

Number of Arteries ___5_____

Remuzzi ARTERY grade (A)

Normal	0
Wall thickness < lumen diameter	1
Wall thickness equal or slightly > lumen diameter	2
Wall thickness much > lumen diameter	3

NOTE: CAMBRIDGE MODIFICATION OF REMUZZI VASCULAR SCORE IS BASED ON ARTERY ONLY
IF SEVERE ARTERIOLAR CHANGES THEN MENTION AS OTHER ADVERSE FEATURE IN COMMENTS

REMUZZI SCORE (Cambridge modification)

(G + TA + IF + A)

0 1 2 3 4 5 6 7 8 9

ADEQUACY

Is the biopsy adequate (≥ 25 glomeruli AND ≥ 3 arteries)

Yes No

OTHER COMMENTS:

REPORTING PATHOLOGIST: Desley Neil

DATE: 22/9/17 **TIME:** 2.30 PM

Remuzzi score

- G + TA + IF + A (0-12)

CURRENT PRACTICE IN CAMBRIDGE WITH REMUZZI SCORE (CAMBRIDGE MOD)

≤4 Single transplant

5-6 Dual transplant*

≥7 Discard

* "good 5s" with minimal (<5%) glomerular sclerosis, tubular atrophy and interstitial fibrosis

Bad arteriolar hyalinosis

Meryl Griffiths Histopathologist from Cambridge will explain what the Cambridge pathologists do in this situation

Reproducibility

- Interobserver variability – kappa statistics
- Known renal pathologists better than "general" on-call pathologists

KAPPA

- <0 no agreement
- 0-0.2 slight agreement
- 0.21-0.4 fair agreement
- 0.41-0.-6 moderate agreement
- 0.61-0.8 substantial agreement
- 0.81-1 near perfect agreement

Glomerulosclerosis interobserver variability

- Eccher et al (2 renal pathologist that work together)
  - %GS 0.429 = moderate agreement
  - Glomerular grade 0.799 = substantial agreement
- 22 renal pathologists (CERTRAP – Furness & Taub)
  - Glomerular number 0.53 = moderate agreement
  - Number GS 0.47 = moderate agreement
- Banff AJT 2016 (ICC >20 renal pathologists)
  - % GS 0.626 = moderate agreement

Tubular atrophy interobserver variability

- Eccher et al (2 renal pathologists that work together)
  - %ta 0.319 = fair agreement
  - Remuzzi grade 0.704 = substantial agreement
- WSI 6 renal pathologists (Banff) Jen et al Human pathology 2012
  - grade 0.36 = fair agreement
- 22 renal pathologists (CERTRAP – Furness & Taub)
  - %ta 0.29 = fair agreement
- Banff AJT 2016 (ICC >20 renal pathologists)
  - ta grade 0.455 = moderate agreement

Interstitial Fibrosis interobserver variability

- Eccher et al (2 renal pathologisgist that work together)
  - %IF 0.269 = fair agreement
  - Grade 0.619 = substantial agreement
- WSI 6 renal pathologists (Banff)
  - grade 0.43 = moderate agreement
- 22 renal pathologists (CERTRAP – Furness & Taub)
  - %if 0.3 = fair agreement
- Banff AJT 2016 (ICC >20 renal pathologists)
  - if grade 0.528 = good agreement

Vascular

- Eccher et al (2 renal pathologist that work together)
  - Remuzzi grade 0.686 = substantial agreement

Remuzzi Score

- Eccher et al (2 renal pathologists that work together)
- OVERALL GRADE 0.863 near perfect agreement

Next steps for pathologists

- Several meetings to discuss and agree definitions
- Still deciding vascular
- 30 preimplantation biopsies from Cambridge scanned
- All pathologists will score
- “expert” group to agree consensus “correct score”
- Pathologists scores compare to “correct score”
- Outlier cases and outlier pathologists identified