IgA nephropathy -Risk Factors and Prediction Models

…can we predict outcome better

…why bother?

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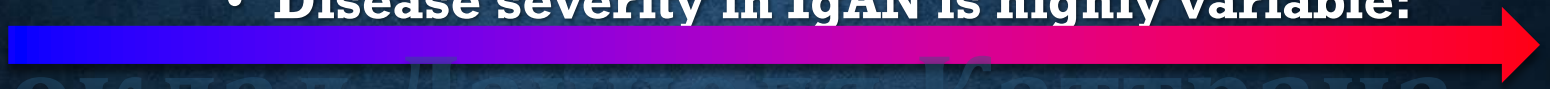
June1,2019

IGAN: INTRODUCTION

- **Worldwide is the most common type of GN**
  - **More common in Asia than Europe or N. America**

- **Disease severity in IgAN is highly variable:**



No clinical phenotype

Asymptomatic hematuria

Majority:

Slowly progressive proteinuric renal disease

Minority (<10%):

RPGN or severe nephrotic syndrome

IgA production, class switch, transition out of lymphoid tissue

Mucosal microbiota?

Mesangial and endothelial cell proliferation

Tubulo-interstitial injury

Suzuki H et al. JASN 2011;22:1795-1803

IGA - NATURAL HISTORY

- **Prognostic Factors**
  Good
  Microhematuria alone
  Recurrent macrohematuria alone
- **Bad**
  Hypertension
  Moderate proteinuria (1-4 g/day)
  Renal insufficiently

Problems

Qualitative

Poor specificity

RISK FACTORS

Sex

Age

Genetics

Ethnicity

Environment(micro and macro)

Socioeconomics

Hypertension

Proteinuria

Pathology

FIRST FOUR IMPORTANT …BUT

AGE

SEX

GENETICS

ETHNICITY

Currently little to act on

But…. Should be part of a risk score

BUT OTHERS POTENTIALLY RISKS MAY BE ABLE TO QUANTITATE

- Socioeconomics
- Environment(micro and macro)
- Hypertension
- Proteinuria
- Pathology

IMPORTANT POINTS

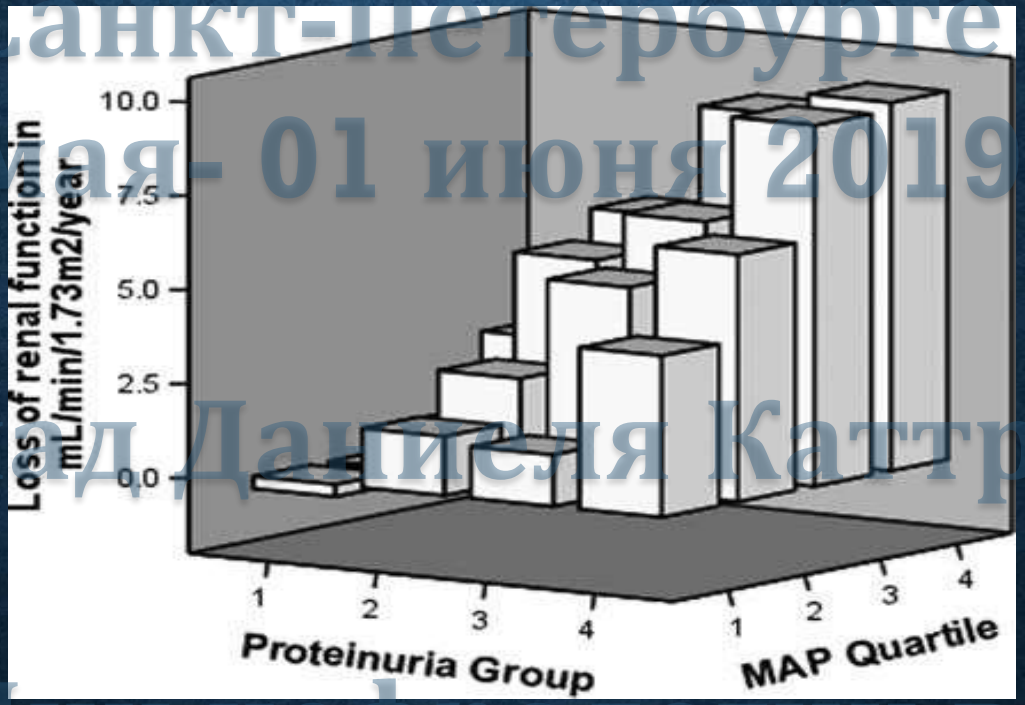
Clinical trials in homogeneous populations may not generalize across ethnic groups

Complexities between ethnic origin genetics, diet , environmental exposures require large study cohorts

Known pathogenic mechanisms may vary across groups
e.g. abnormal glycosylated

Pathological determinants may vary by ethnicity eg endocapillary proliferation

HYPERTENSION IS VERY RELEVANT

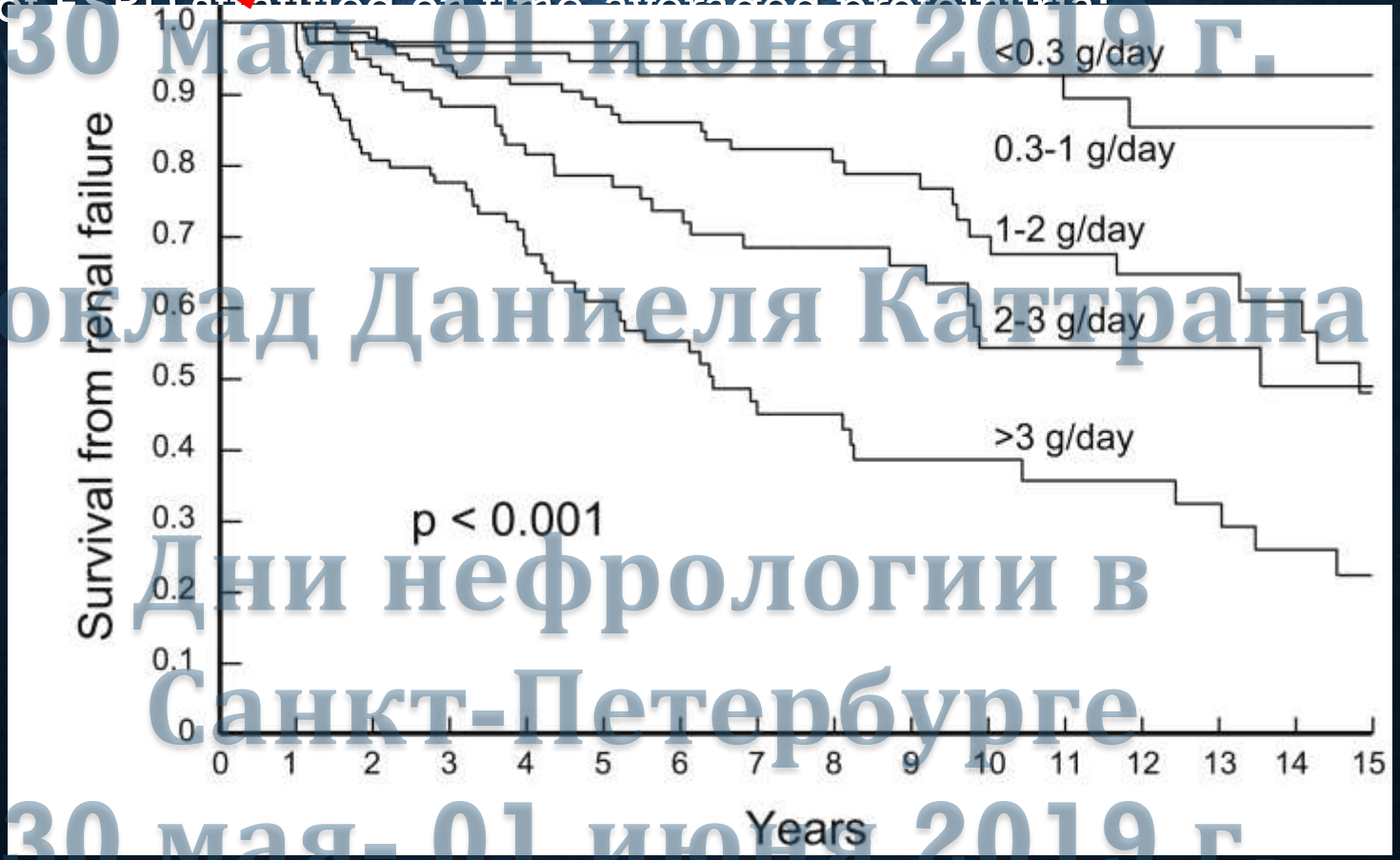


Reich ……..Cattran JASN 2008

RENAL OUTCOME IS HIGHLY VARIABLE

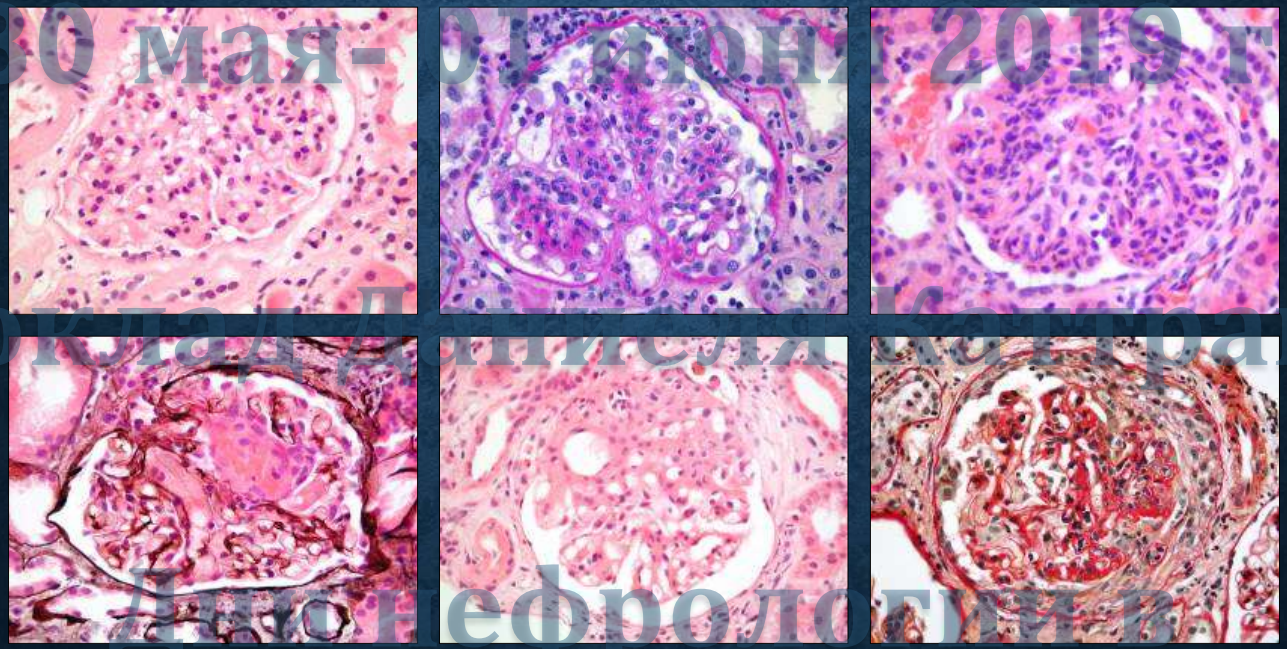
Risk of ESRD stratified on time-averaged proteinuria:

How do we identify high-risk patients at time of biopsy?



Reich et al, JASN 2007

IGA NEPHROPATHY IS MORPHOLOGICALLY HETEROGENEOUS



Roberts SD et al. Kidney Int 76:546-56, 2009

OXFORD-JUST ANOTHER IGAN CLASSIFICATION?

Table 1 | Histological risk factors for progressive renal failure in IgA nephropathy

Reference	Mesangial cellularity	Endocapillary proliferation	Crescents	Capillary wall IgA	Focal segmental sclerosis	Glomerulosclerosis	Interstitial fibrosis/tubular atrophy
Nozawa *et al.*[1]							X
Ballardie *et al.*[2]	X						
To *et al.*[3]						X	
Mera *et al.*[4]							X
Daniel *et al.*[5]							X
Vleming *et al.*[6]							X
Freese *et al.*[7]			X	X			X
Hogg *et al.*[8]			X			X	
Katafuchi *et al.*[9]					X		X
Ibels *et al.*[10]					X	X	
Okada *et al.*[11]						X	X
Bogenschutz *et al.*[12]							X
Rekola *et al.*[13]	X						
D'Amico *et al.*[14]		X		X		X	
Boyce *et al.*[15]			X				

15 classifications re risks

Roberts et al K I 2009

MEST SCORE INDEPENDENT VALUE OF PATHOLOGY FROM CLINICAL PARAMETERS INITIAL AND FOLLOW-UP IN REGARDS TO RATE OF CHANGE IN RENAL FUNCTION

	Rate of renal function decline (linear regression)		
	Univariate slope (ml/min per 1.73 m² per year)	Multivariate[a] Model A β (s.d.)	Multivariate[a] Model B β (s.d.)
Mesangial hypercellularity score			
⩽0.5	−0.5 ± 3.3	−2.2 (1.3)	−0.8 (1.2)
>0.5	−4.2 ± 9.0		
	$P<0.001$	$P=0.10$	$P>0.1$
Segmental glomerulosclerosis			
Absent	−0.5 ± 7.5		
Present	−4.4 ± 8.4	−3.6 (1.3)	−2.5 (1.1)
	$P=0.001$	$P=0.005$	$P=0.03$
Tubular atrophy/interstitial fibrosis[b]			
0–25%	−2.5 ± 7.6	−5.2 (1.1)	−3.7 (1.0)
26–50%	−5.7 ± 8.8		
>50%	−11.1 ± 12.6		
	$P<0.001$	$P<0.001$	$P<0.001$

[a]Model A: multivariate with three pathological features + initial GFR, MAP, proteinuria. Model B: multivariate with three pathological features + initial GFR and follow-up MAP and proteinuria.

[b]Outcomes with 0% tubular atrophy/interstitial fibrosis were identical to 1–25% tubular atrophy/interstitial fibrosis, hence the two categories were combined to maximize statistical power.

INDEPENDENT VALUE RELATED TO HARD ENDPOINTS (END-STAGE RENAL DISEASE OR 50% REDUCTION IN INITIAL GFR)

Survival–from renal failure or a 50% drop in GFR (Cox regression)		
Univariate hazard ratio (95% CI)	Multivariate[a]	
	Model A	Model B
0.06 (0.01–0.45) 1 *P*=0.006	0.07 (0.01–0.53) 1 *P*=0.01	0.11 (0.01–0.80) 1 *P*=0.03
1 3.1 (1.4–7.3) *P*=0.009	1 1.8 (0.6–5.3) *P*>0.1	1 2.5 (0.9–7.3) *P*=0.09
1 3.5 (1.9–6.5) 15.5 (7.5–31.9) *P*<0.001	1 6.0 (2.7–13.9) 17.3 (5.9–50.9) *P*<0.001	1 5.0 (2.3–11.1) 8.8 (2.9–26.4) *P*<0.001

[a]Model A: multivariate with three pathological features + initial GFR, MAP, proteinuria. Model B: multivariate with three pathological features + initial GFR and follow-up MAP and proteinuria.

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MEST HISTOLOGY SCORE: META-ANALYSIS

	Number of Patients	Pooled HR	95% CI
M0 vs M1	3629	0.6	0.5-0.8
E1 vs E0	3511	1.4	0.9-2.0
S1 vs S0	3771	1.8	1.4-2.4
T1 vs T0	2719	2.7	1.6-4.6
T2 vs T0	2558	7.2	4.9-10.6

Adjusted for other predictor variables, including eGFR, BP, proteinuria

Lv et al, AJKD 2013

RISK STRATIFICATION IN IGAN

- Accurately predict an individual's risk of future renal function decline
- Use variables readily available in clinical practice
- Pathology: use a scoring system that is widely accepted and available on routine biopsy reports, reproducible and validated
- Applied at clinically relevant time points with minimal need for prolonged observation
- Applicable in multiple-ethnic groups worldwide

PURPOSE OF STRATIFICATION IN IGAN

1. Inform patients of their prognosis
   - Alleviate anxiety in low-risk
   - Target health care resources in high-risk

2. Identify patients at sufficiently high risk to justify the risks of immunosuppression

Risk of immunosuppression

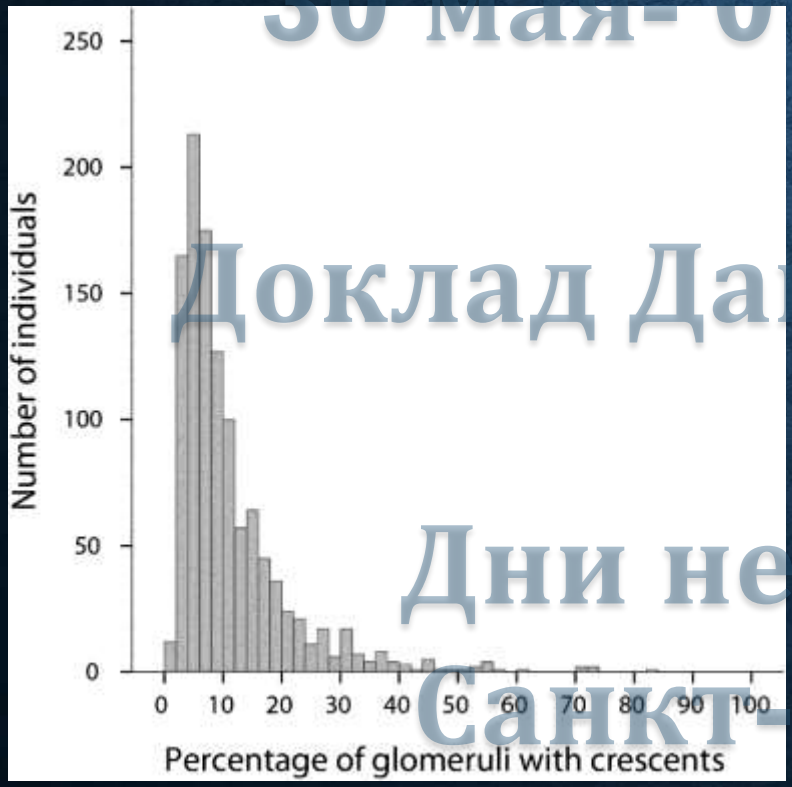
Risk of disease progression

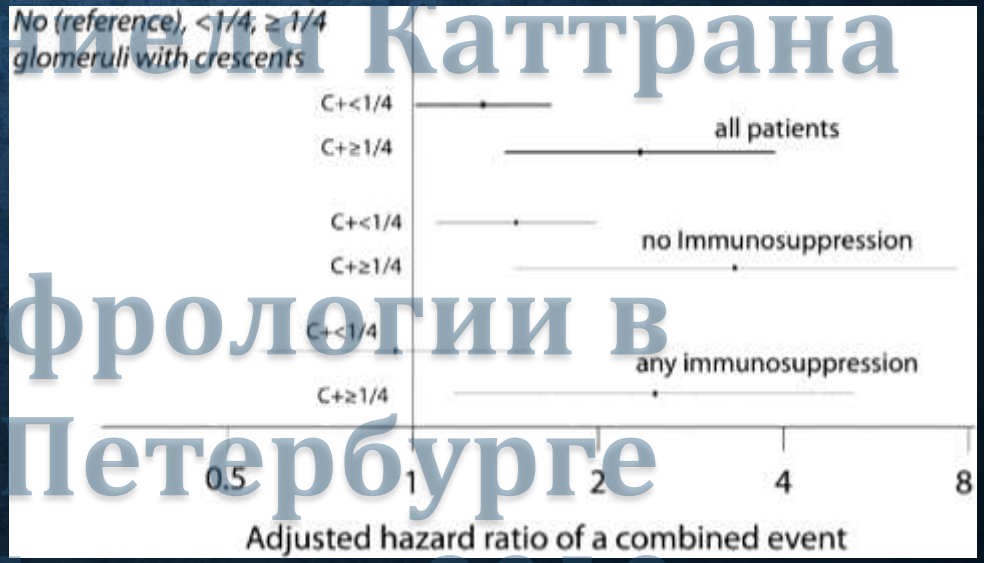
RISK FACTORS FOR DISEASE PROGRESSION

- Established clinical risk factors:
  - eGFR, blood pressure, proteinuria (>0.5-1g/day)
- Uncertain clinical risk factors:
  - Age, sex, race, BMI, hematuria
- Pathology:
  - MEST score, crescents
- Novel risk factors of uncertain significance:
  - Biomarkers: ex. Gd-IgA levels, anti-Gd-IgA Ab
  - Pathology: ex. C4d staining
  - Genetics
- Unclear how to integrate these together? What is the absolute risk?
- Insert list of clinical risk factors for disease progression
- Insert MEST-C score as pathology risk factor, consider as well:
- Novel risk factors:
  - ?Gd-IgA levels
  - Complement dysregulation
  - C4d staining
  - See Seminars review paper

CRESCENTS AND PROGNOSIS

Combined cohort N=3096 from Oxford derivation study, VALICA, Nanjing and Fukuoka





Haas et al, JASN 2017

Oxford Classification of IgA nephropathy 2016: an update from the IgA Nephropathy Classification Working Group

Table 3 | Recommendations for the renal biopsy report in IgA nephropathy (updated from refs. 1, 2, and 32)

Detailed description of the features present on:
- Light microscopy
- Immunohistochemistry or immunofluorescence
- Electron microscopy

Summary of 5 key pathologic features
- Mesangial score <0.5 (M0) or >0.5 (M1)
- Endocapillary hypercellularity absent (E0) or present (E1)
- Segmental glomerulosclerosis absent (S0) or present (S1); presence or absence of podocyte hypertrophy/tip lesions in biopsy specimens with S1
- Tubular atrophy/interstitial fibrosis ≤25% (T0), 26%–50% (T1), or >50% (T2)
- Cellular/fibrocellular crescents absent (C0), present in at least 1 glomerulus (C1), in >25% of glomeruli (C2)

Quantitative data
- Total number of glomeruli
- Number of glomeruli with endocapillary hypercellularity, necrosis, extracapillary hypercellularity (cellular/fibrocellular crescents), global glomerulosclerosis, and segmental glomerulosclerosis

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Trimarchi et al, KI 2017

2012 KDIGO GUIDELINE RECOMMENDATIONS

10.1: Initial evaluation including assessment of risk of *progressive kidney disease*

- 10.1.2: Assess the risk of progression in all cases by evaluation of proteinuria, blood pressure, and eGFR at the time of diagnosis and during follow-up. (Not Graded)
- 10.1.3: Pathological features may be used to assess prognosis. (Not Graded)

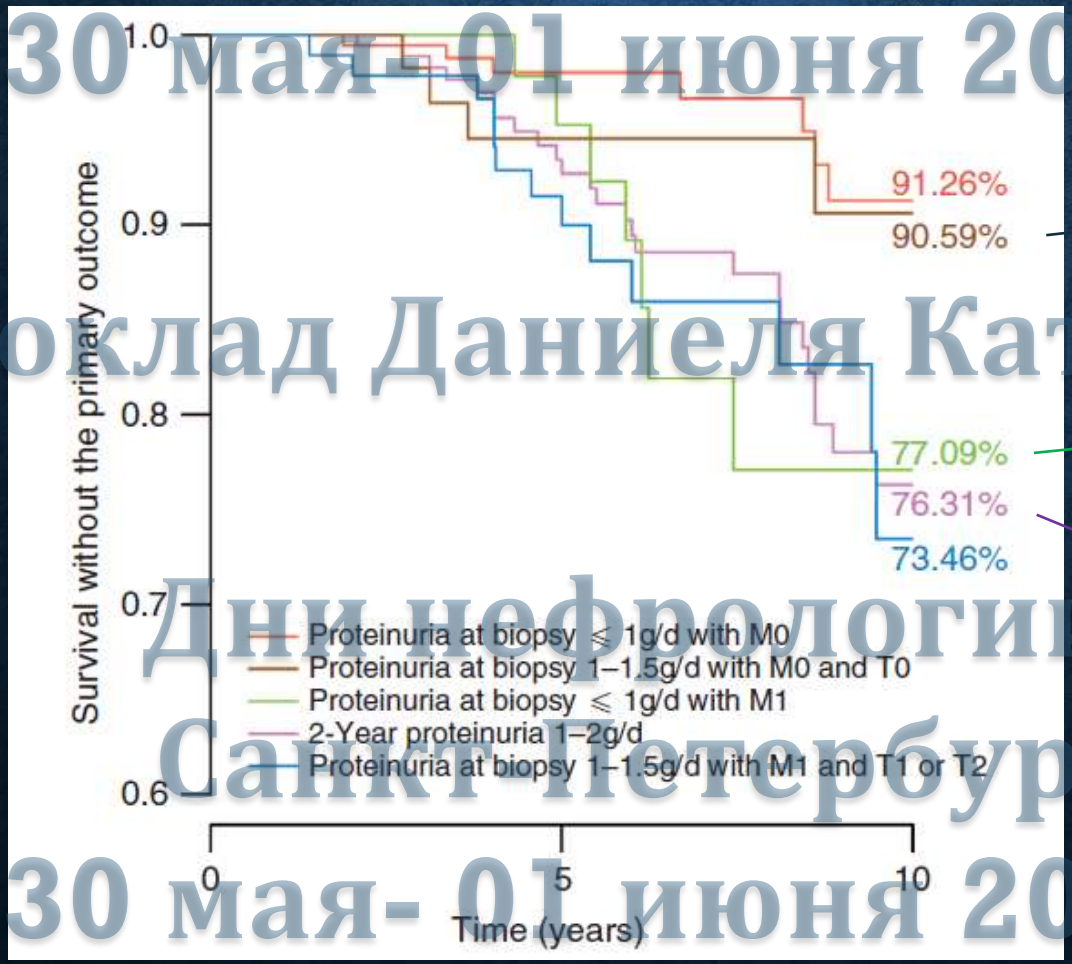
10.3: *Corticosteroid treatment*

- 10.3.1: We suggest that patients with persistent proteinuria ≥1 g/d, despite 3–6 months of optimized supportive care (including ACE-I or ARBs and blood pressure control), and GFR>50 ml/min per 1.73m2, receive a 6-month course of corticosteroid therapy. (2C)

Is proteinuria categorization ≥ 1g/d sufficient for these two concepts?

PROTEINURIA ALONE IS NOT SUFFICIENT FOR RISK STRATIFICATION

Subgroup eGFR>50: risk of 50% decline eGFR or ESRD



≤1g/d + M1
Don't qualify for steroids

Persistent proteinuria 1-2g/d
Qualify for steroids

Barbour et al, KI, 2016

POTENTIAL IMPACT OF CLINICAL AND PATHOLOGY

Cattran,Moran NDT EDU 2019

WHAT ABOUT PREDICTION MODELS?

	Multi-Ethnic	Pathology	External Validation
Bartosik AJKD 2001	Yes	Lee Grade	In Caucasians (Mackinnon 2008)
Goto NDT 2009 (decision tree model)	No, Japanese	Japanese System	No
Wakai NDT 2006 + Goto NDT 2009 (survival model)	No, Japanese	Japanese System	Partially in Caucasians using different pathology system (Bjorneklett 2012)
Berthoux JASN 2011	Unclear	Global Optical Score	Yes in remote cohort with poor calibration Partially in Caucasians generated new model (Knoop 2015)
Xie PlosOne 2012	No, Chinese	Haas	No
Tanaka CJASN 2013	No, Japanese	MEST	Yes, Japanese
Pesce NDT 2016	No, mostly Caucasian	Manno	No
Xie, AJKD 2018	No, Chinese	MEST	Yes, Chinese

Major barrier to research is the lack of large, international, multi-ethnic datasets

SUMMARY: RISK STRATIFICATION

- Well established risk factors for disease progression:
  - eGFR, proteinuria, BP, MEST-C
- Intuitively we consider simple categories of each predictor separately
  - Inaccurate
  - Potential for erroneous treatment decisions
- Currently no accepted prediction model for integrating risk factors together

INTERNATIONAL IGAN RISK PREDICTION TOOL

Goal: derive and externally validate prediction tool that is applicable in multiple ethnic groups at the time of biopsy

INTERNATIONAL IGAN NETWORK COLLABORATION

INTERNATIONAL IGAN PREDICTION TOOL

- Inclusion criteria:
  - Adults age ≥ 18 years
  - Did not have ESRD at the time of biopsy
- Primary outcome:
  - Time from biopsy to a ≥ 50% reduction in eGFR or ESRD

	Derivation Cohort	Validation Cohort
Number of patients	2781	1146
Follow up (years)	4.8 [3.0, 7.6]	5.8 [3.4, 8.5]
Year of biopsy	2006 [2004, 2008]	1998 [1993, 2003]
Age (years)	35.6 [28.2, 45.4]	34.8 [26.9, 45.0]
Male sex	1608 (57.8%)	565 (49.3%)
Race		
Caucasian	1167 (42%)	176 (15.5%)
Japanese	569 (20.5%)	616 (54.4%)
Chinese	1021 (36.7%)	292 (25.8%)
Other	22 (0.8%)	49 (4.3%)
eGFR at biopsy (ml/min/1.73m^2)	83.0 [56.7, 108.0]	89.7 [65.3, 112.7]
MAP at biopsy (mmHg)	96.7 [88.7, 106.3]	93.3 [85.0, 103.3]
Proteinuria at biopsy (g/day)	1.2 [0.7, 2.2]	1.3 [0.6, 2.4]
Pathology:		
M1	1054 (38%)	481 (42%)
E1	478 (17.3%)	476 (41.5%)
S1	2137 (77%)	912 (79.6%)
T1	686 (24.7%)	207 (18.1%)
T2	128 (4.6%)	122 (10.6%)
Crescents	953 (34.3%)	642 (56.1%)
RASB use at biopsy	862 (32.4%)	320 (30%)
RASB use during follow-up	2400 (86.7%)	708 (66.4%)
Immunosuppression prior to biopsy	252 (9.1%)	81 (7.1%)

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DERIVATION OF PREDICTION MODEL

1. **Clinical model**:
   - eGFR, MAP, proteinuria at biopsy
2. **Full models**:
   - Full model with race:
     - eGFR, MAP, proteinuria, MEST, age, RASB at biopsy, prior use of immunosuppression, interaction terms, and Caucasian, Chinese, or Japanese race
   - Full model without race:
     - Same but without race
     - For use in other ethnic groups
   - Crescents were considered, but not selected in either model

PREDICTION MODEL PERFORMANCE

Full Model
(with or without race)

Clinical Model
(eGFR, MAP, Prot)

Model fit: AIC, R^2
Discrimination: C-statistic
Reclassification: NRI, IDI

Results were similar in the external validation cohort

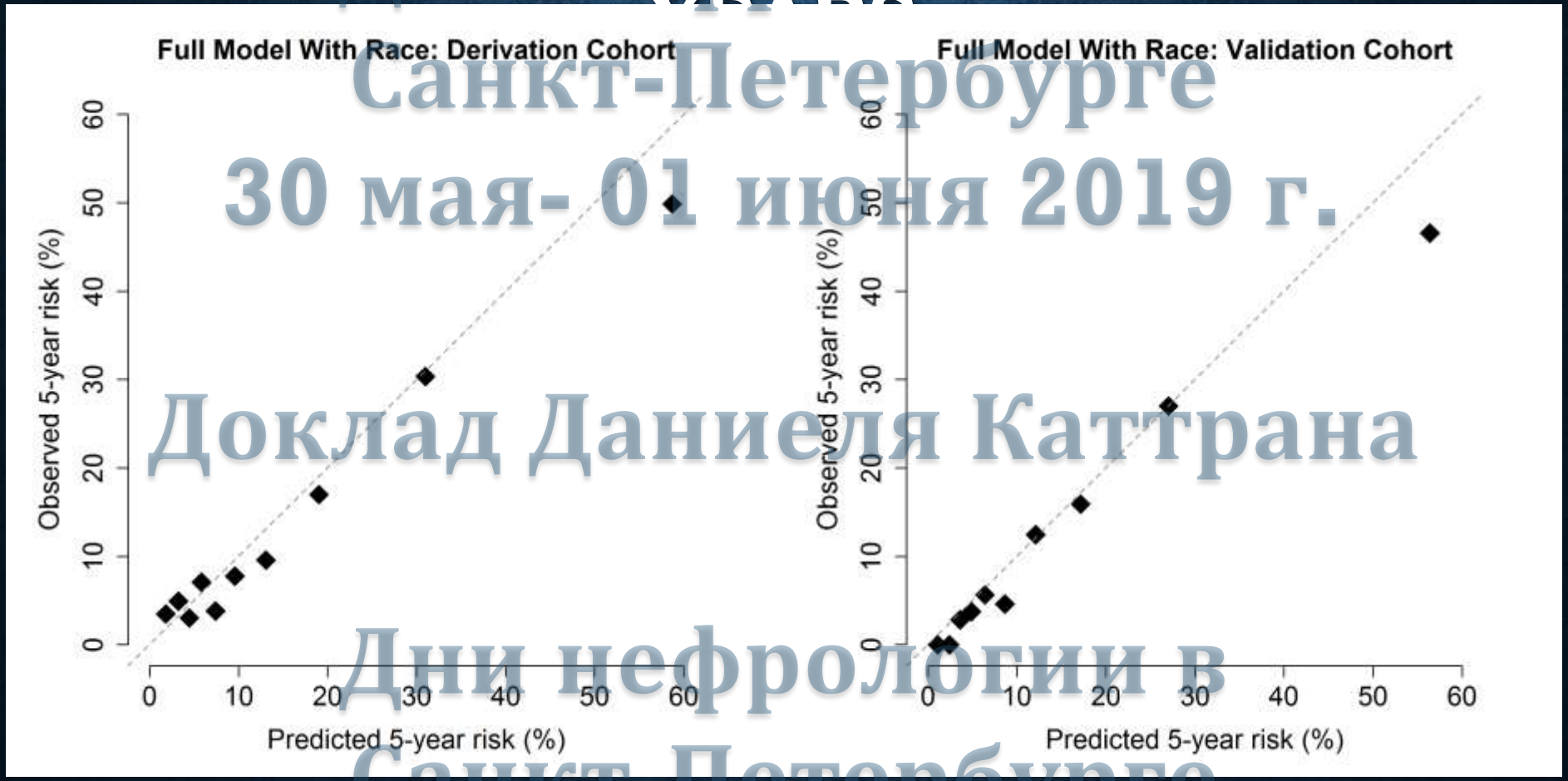
No difference between the full models → both full models provide similar prediction

PREDICTION PERFORMANCE IN DERIVATION COHORT

	Clinical Model (eGFR, MAP, Prot)	Full Model With Race	Full Model Without Race
Model Fit			
AIC	6485	6338	6379
R^2	20.3%	26.3%	25.3%
Discrimination			
C-statistic (95% CI)	0.78 (0.77, 0.78)	0.82 (0.81, 0.82)	0.81 (0.80, 0.81)
ΔC-statistic (95% CI)	Ref	0.04 (0.03, 0.04)	0.03 (0.02, 0.03)
Reclassification			
NRI (95% CI)	Ref	0.18 (0.07, 0.29)	0.51 (0.39, 0.62)
IDI (95% CI)	Ref	0.07 (0.06, 0.08)	0.06 (0.05, 0.06)

No difference between the full models → both full models provide similar prediction

MODEL CALIBRATION AT 5-YEARS



Calibration results similar for full model without race

RATE OF EGFR DECLINE

Risk Subgroup	Mean Predicted 5-year Risk	Rate of eGFR Decline (ml/min/1.73m^2/year)		
		Mean	95% CI	P-value
Full Model With Race				
Low risk	1.5%	-1.24	-1.63, -0.85	<0.0001
Intermediate risk	4.7%	-1.76	-2.01, -1.50	
Higher risk	13.9%	-2.35	-2.35, -2.10	
Highest risk	46.5%	-3.43	-3.80, -3.06	

Results similar for full model without race

SUMMARY OF RESULTS

- Either full risk prediction model can accurately predict renal outcome in IgAN
  - MEST, eGFR, BP, proteinuria, age, RASB at biopsy, immunosuppression prior to biopsy
  - With or without race
- Confirmed in external validation
- Can be applied in multiple ethnic groups
- Limitations:
  - Requires validation in pediatrics
  - Only applicable at the time of biopsy
  - Not applicable in IgA vasculitis

Research

JAMA Internal Medicine | Original Investigation

Evaluating a New International Risk-Prediction Tool in IgA Nephropathy

Sean J. Barbour, MD, MSc; Rosanna Coppo, MD, FERA; Hong Zhang, MD, PhD; Zhi-Hong Liu, MD; Yusuke Suzuki, MD, PhD; Keiichi Matsuzaki, MD, PhD; Ritsuko Katafuchi, MD, PhD; Lee Er, MSc; Gabriela Espino-Hernandez, MSc; S. Joseph Kim, MD, PhD; Heather N. Reich, MD, PhD; John Feehally, FRCP; Daniel C. Cattran, MD, FRCPC; for the International IgA Nephropathy Network

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Published online April 14, 2019

CLINICAL IMPLEMENTATION OF PREDICTION TOOL

- **Mobile app calculator:**

- **Web-based calculator:**

https://qxcalc.app.link/igarisk

CALCULATOR FULL MODEL

The 13 questions to answer in clinic at time of biopsy

- **eGFR**
- **SYSTOIC BP**
- **DIASTOLIC BP**
- **PROTEINURIA g/d**
- **AGE**
- **RACE**
- **RAS inhibition Y/N**
- **MEST Score**
- **M 0/1**
- **E 0/1**
- **S 0/1**
- **T 0/1/2**
- **C 0/1,2**
- **Immunosuppression (IS prior or at bopsy) Y/N**

=Estimated risk 24-60 mos post biopsy

FURTHER APPLICATIONS OF PREDICTION TOOL

- Integration into a risk-based treatment approach
  - Treatment criteria based on predicted risk of progression
  - Instead of proteinuria alone >1g/d

- Clinical trials:
  - Targeted recruitment of high-risk patients
  - Improve study power, reduce sample size, improve feasibility and cost

- Validation of biomarker research in clinical domain

CONSIDER HYPOTHETICAL PATIENTS

	Patient 1	Patient 2	Patient 3
Age (years)	39	43	42
Sex	Male	Male	Male
Race	Chinese	Caucasian	Caucasian
eGFR (ml/min/1.73m^2)	60	61	94
SBP (mmHg)	124	124	124
DBP (mmHg)	79	77	77
Proteinuria (g/d)	2.6	1.8	1.6
Use RASB	Yes	Yes	Yes
Prior immunosuppression	No	No	No
MEST	M1 E0 S1 T1	M1 E0 S1 T1	M1 E0 S1 T1
5-year risk of progression:	????	????	????

CONSIDER HYPOTHETICAL PATIENTS

	Patient 1	Patient 2	Patient 3
Age (years)	39	43	42
Sex	Male	Male	Male
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DBP (mmHg)	79	77	77
Proteinuria (g/d)	2.6	1.8	1.6
Use RASB	Yes	Yes	Yes
Prior immunosuppression	No	No	No
MEST	M1 E0 S1 T1	M1 E0 S1 T1	M1 E0 S1 T1
5-year risk of progression:	**52.7%**	**21.6%**	**11.3%**

CONCLUSIONS

- Current methods of risk stratification use simplistic categorization of individual predictors
    - Inaccurate, can't be combined
- Using clinical predictors over >3 years of follow-up improves prediction
    - Not clinically applicable
- International IgAN Prediction Tool provides accurate risk prediction near the time of biopsy
    - Personalized accurate risk stratification is now readily available in IgAN in multiple ethnic groups

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THANK YOU
SPASIBA

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