



## **The BC GN Atlas:**

**A first look at the epidemiology of GN  
in BC**

# Objectives

1. Describe the data logistics for the BC GN Registry
2. The BC GN Atlas: using the GN Registry to describe the epidemiology of GN in BC
3. Provide a detailed look at the epidemiology of IgA nephropathy in BC
4. Using the GN Registry data for observational research and clinical trials

# Prior to 2013: data on GN patients in BC



Data infrastructure linked to funding for health services  
specific to CKD and ESRD

# BC GN Committee

In 2013, BC Renal created the **GN Committee**

Overarching mandate:

Ensure high-quality GN-related health services are available to patients throughout BC

# BC GN Committee: vision

1. To coordinate the delivery of GN-specific health care at the provincial level
  - Analogous to existing CKD/ESRD, transplantation strategies
2. Capture necessary data to develop and evaluate health services initiatives
  - In real-time
  - Accountability
3. Integrate health administration and research activities to create a sustainable framework to study rare diseases across a large population

# BC GN Registry

- Goal of the GN Registry:
  - To ensure high quality data is available to develop and evaluate clinical care and health policy initiatives implemented by the BC GN Committee
- Embedded within the existing information system (PROMIS)
- Captures prospective data on all GN patients in BC as of kidney biopsy

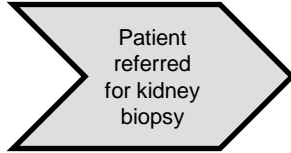
# BC GN Registry

- Ensure sustainability:
  - Uses existing administrative resources to capture data
  - Integration into processes of care
  - Interfaces with existing information systems

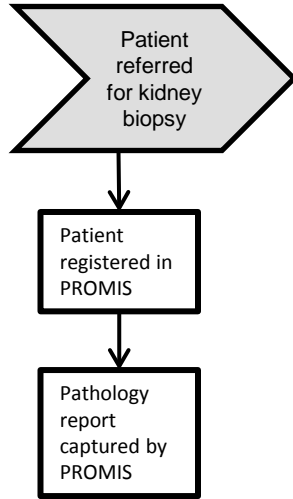
# BC GN Registry: logistics of data capture



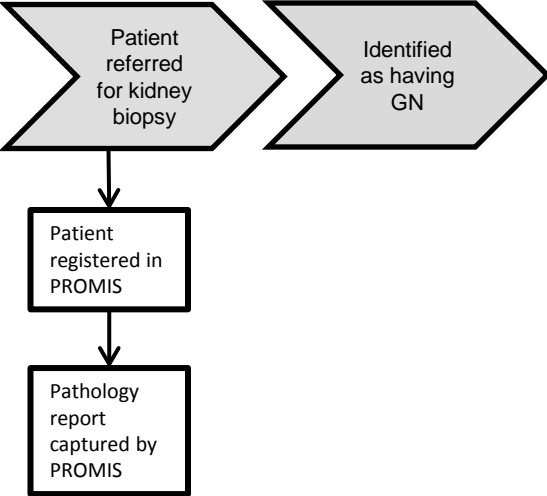
# BC GN Registry: logistics of data capture



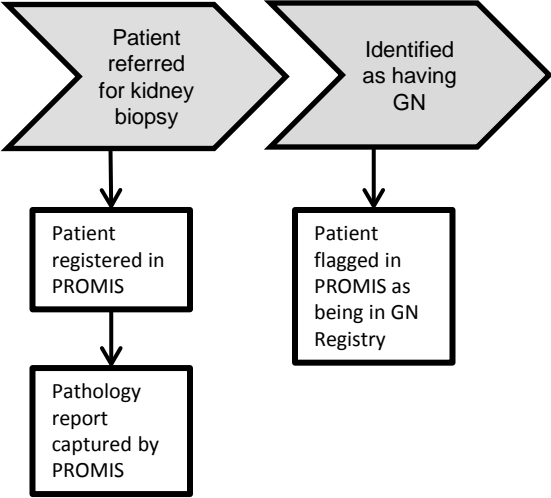
# BC GN Registry: logistics of data capture



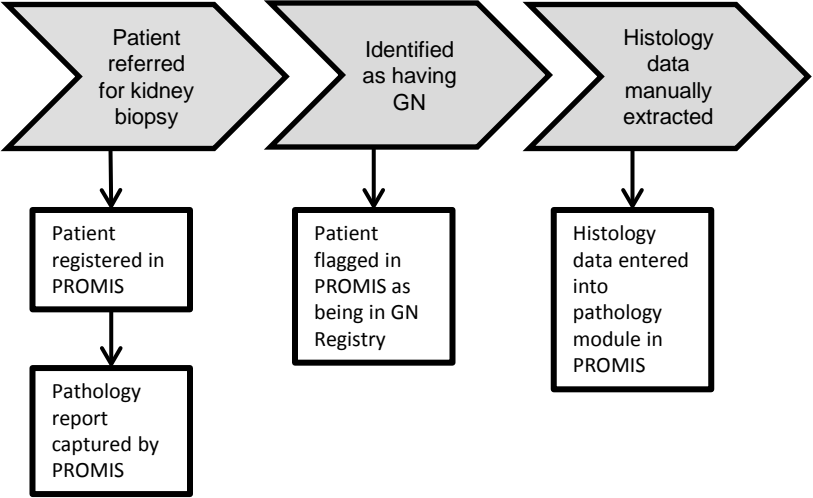
# BC GN Registry: logistics of data capture



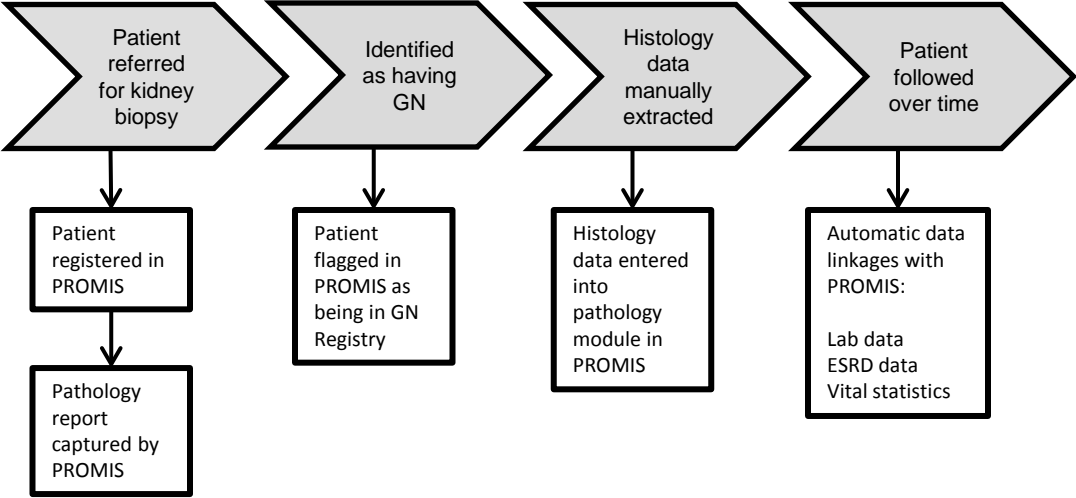
# BC GN Registry: logistics of data capture



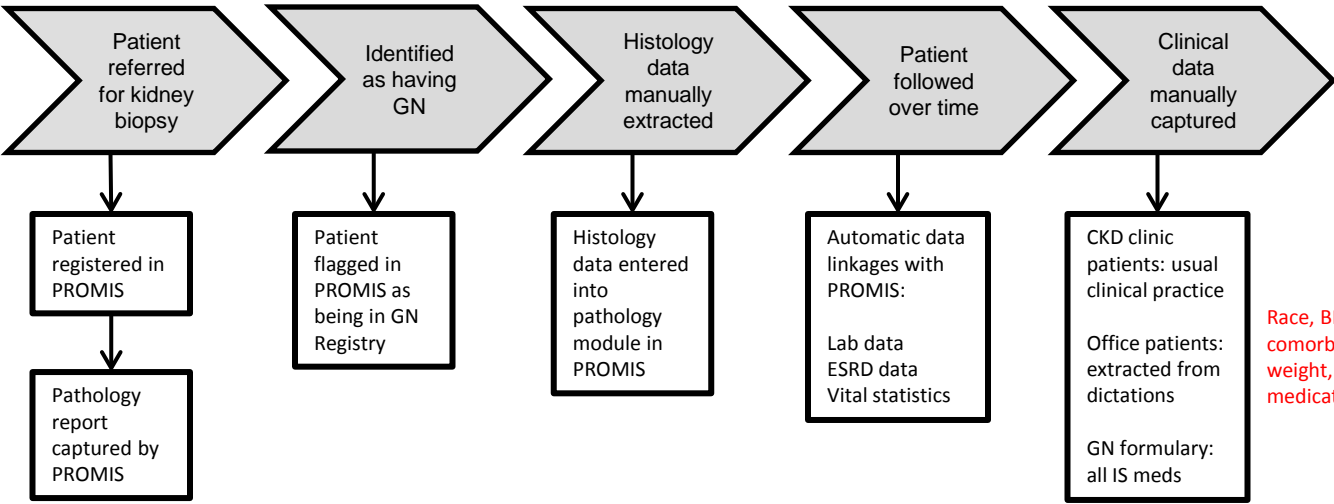
# BC GN Registry: logistics of data capture



# BC GN Registry: logistics of data capture

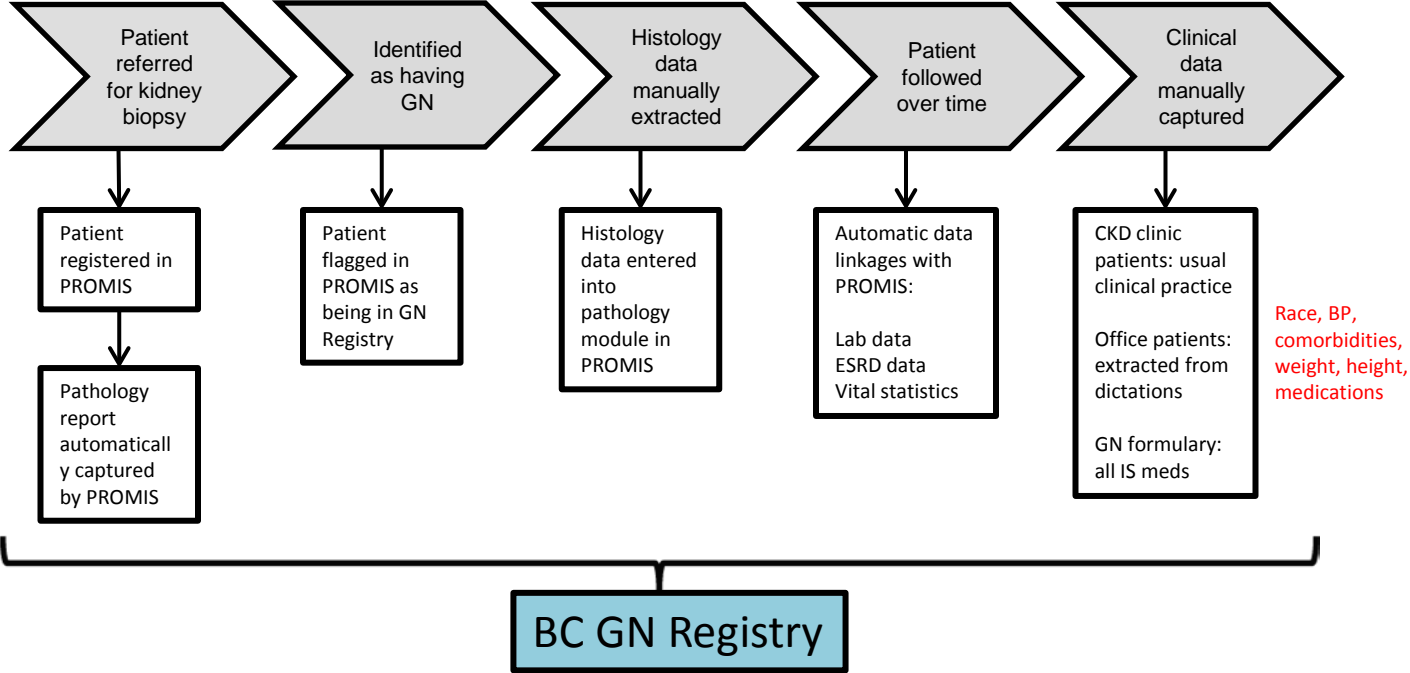


# BC GN Registry: logistics of data capture



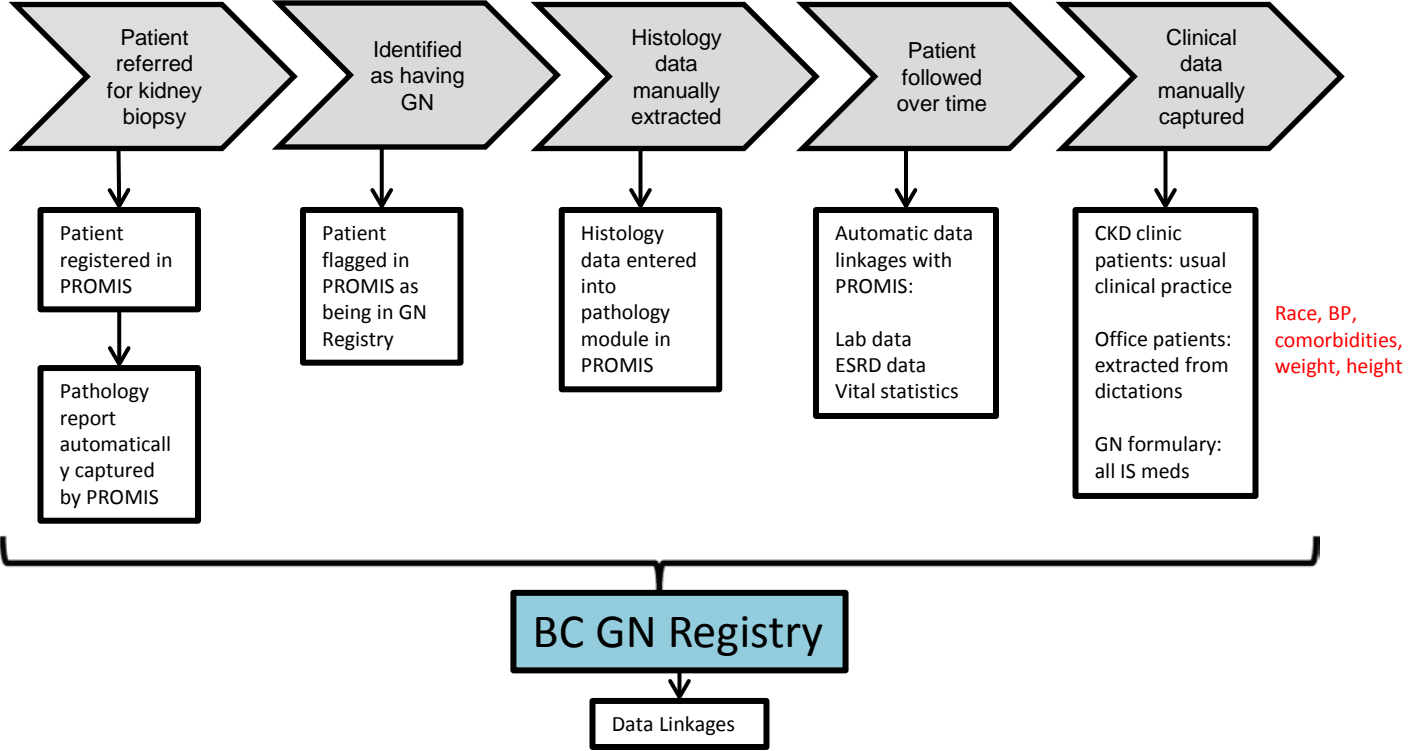
Race, BP, comorbidities, weight, height, medications

# BC GN Registry: logistics of data capture

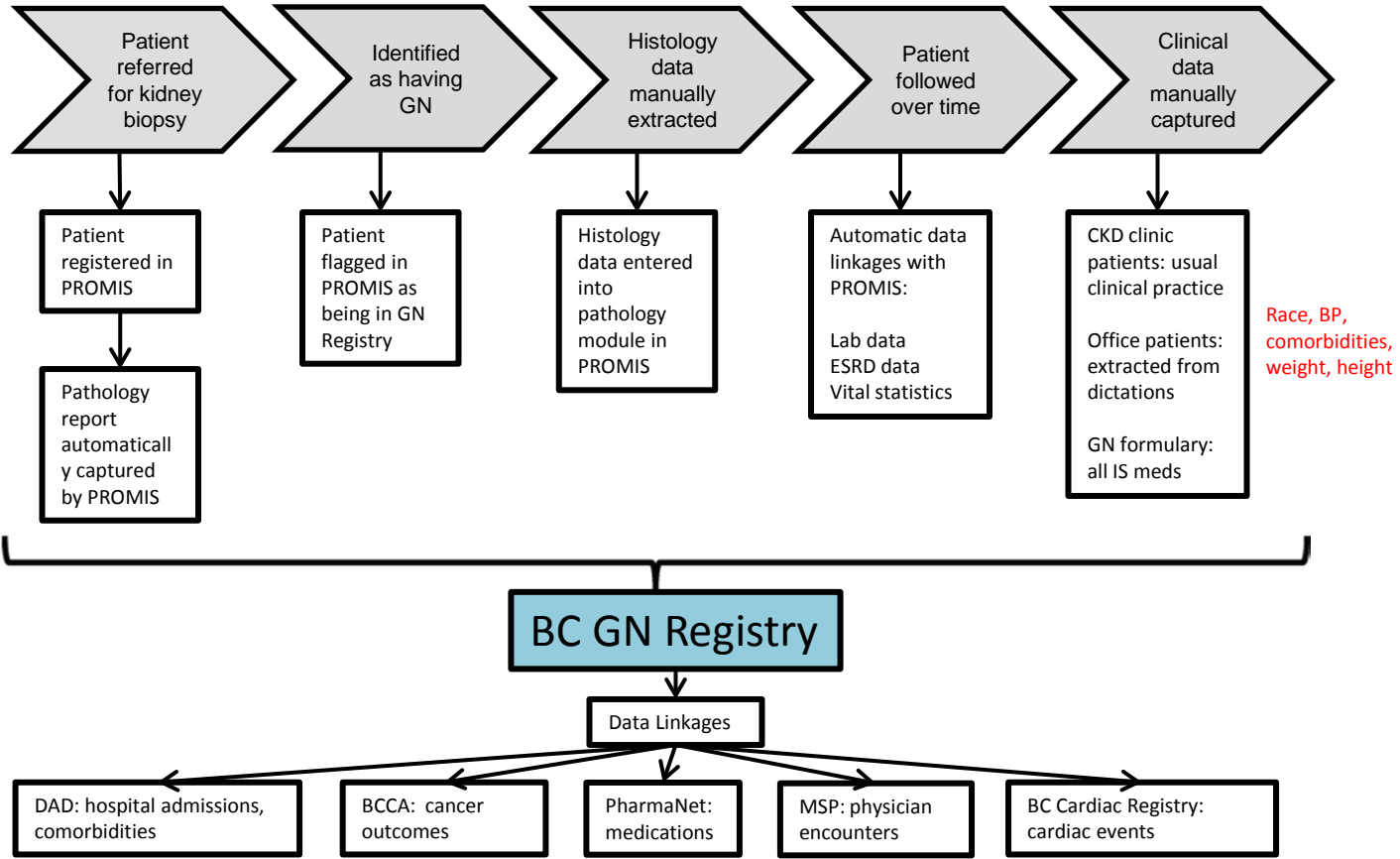




# BC GN Registry: logistics of data capture



# BC GN Registry: logistics of data capture



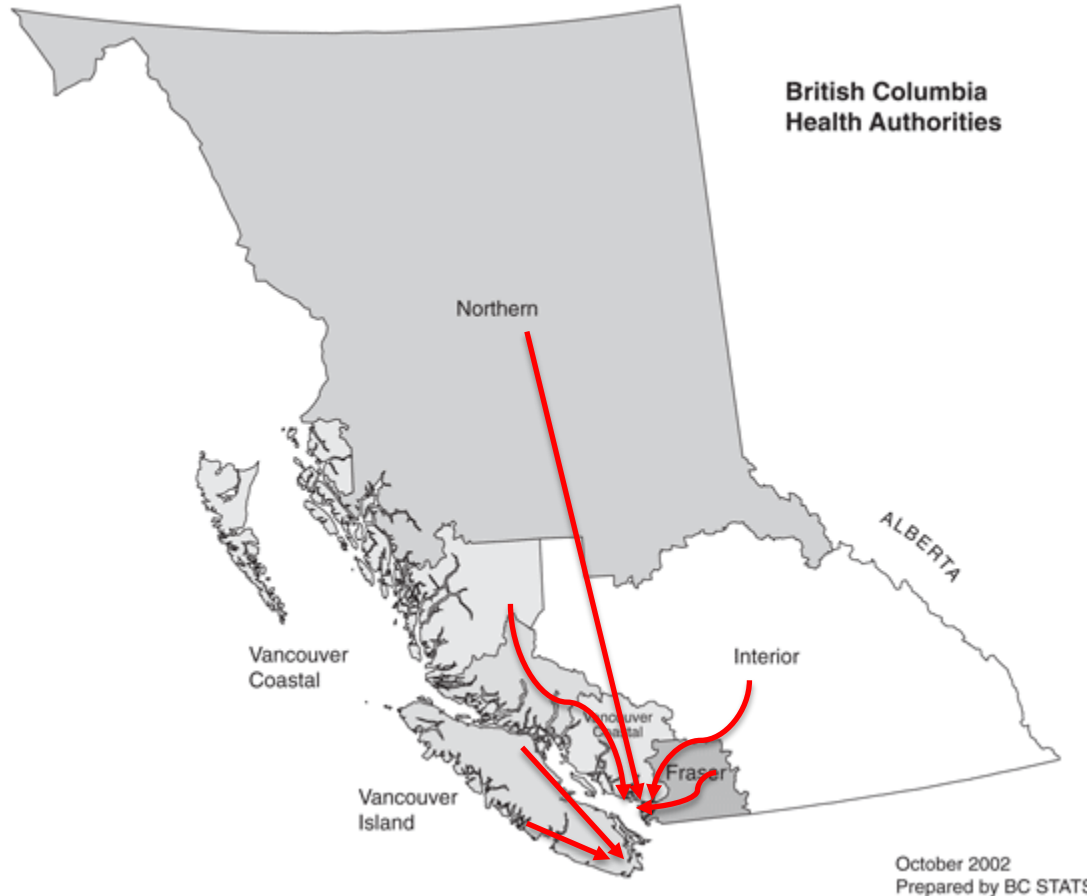
## Histologic Diagnoses Enrolled in the BC GN Registry

Amyloidosis	IgA nephropathy
Anti-GBM antibody (Goodpasture' s) GN	IgM nephropathy
Autoimmune / Connective tissue disease associated GN	Immunotactoid GN
Cryoglobulinemic GN	Light chain deposition disease
C3 GN	Light and heavy chain deposition disease
C1q nephropathy	Lupus nephritis
Dense deposit disease	Minimal change disease
Fibrillary GN	Membranoproliferative GN, IC mediated
Focal segment glomerulosclerosis	Membranous nephropathy
GN with monoclonal immunoglobulin deposits	Mesangial proliferative GN
GN not otherwise specified	Pauci-immune (ANCA) GN
Heavy chain deposition disease	Post-infectious GN
Henoch-Schonlein purpura	Thrombotic microangiopathy

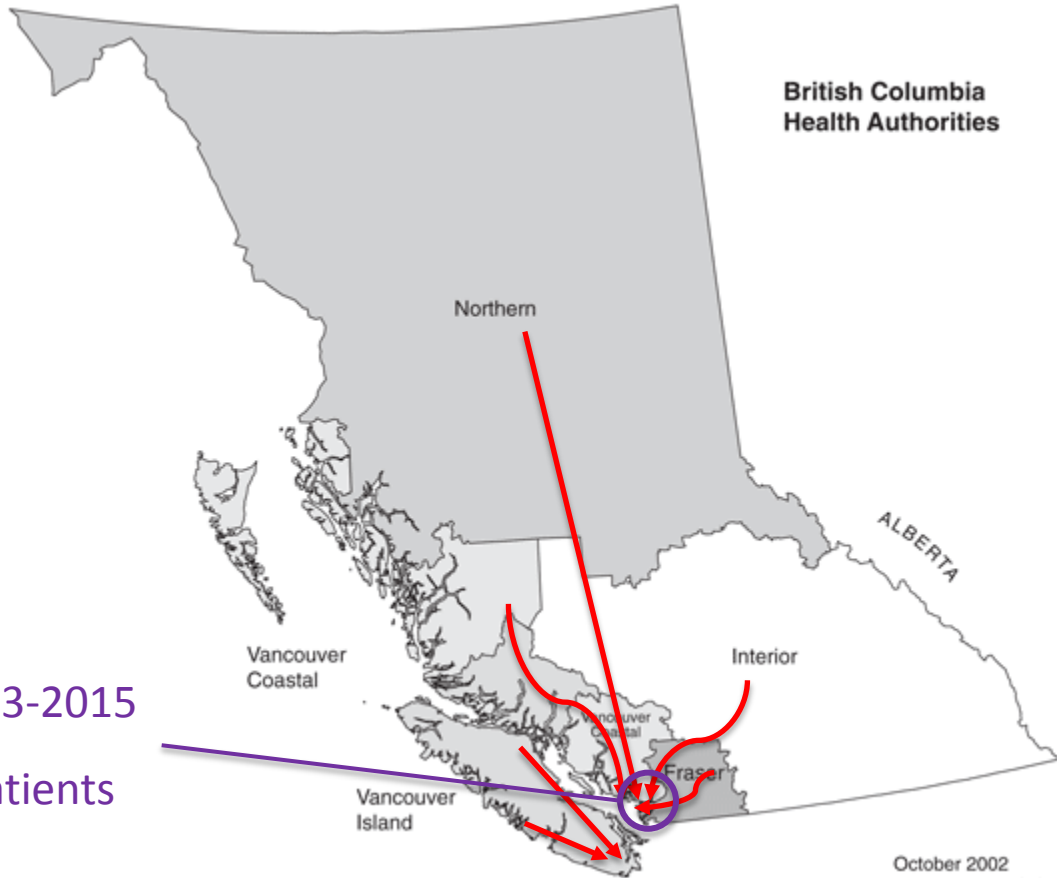
# BC GN Registry Clinical Data Capture

- Clinical information:
  - BP, height, weight, comorbidities, medications
- Maximize existing data entry processes that are currently part of usual care:
  - Kidney care clinics
  - Biopsy request form
  - Immunosuppression medications: directly by pharmacy at time of drug dispensing for GN Formulary

# Kidney biopsies in BC 2013 – early 2019



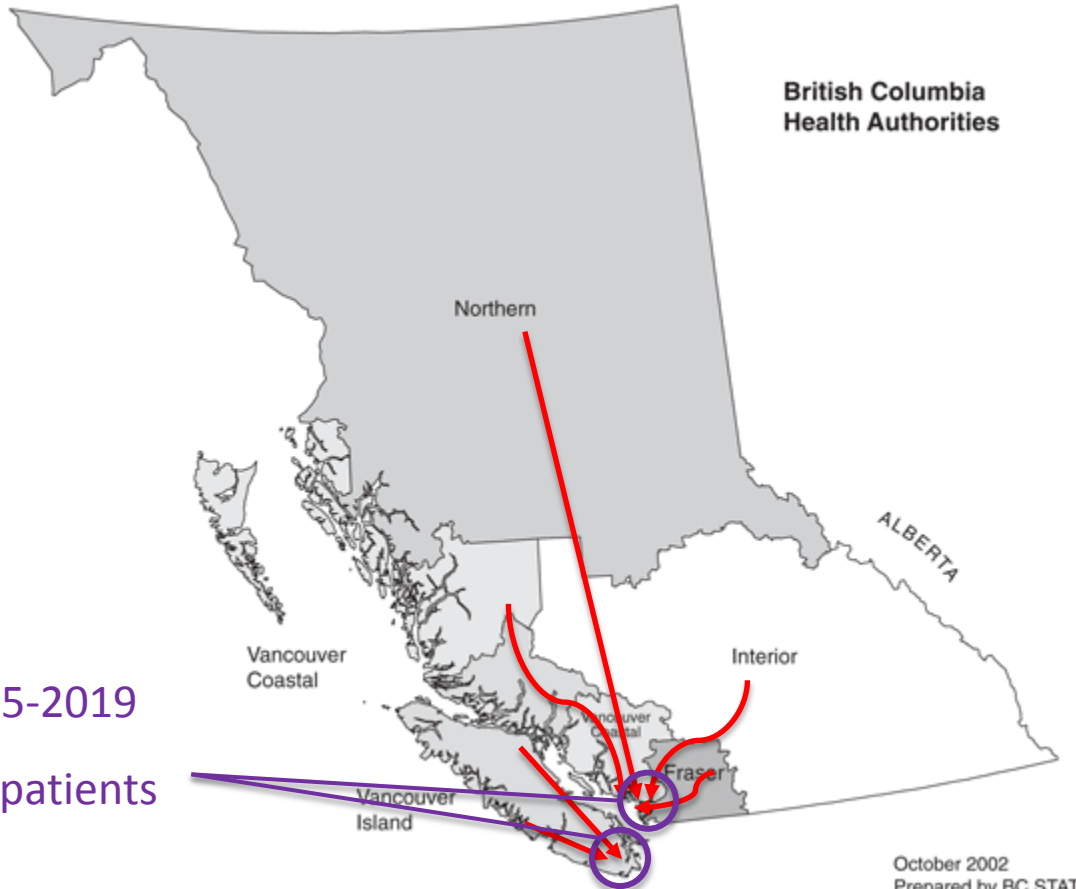
# Kidney biopsies in BC 2013 – early 2019



GN Registry 2013-2015

Missing VIHA patients

# Kidney biopsies in BC 2013 – early 2019



GN Registry 2015-2019

Capturing VIHA patients  
(manual)

# Kidney biopsies in BC early 2019 - Present



Dr. Susanna McRae



Dr. Mei Lin Bissonnette

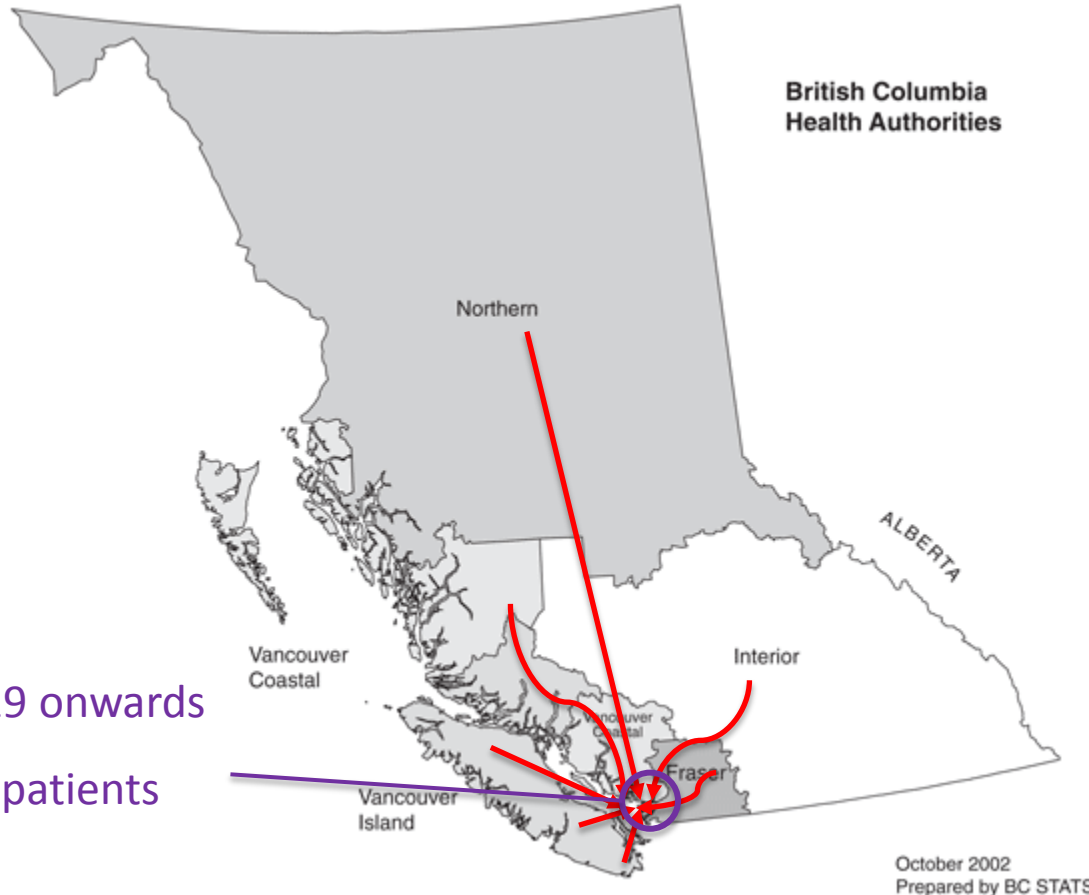


Dr. Maziar Riazzy





# Kidney biopsies in BC early 2019 - Present



GN Registry 2019 onwards

Capturing VIHA patients  
(automatic)

# BC GN Registry as of March 2019

	BC	PHC/VCHA	FHA	IHA	NHA	VIHA	BCCH
All GN patients	2670	1035	710	342	158	350	75
<b>Minimal change disease</b>	156	60	44	14	6	21	11
<b>FSGS</b>	526	191	144	60	33	91	7
<b>FSGS likely idiopathic</b>	69	24	23	9	4	5	4
<b>Membranous nephropathy</b>	285	95	91	35	20	38	6
<b>ANCA vasculitis</b>	343	110	94	61	21	49	8
<b>IgA nephropathy</b>	501	204	146	55	27	66	3
<b>Lupus nephritis</b>	240	136	38	20	9	17	20
<b>C3 glomerulopathy</b>	25	10	2	3	2	6	2
<b>PGNMID</b>	32	11	7	3	3	8	--
<b>Fibrillary/Immunotactoid GN</b>	20	2	4	4	4	6	--

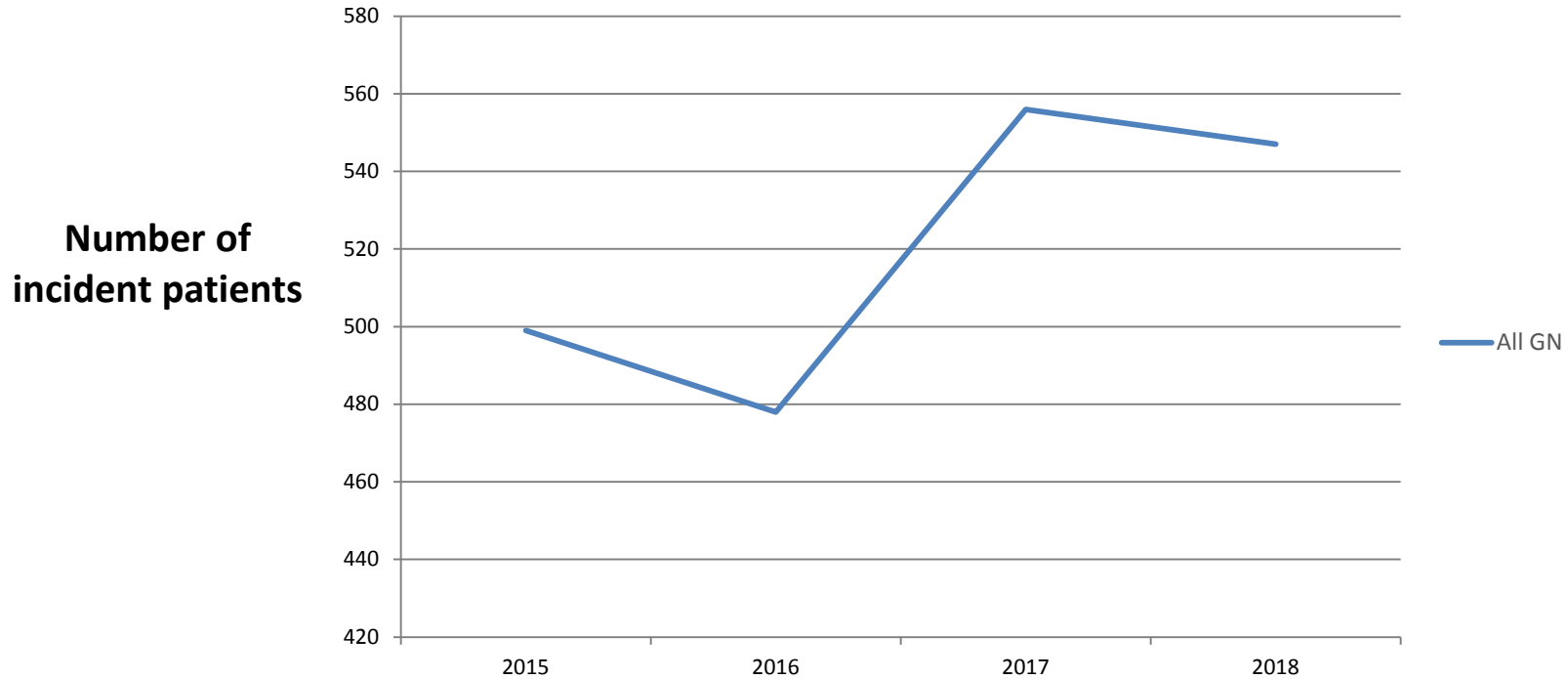
# BC GN Atlas

Using the GN Registry data to describe the  
epidemiology of GN in BC

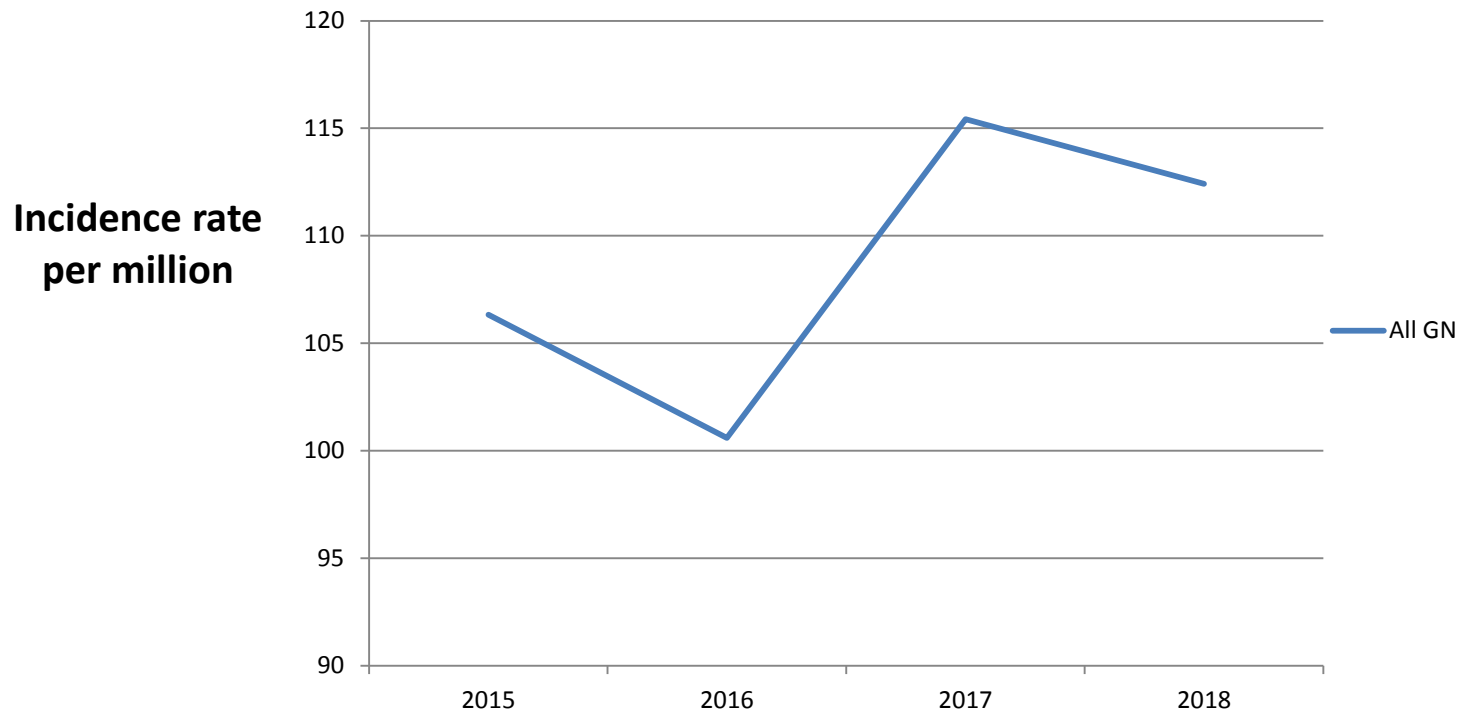
# BC GN Atlas

- Reporting period from 2015 to end of 2018
  - To ensure sufficient capture of VIHA patients after 2015
- To assess disease prevalence, compared to historical biopsy data from 2000-2012 from St. Paul's Hospital Pathology Lab
  - Prevalent patients with a first biopsy prior to 2000 and a repeat biopsy in the GN registry erroneously classified as “incident”
  - No historical data available for VIHA -> any patient with a repeat biopsy in the GN registry erroneously classified as “incident”

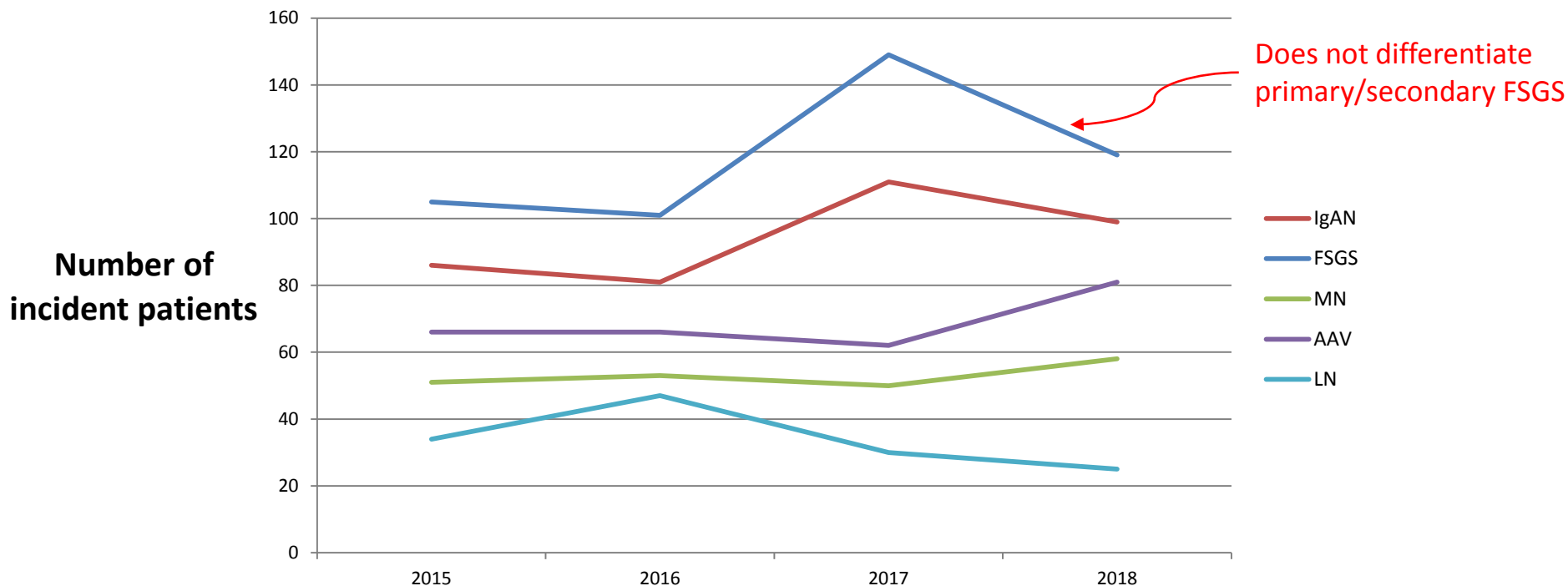
# Number of incident GN patients in BC



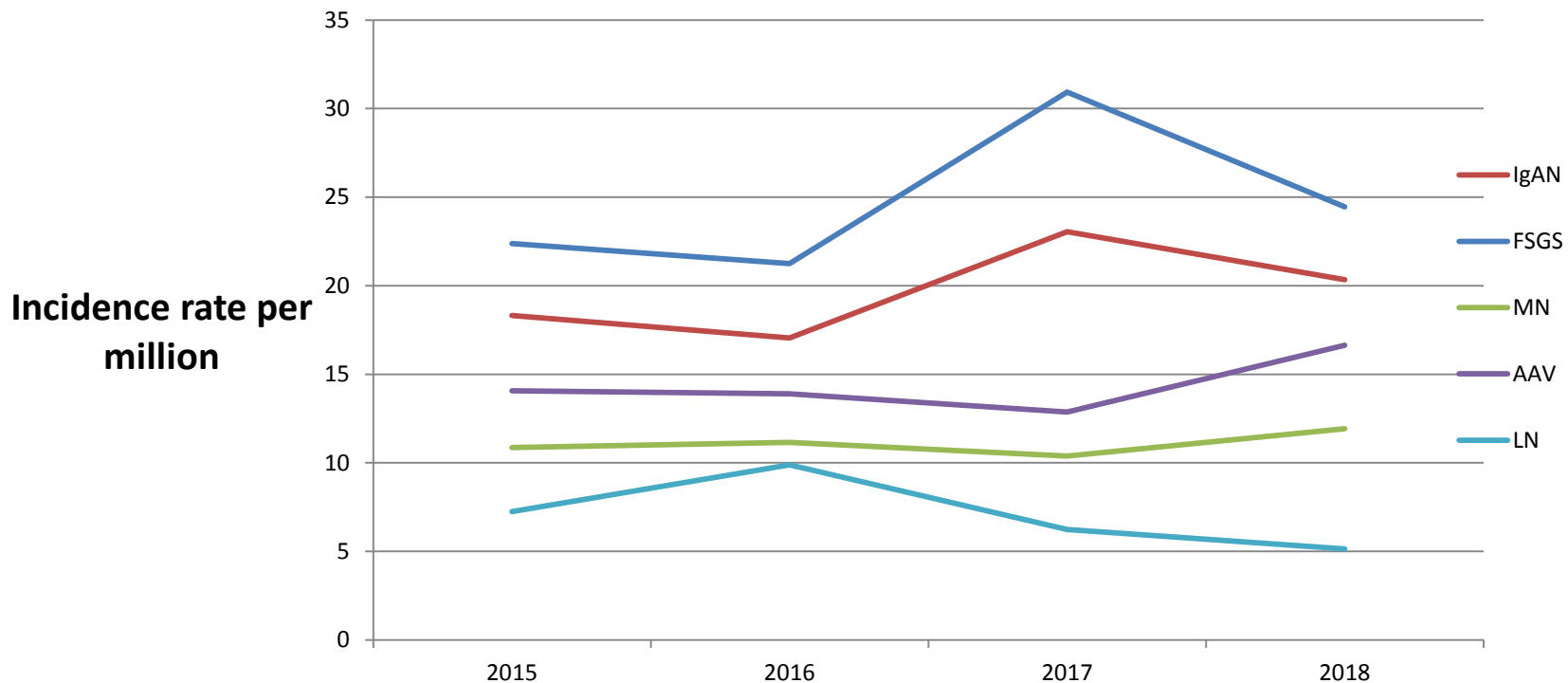
# Incidence rate of GN in BC



# Number of incident GN subtypes in BC



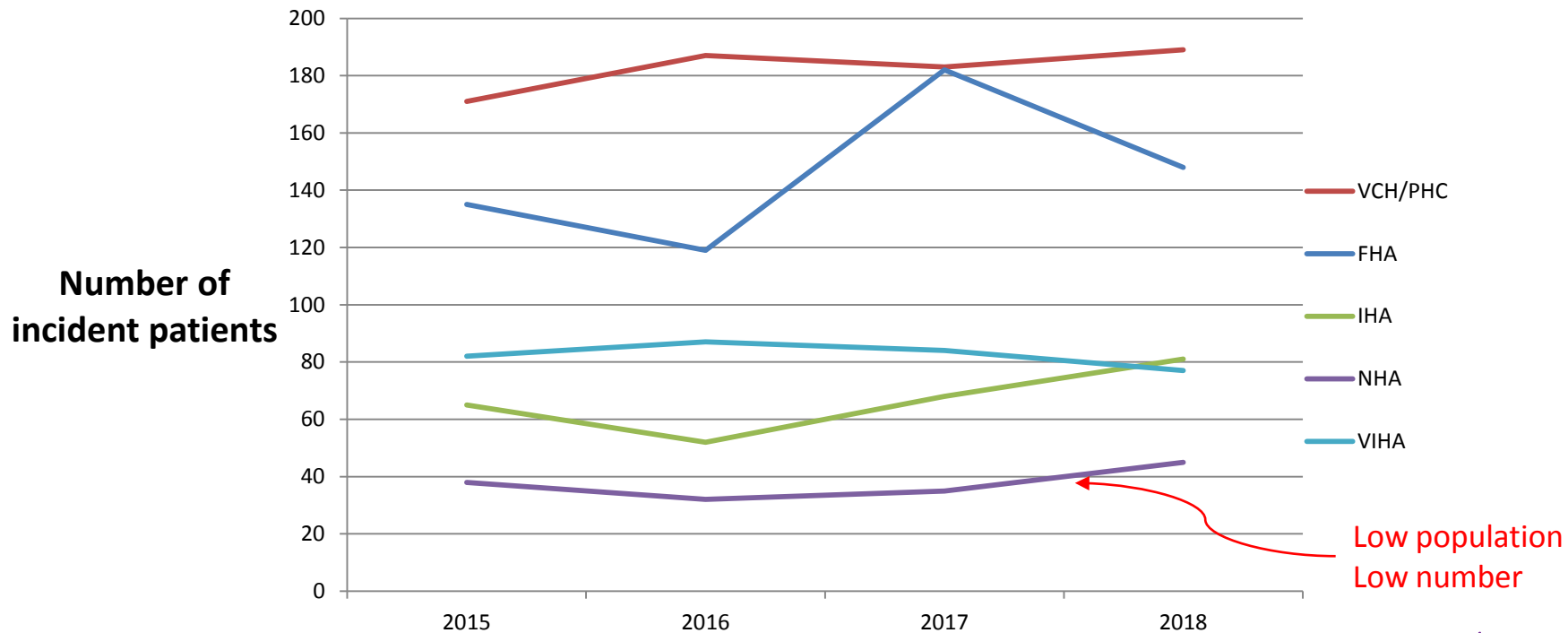
# Incident rate of GN subtypes in BC



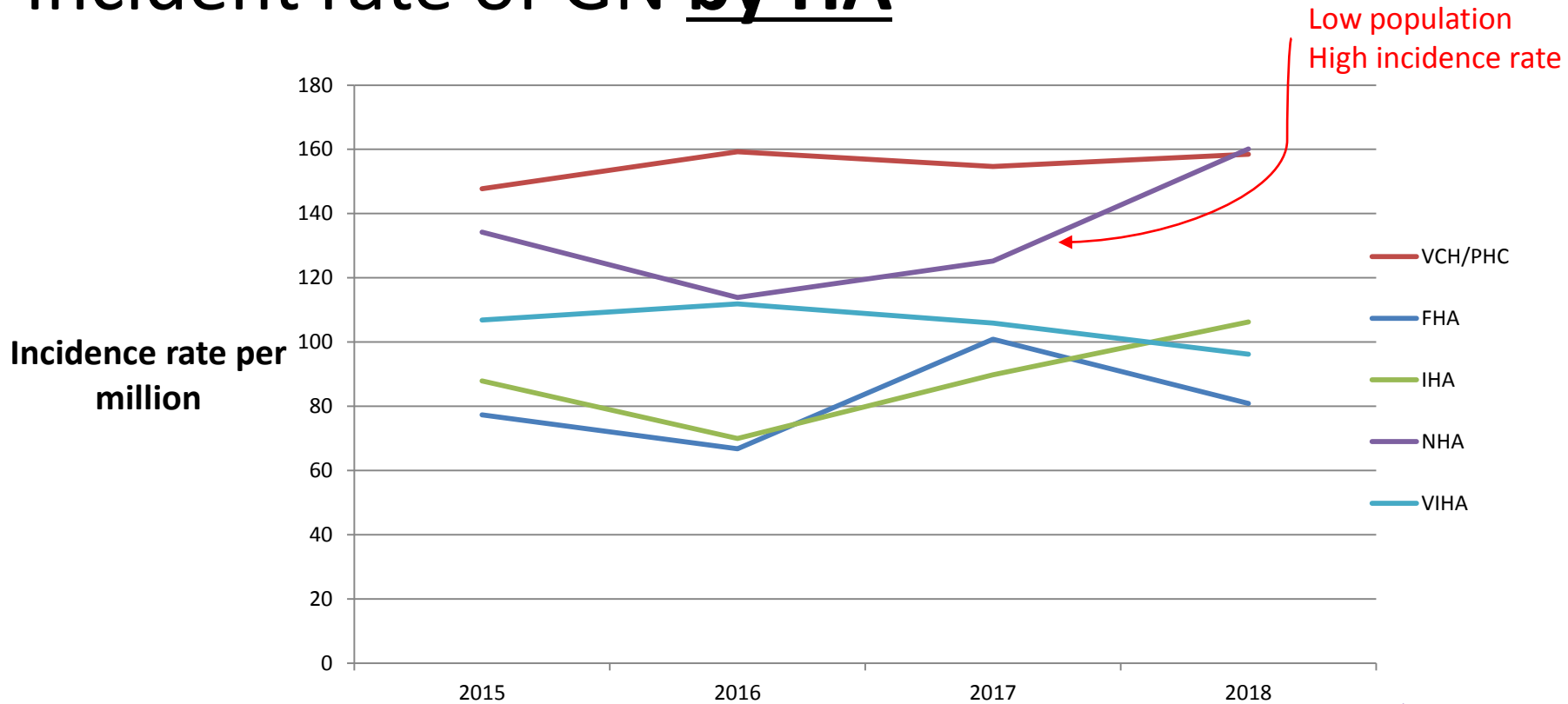
Incidence rates appear stable over time, and match existing literature



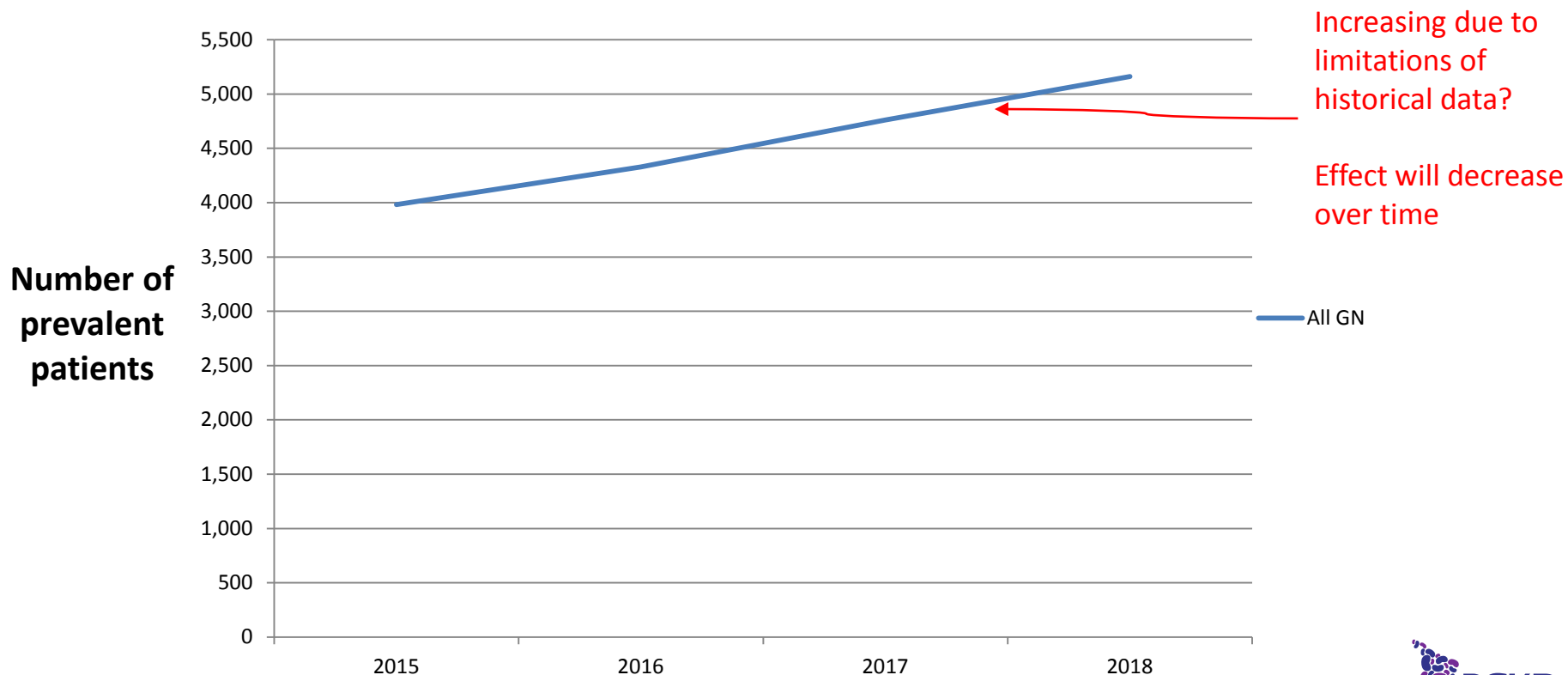
# Number of incident GN patients by HA



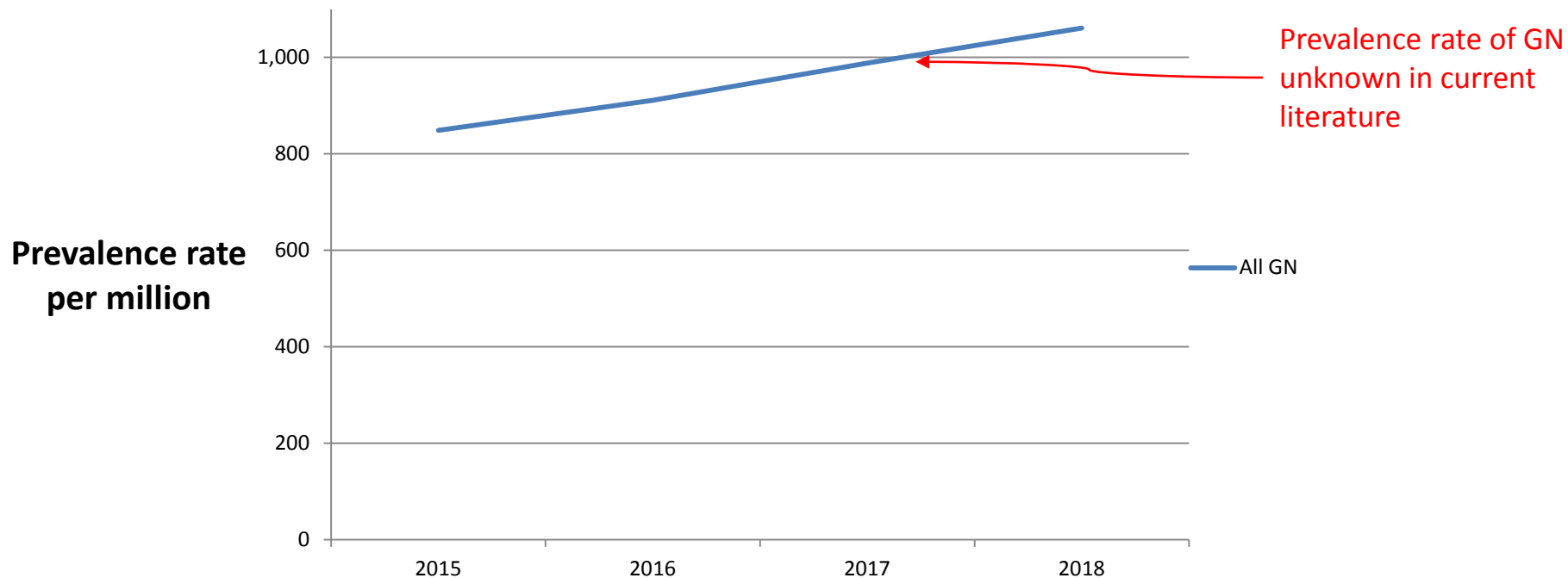
# Incident rate of GN by HA



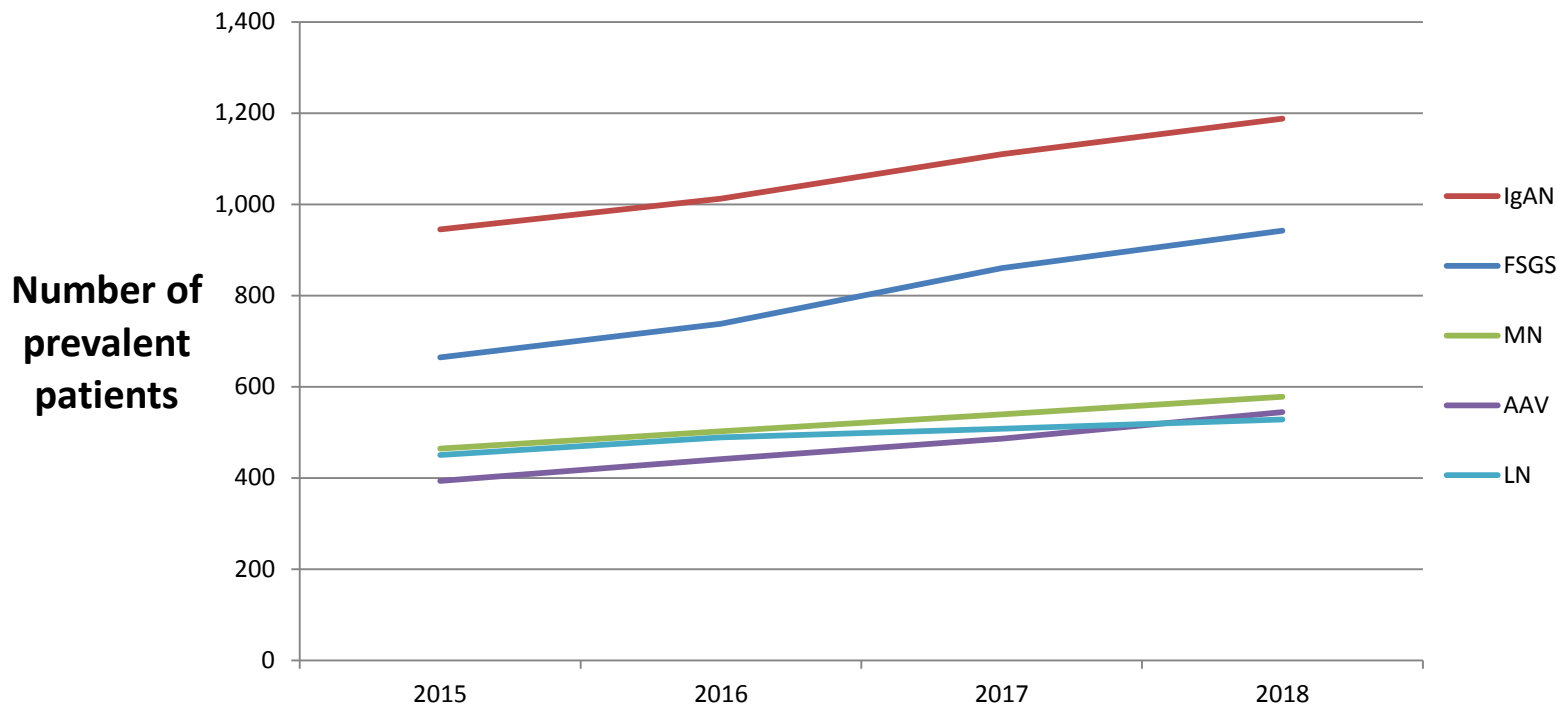
# Number of prevalent GN patients in BC



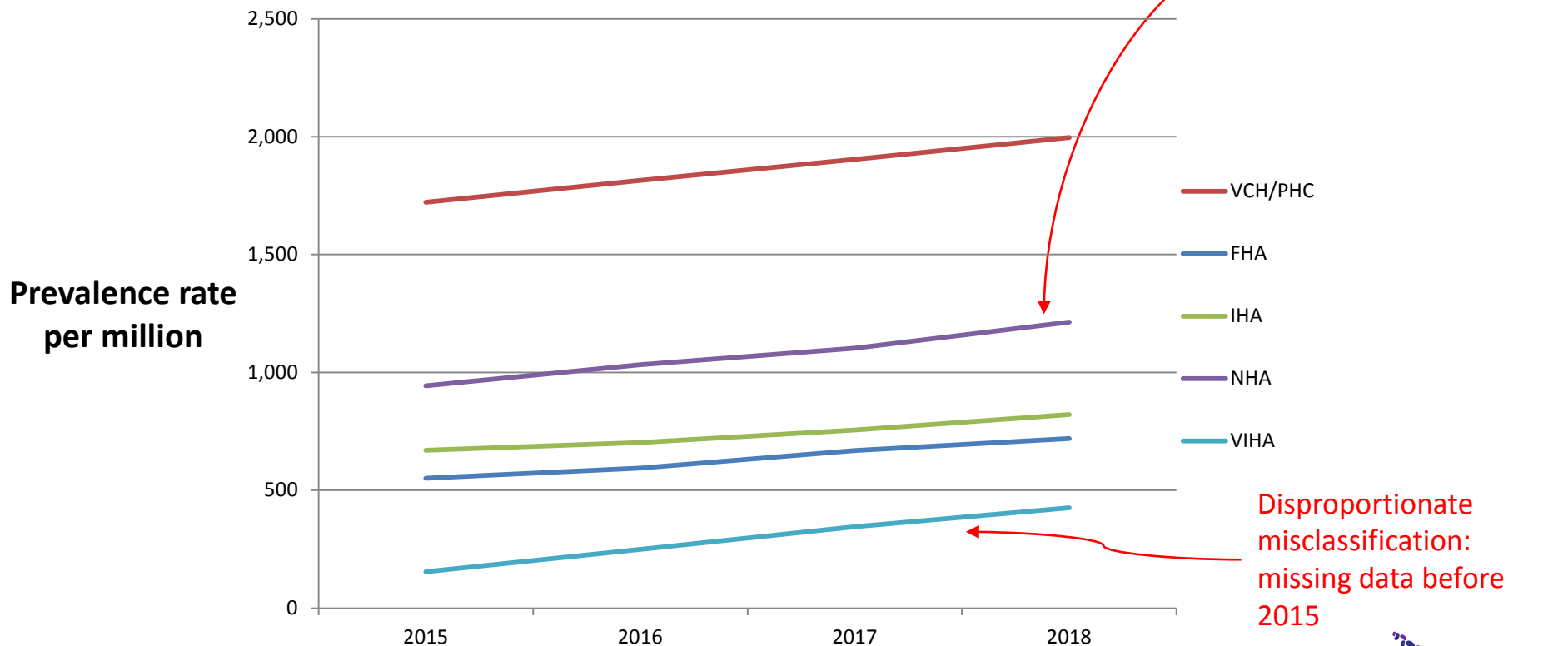
# Prevalence rate of GN in BC



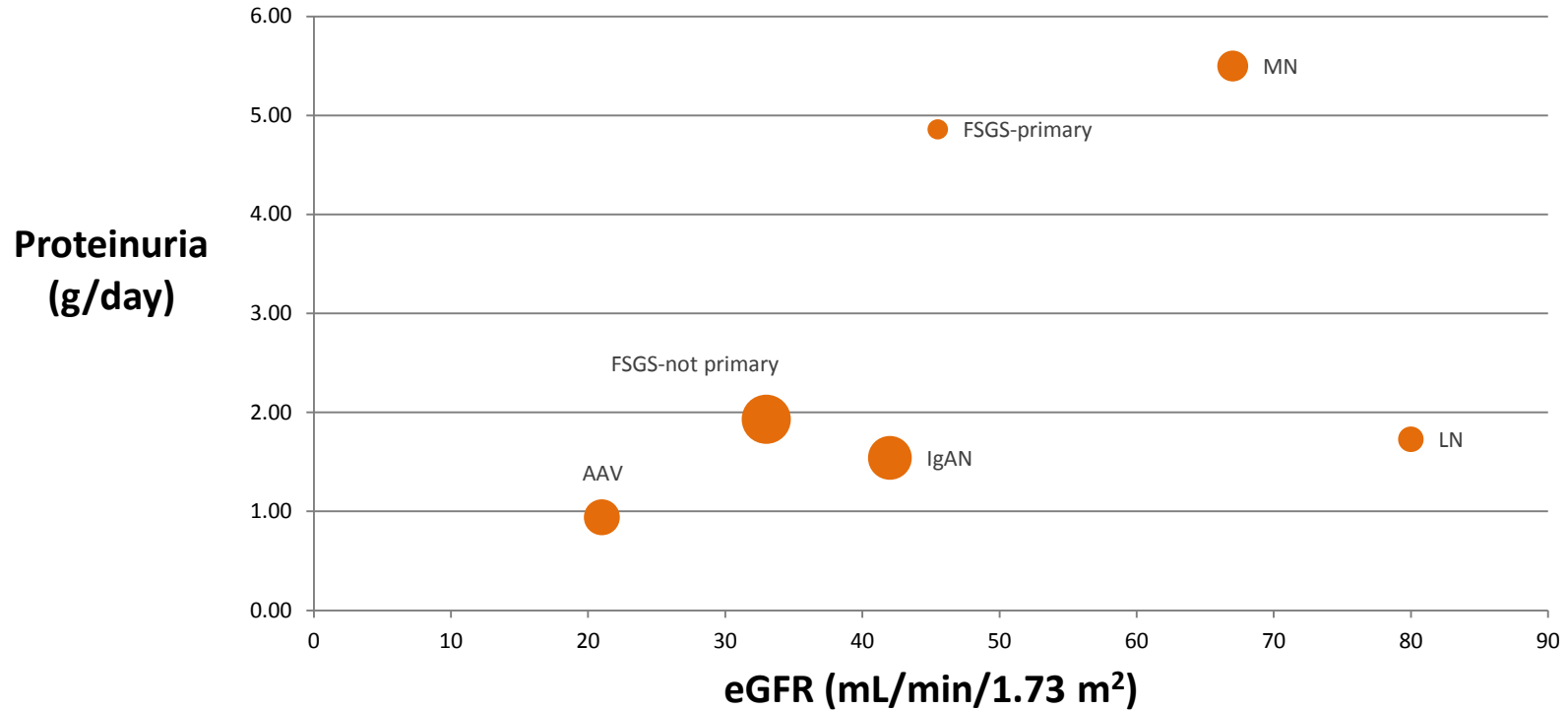
# Number of prevalent GN subtype in BC



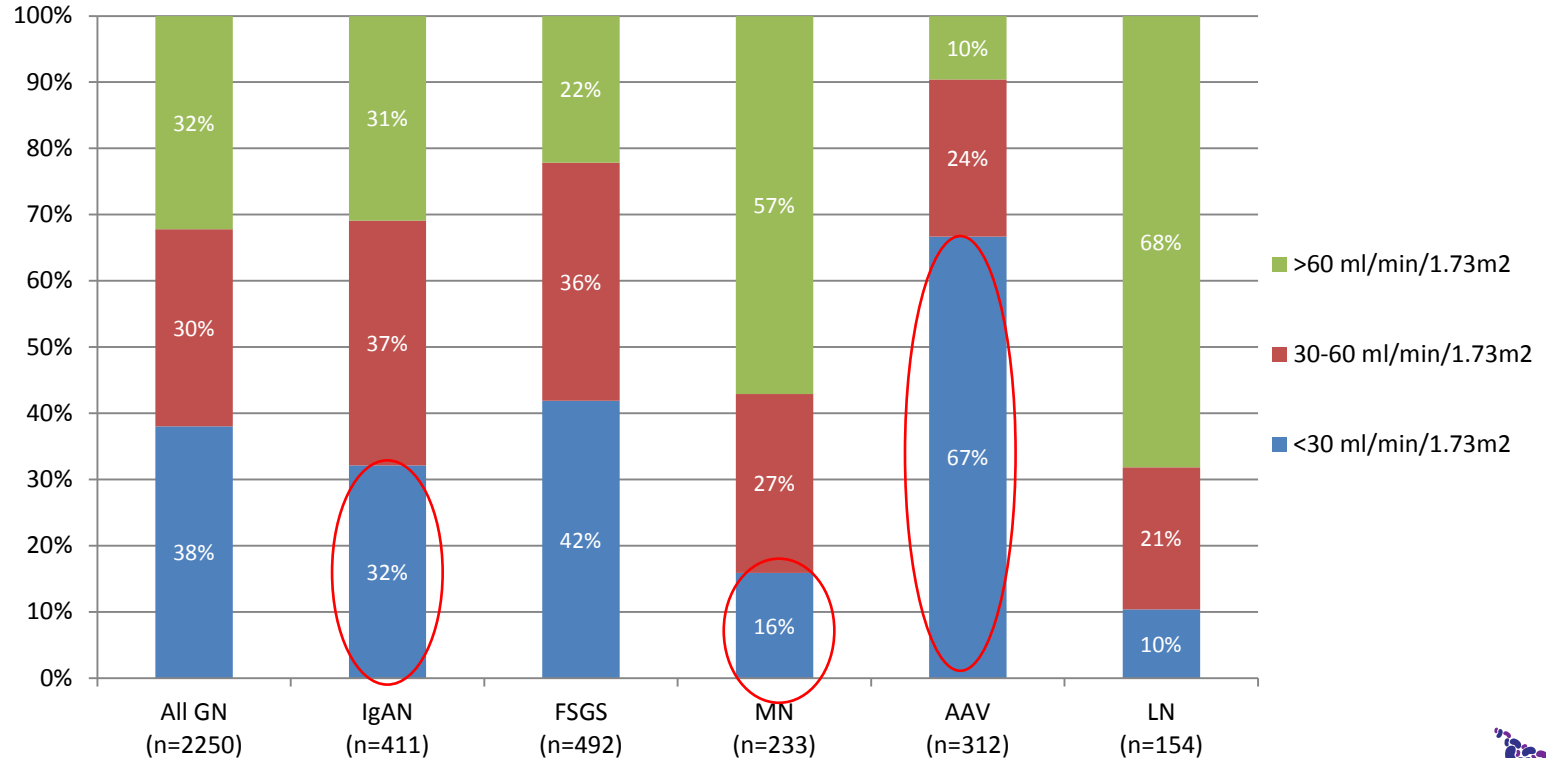
# Prevalence rate of GN by HA



# Clinical characteristics at biopsy

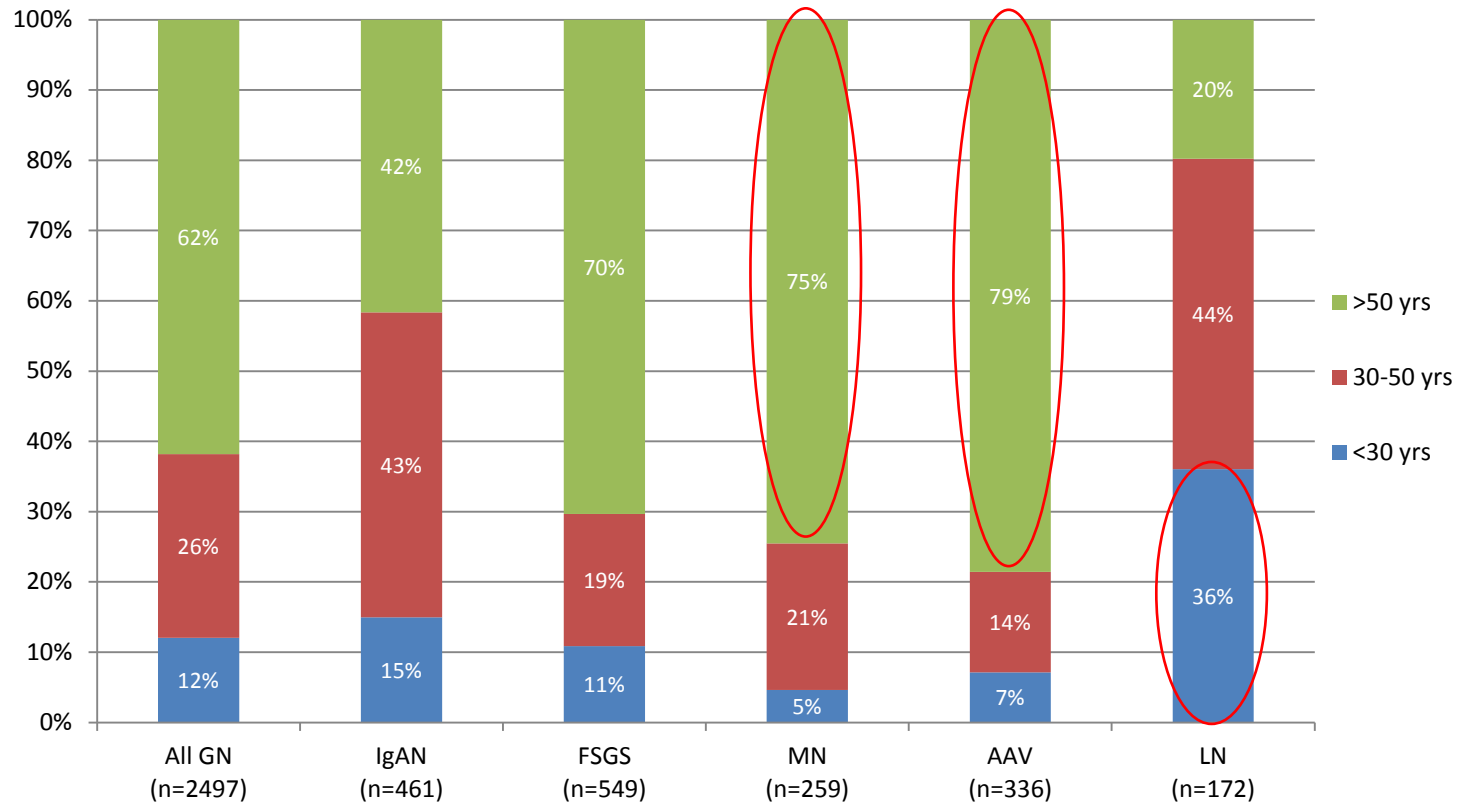


# eGFR at biopsy





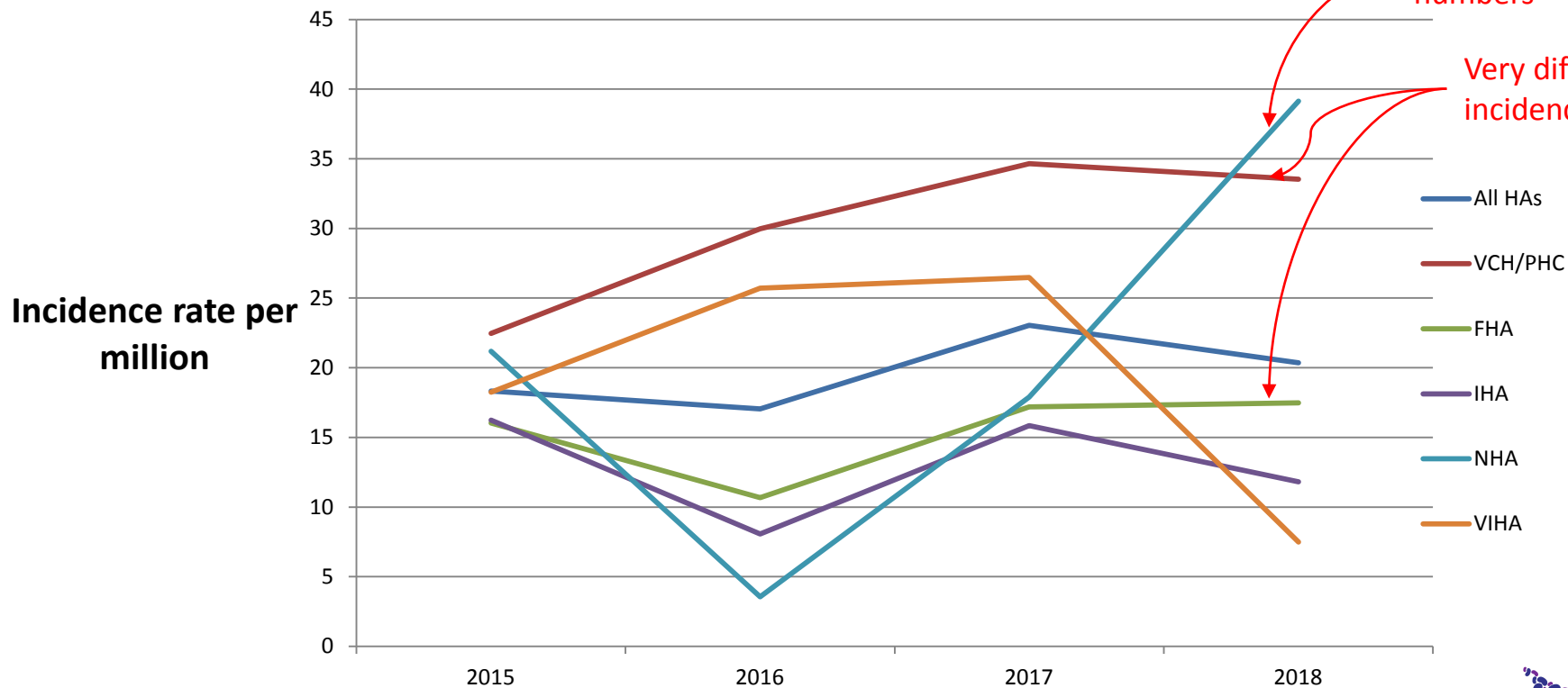
# Age at biopsy



# BC GN Atlas

The epidemiology of IgA nephropathy in BC

# Incidence rate of IgAN in BC

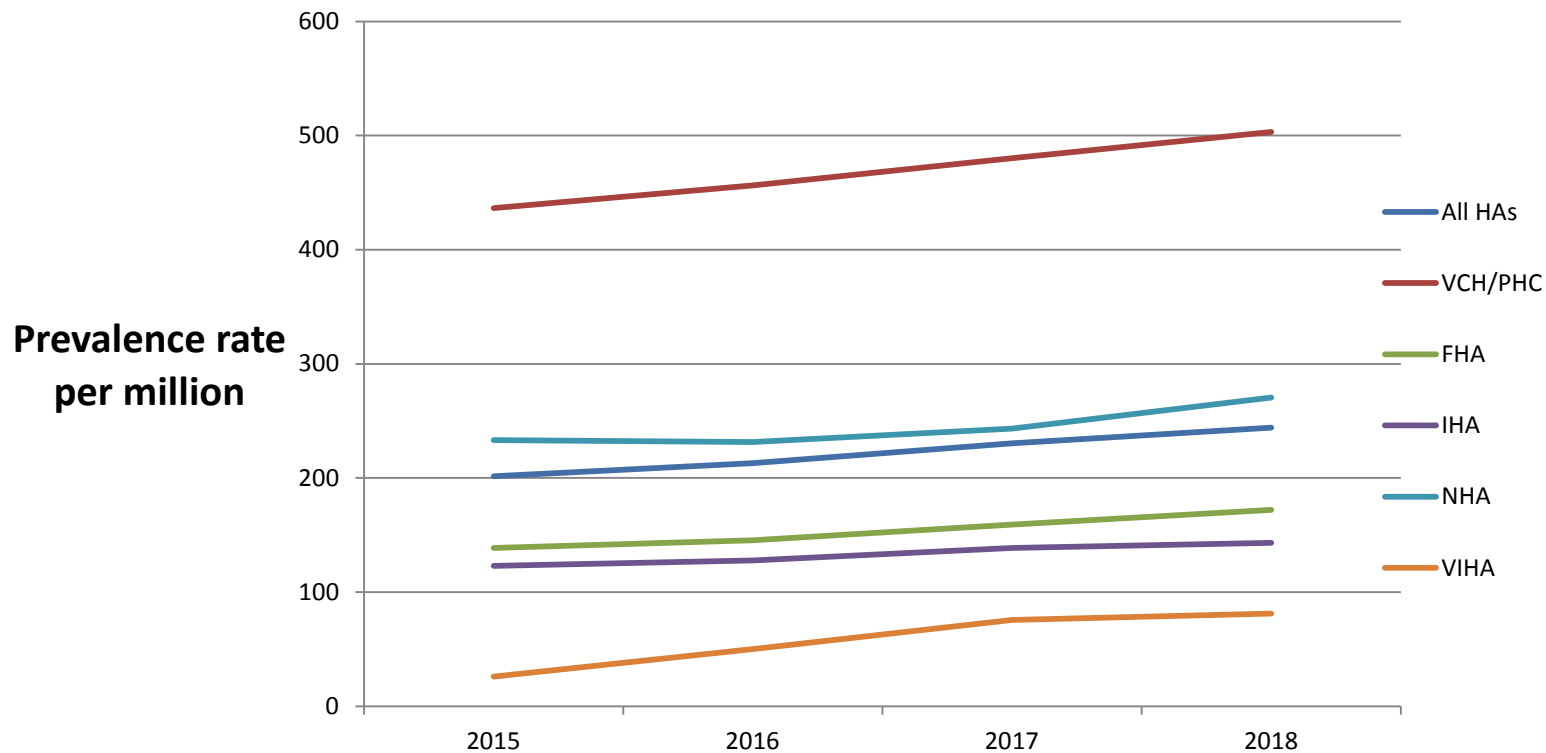


Imprecise due to low numbers

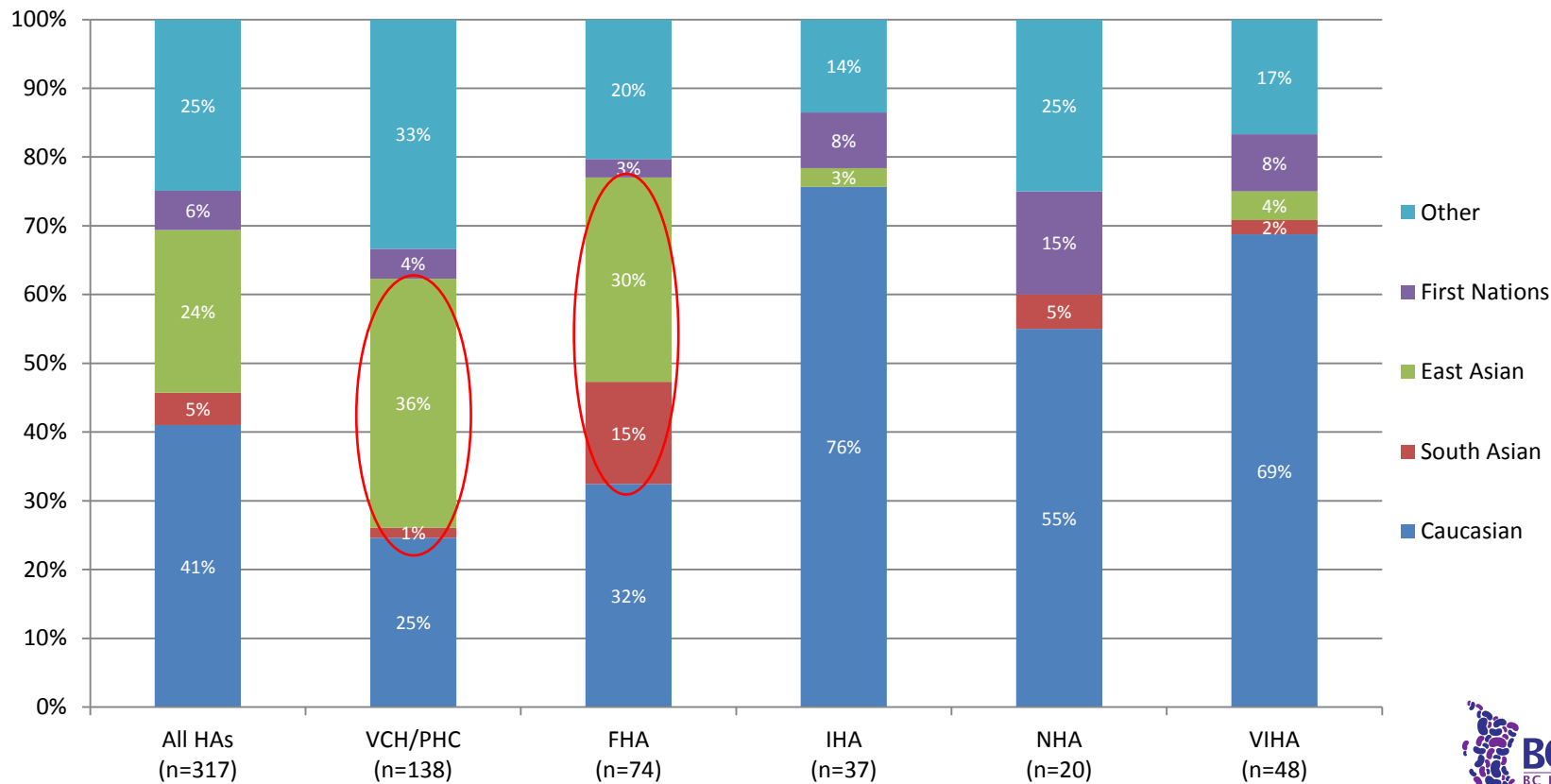
Very different incidence rates

- All HAs
- VCH/PHC
- FHA
- IHA
- NHA
- VIHA

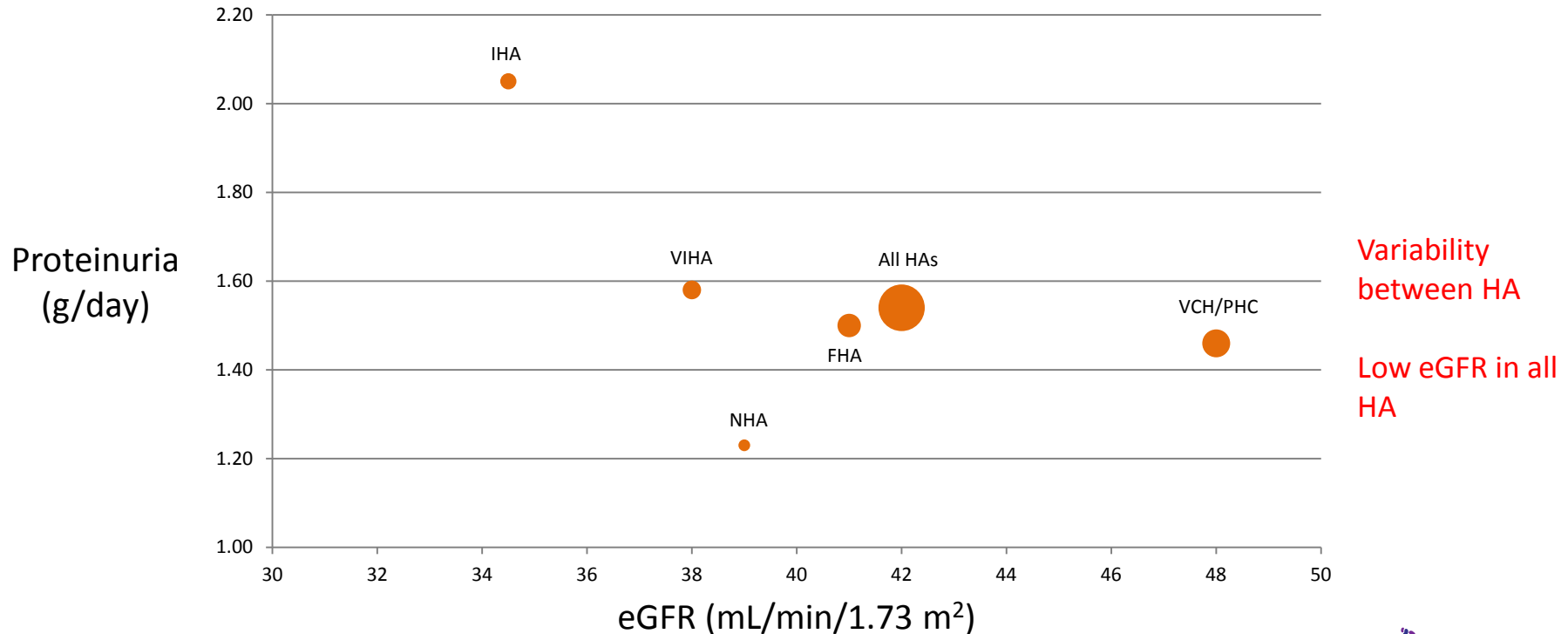
# Prevalence rate of IgAN in BC



# Race/ethnicity in IgAN



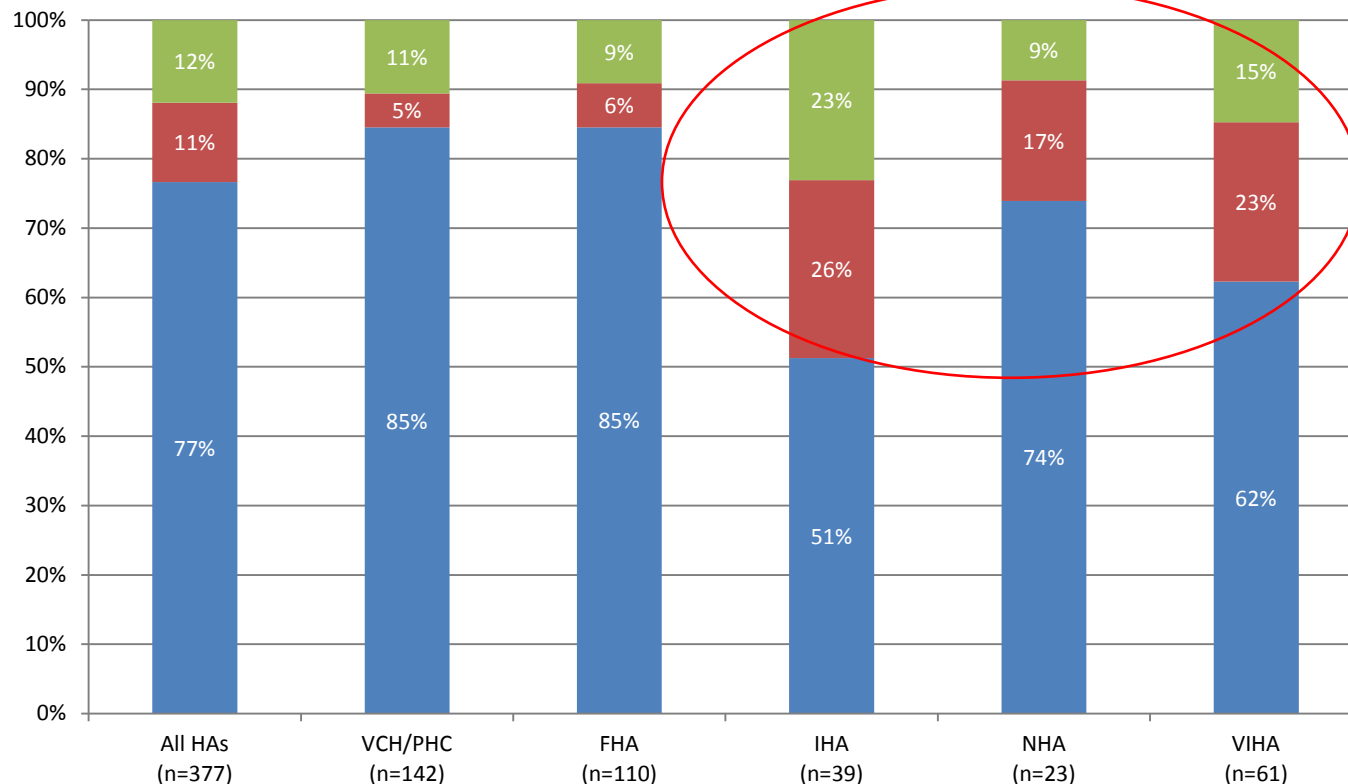
# Clinical characteristics at biopsy in IgAN



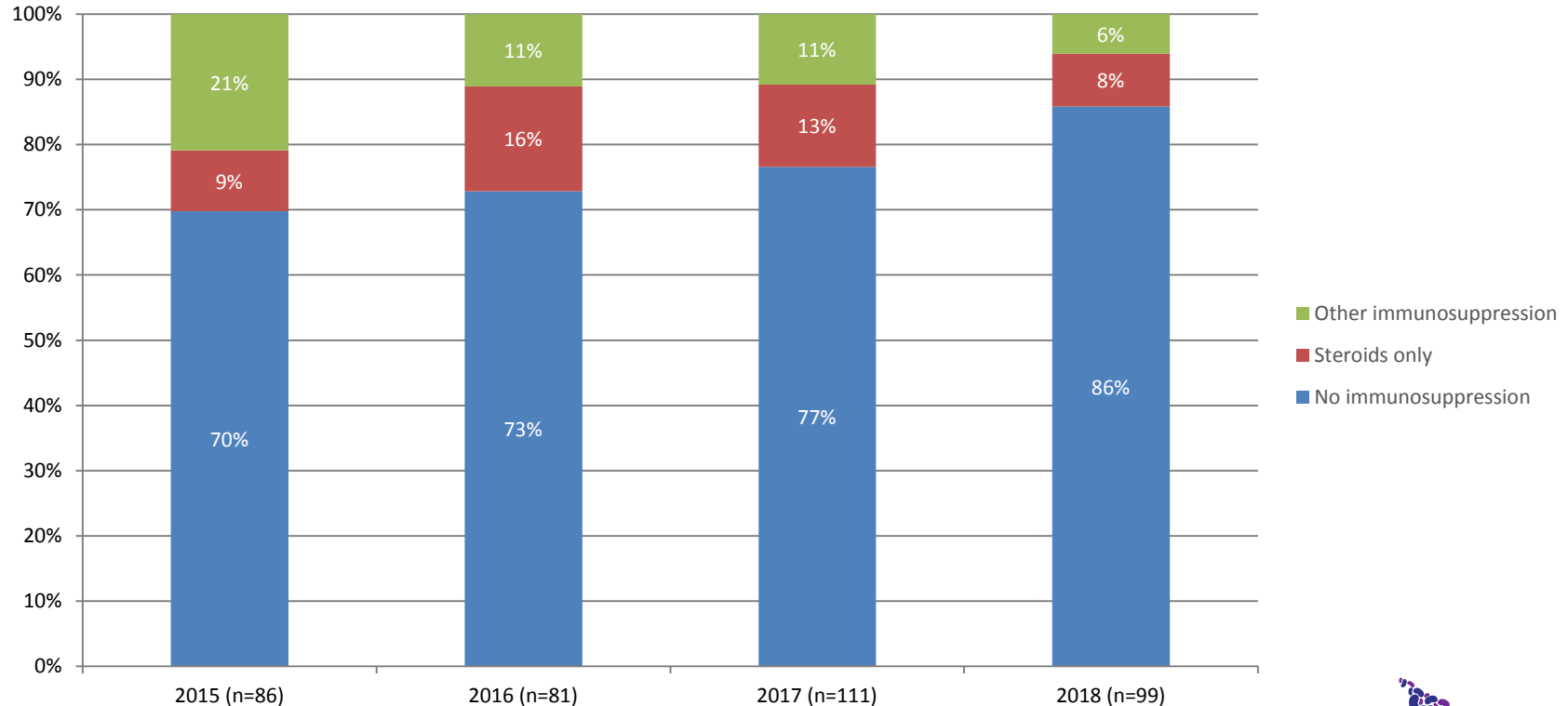
# Immunosuppression in IgAN by HA

GN formulary started in 2014

Different patterns of data capture for steroids?

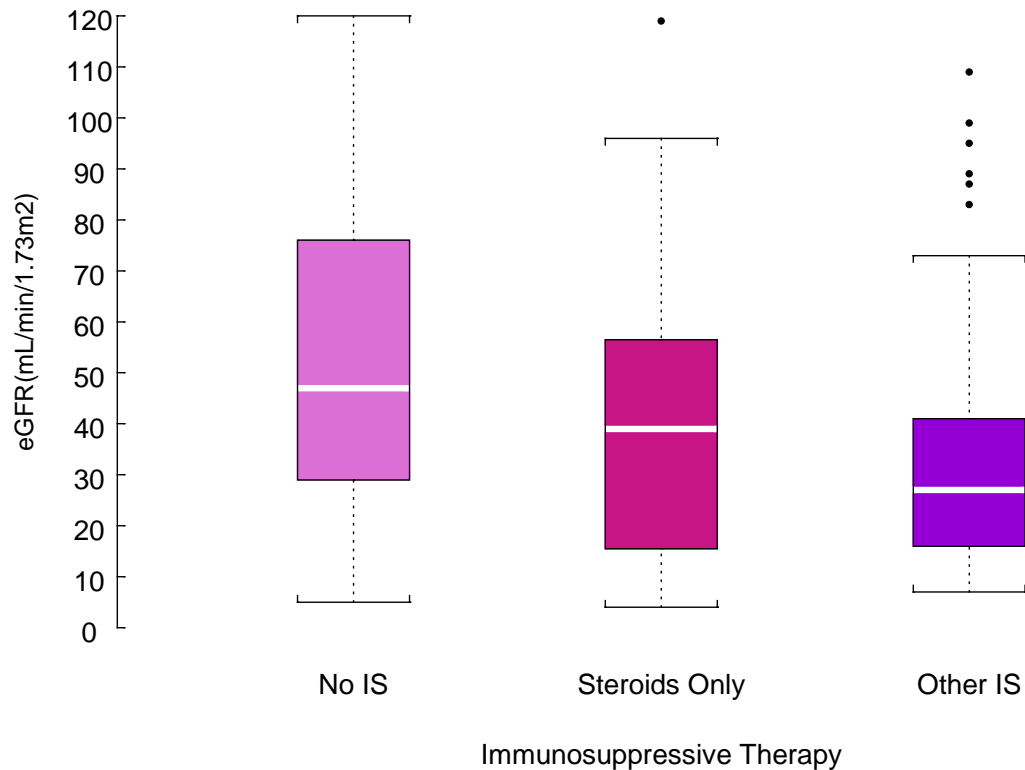


# Immunosuppression use in IgAN over time



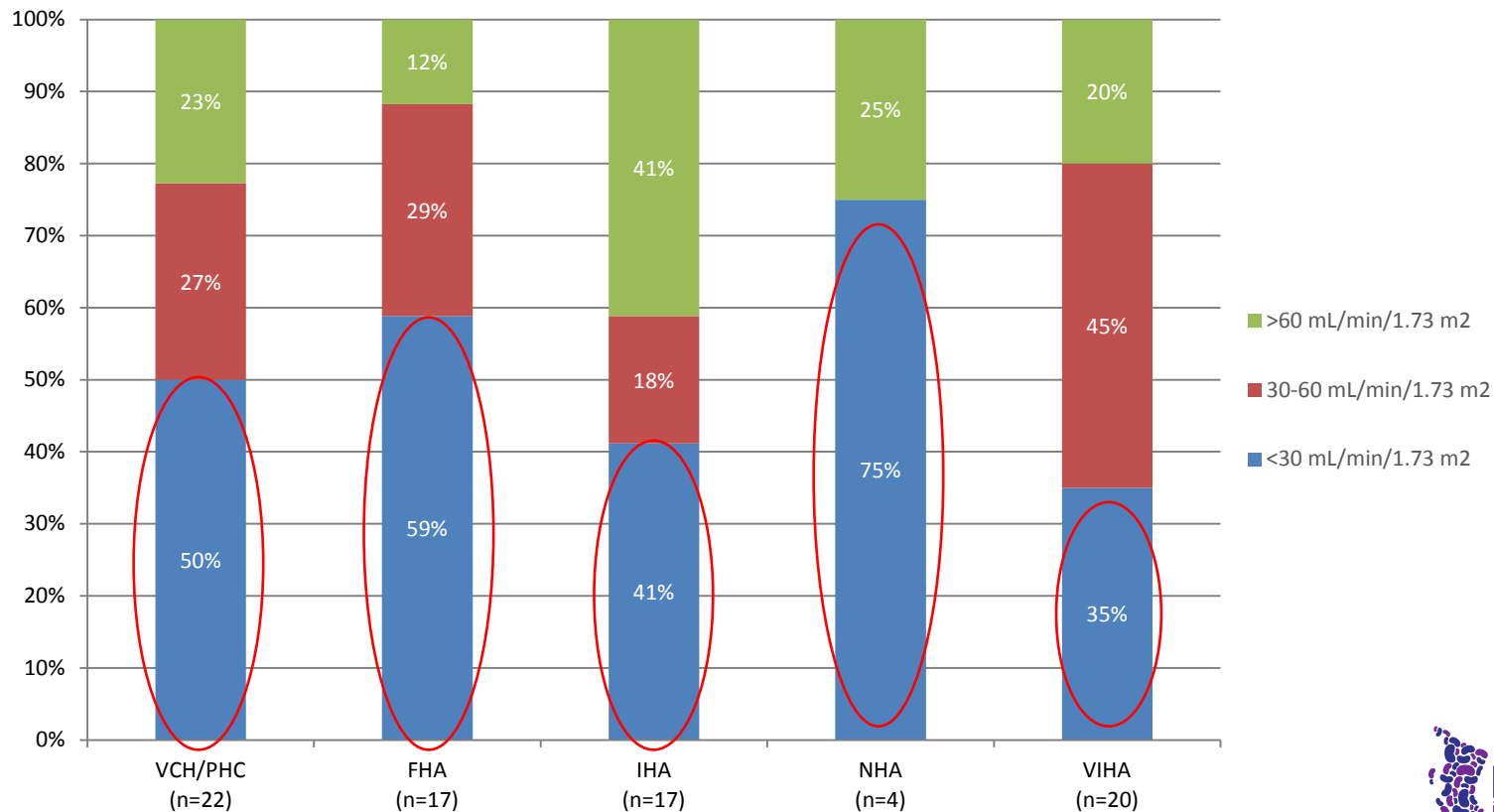


# eGFR at biopsy by immunosuppression exposure

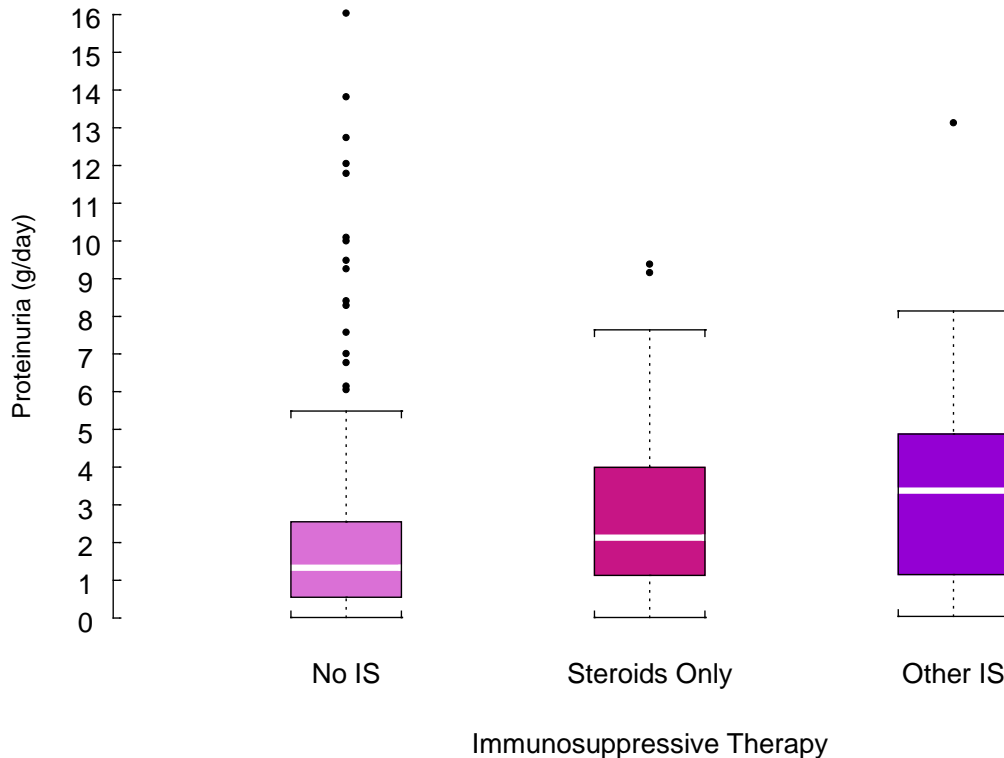


IS being used mostly in those with low eGFR

# eGFR at biopsy in treated patient by HA

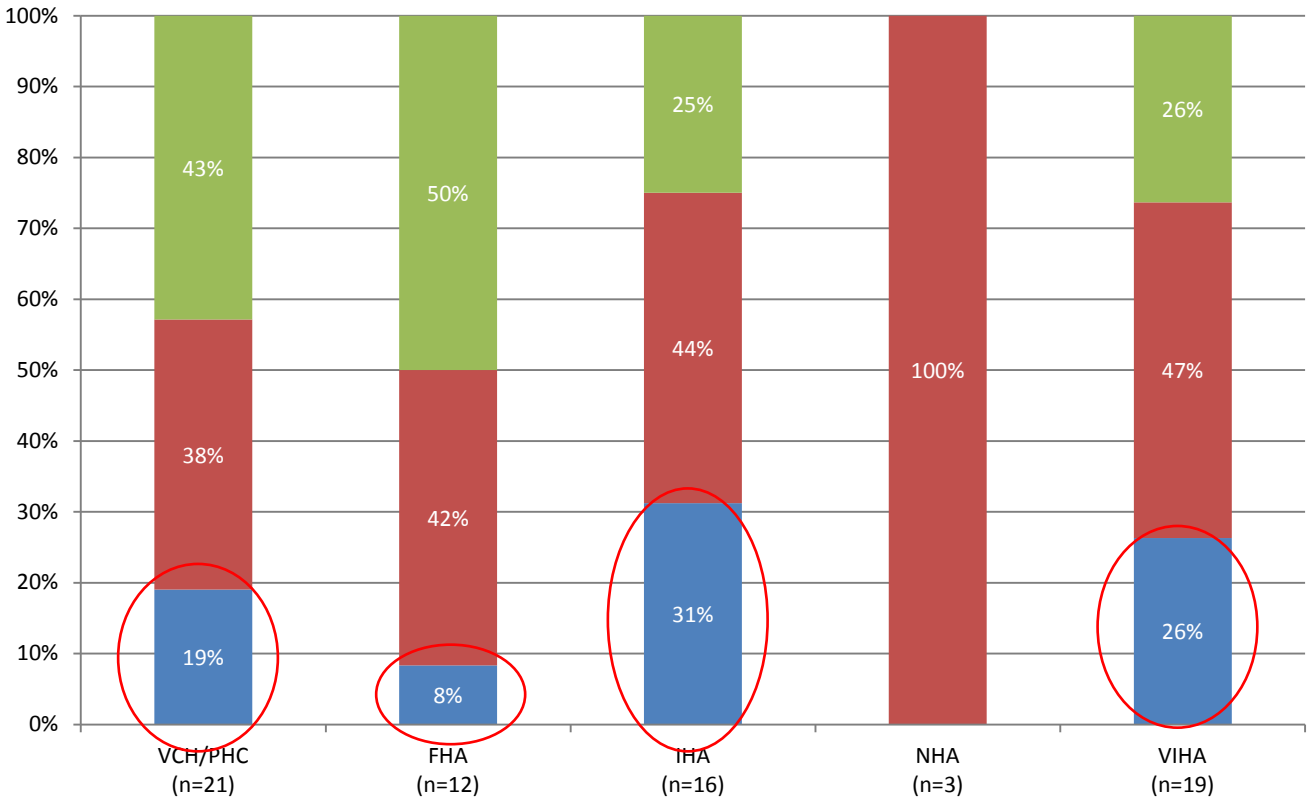


# Proteinuria at biopsy by immunosuppression exposure



Non-steroid IS being used in those with higher proteinuria

# Proteinuria at biopsy in treated patient by HA

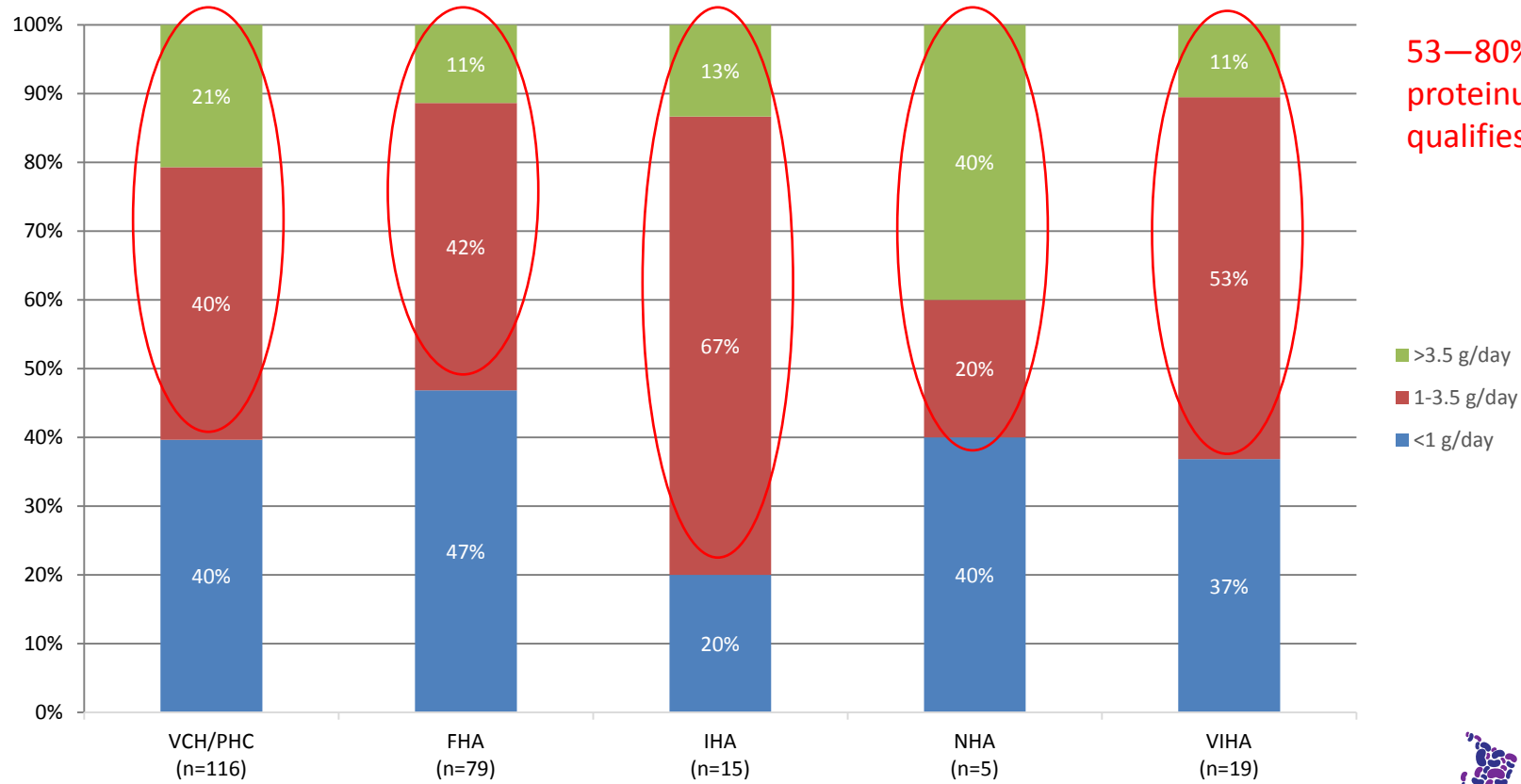


Proteinuria at biopsy may not be only determinant of treatment

- >3.5 g/day
- 1-3.5 g/day
- <1 g/day

# Proteinuria at biopsy in untreated patient by HA

53—80% have proteinuria that qualifies for IS

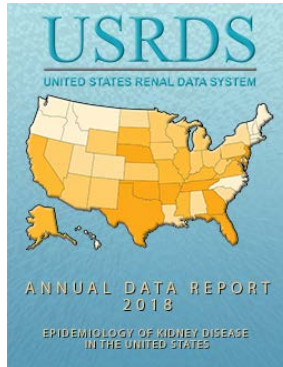


# BC GN Atlas: Conclusions

- Unique population-level data infrastructure in the GN Registry
  - Amount of data is increasing over time
  - Provide the first overview of the epidemiology of GN in BC
  - Address knowledge gaps: incidence/prevalence of GN, patterns of practice
- Raises interesting questions:
  - Is incidence/prevalence stable or increasing?
  - Geographic locations of high-incidence regions?
  - Are there different patterns of practice vs data capture?

# BC GN Atlas: Next Steps

- Edit and refine the figures
- Add outcome data: ESKD, mortality, time from biopsy to IS, locations of clinical care
- Generate an official GN Atlas report for distribution



## Annual Statistics on Organ Replacement in Canada

Dialysis, Transplantation and Donation,  
2008 to 2017



# BC GN Registry

Research applications



# Disease-specific incident glomerulonephritis displays geographic clustering in under-serviced rural areas of British Columbia, Canada

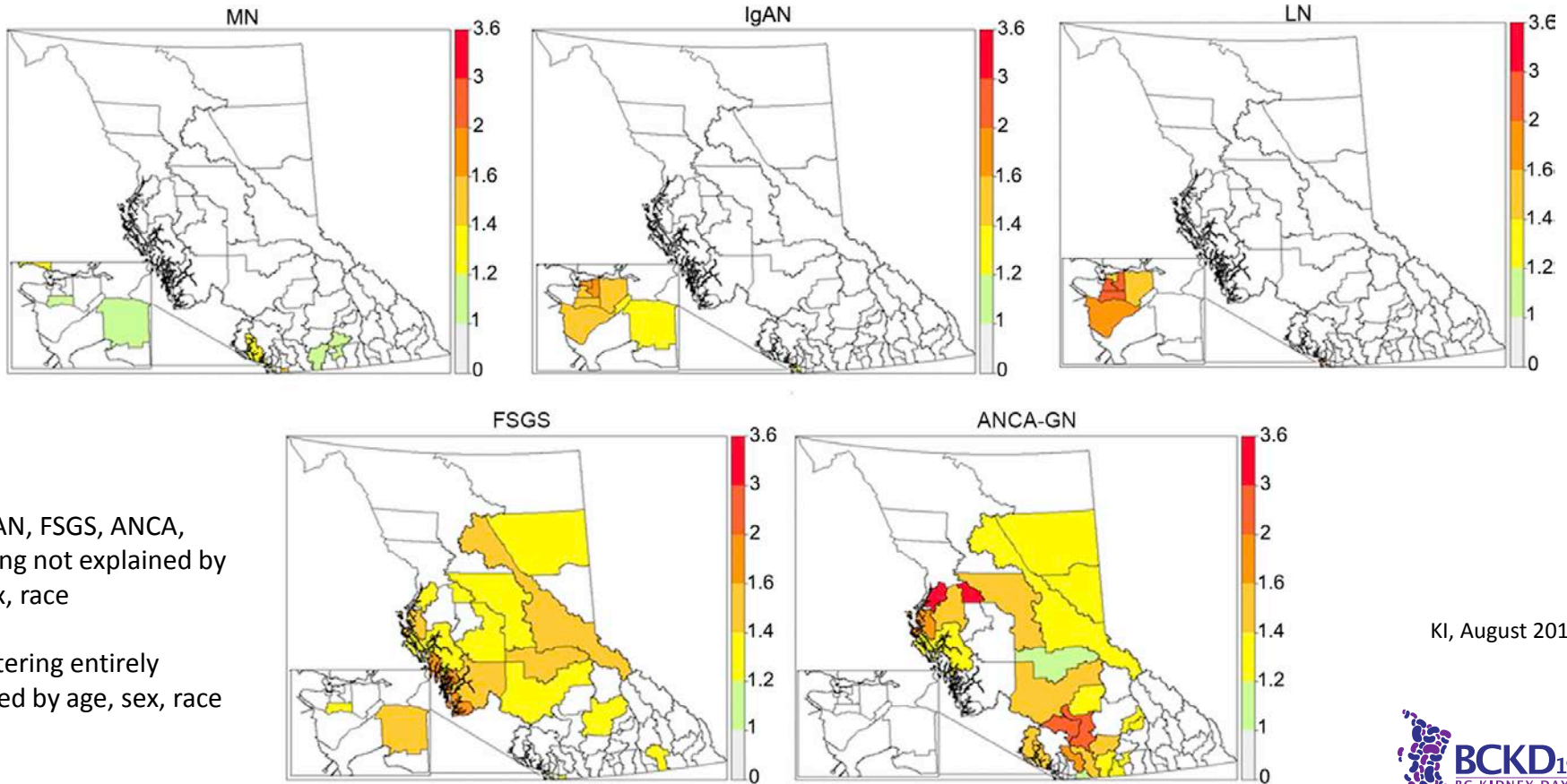
Mark Canney<sup>1,2</sup>, Dilshani Induruwage<sup>2</sup>, Lawrence C. McCandless<sup>3</sup>, Heather N. Reich<sup>4</sup> and Sean J. Barbour<sup>1,2</sup>



Kidney International, August 2019

- Used historical SPH biopsy data from 2000-2012 to explore geographic clustering of incident GN in BC
  - VIHA excluded due to lack of data
- Bayesian spatial model to adjust for correlation between adjacent regions, and region-level age, sex and race demographics
- Compared incidence rate in each region to overall average incidence in BC

# Geographic clusters of GN in BC

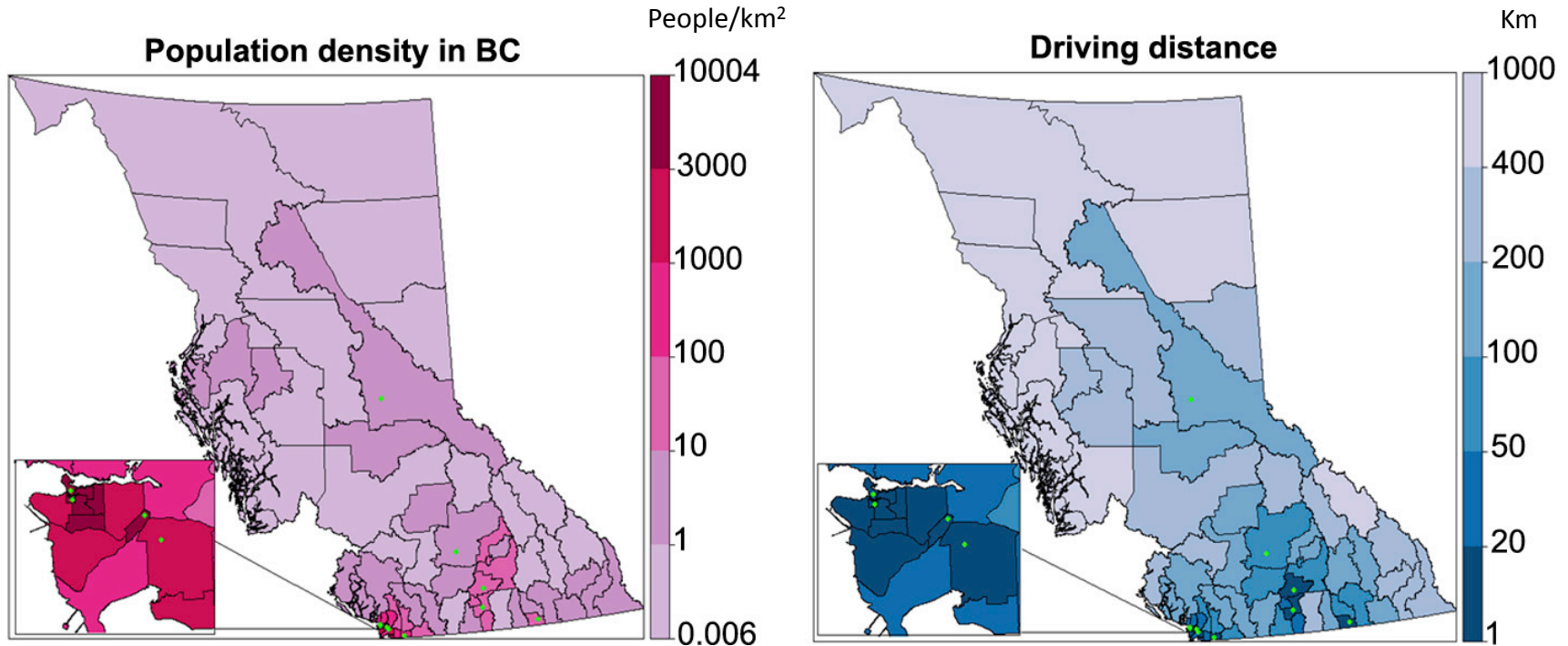


MN, IgAN, FSGS, ANCA,  
clustering not explained by  
age, sex, race

LN clustering entirely  
explained by age, sex, race

KI, August 2019

# Geographic clusters of GN in BC



# Urban vs rural clusters of GN in BC

Variable	MN	IgAN	FSGS	ANCA-GN	LN
<b>Rural clusters<sup>a</sup></b>					
N (%) of all clusters	6 (75)	0	15 (88)	25 (100)	0
Population density	45.3 (0.9–334.7)	n/a	0.6 (0.1–334.7)	1.2 (0.4–67.9)	n/a
Driving distance	23 (7–130)	n/a	386 (7–950)	154 (10–676)	n/a
<b>Urban clusters</b>					
N (%) of all clusters	2 (25)	8 (100)	2 (12)	0	6 (100)
Population density	1678.5 <sup>b</sup> 4677.2 <sup>b</sup>	4240.9 (1304.3–6714.6)	1678.5 <sup>b</sup> 4677.2 <sup>b</sup>	n/a	5079.7 (1304.3–6714.6)
Driving distance	7 <sup>b</sup> 7 <sup>b</sup>	7 (3–15)	7 <sup>b</sup> 7 <sup>b</sup>	n/a	7.5 (3–15)

These findings could not have been predicted by age, sex, race demographics from local regions

Argues for mandatory reporting of GN to plan health services delivery

# Using the BC GN Registry for clinical trials

- Population-level biopsy results linked to laboratory data
  - Allows screening for eligible patients and targeted recruitment
  - Beneficial for rare diseases in which clinic-based recruitment is not effective

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Rituximab or Cyclosporine in the Treatment of Membranous Nephropathy

F.C. Fervenza, G.B. Appel, S.J. Barbour, B.H. Rovin, R.A. Lafayette, N. Aslam, J.A. Jefferson, P.E. Gipson, D.V. Rizk, J.R. Sedor, J.F. Simon, E.T. McCarthy, P. Brenchley, S. Sethi, C. Avila-Casado, H. Beanlands, J.C. Lieske, D. Philibert, T. Li, L.F. Thomas, D.F. Green, L.A. Juncos, L. Beara-Lasic, S.S. Blumenthal, A.N. Sussman, S.B. Erickson, M. Hladunewich, P.A. Canetta, L.A. Hebert, N. Leung, J. Radhakrishnan, H.N. Reich, S.V. Parikh, D.S. Gipson, D.K. Lee, B.R. da Costa, P. Jüni, and D.C. Cattran, for the MENTOR Investigators

NEJM, July 2019

N=12 out of 130 patients

JAMA | Original Investigation

## Effect of Oral Methylprednisolone on Clinical Outcomes in Patients With IgA Nephropathy: The TESTING Randomized Clinical Trial

Jicheng Lv, MD; Hong Zhang, PhD; Muh Geot Wong, PhD; Meg J. Jardine, PhD; Michelle Hladunewich, MD; Vivek Jha, MD; Helen Monaghan, PhD; Minghui Zhao, MD; Sean Barbour, MD; Heather Reich, MD; Daniel Cattran, MD; Richard Glassock, MD; Adeera Levin, FRCP; David Wheeler, FRCP; Mark Woodward, PhD; Laurent Billot, MSc; Tak Mao Chan, MD; Zhi-Hong Liu, MD; David W. Johnson, MD; Alan Cass, FRACP; John Feehally, MD; Jürgen Floege, MD; Giuseppe Remuzzi, MD; Yangfeng Wu, MD; Rajiv Agarwal, MD; Hai-Yan Wang, MD; Vlado Perkovic, PhD; for the TESTING Study Group

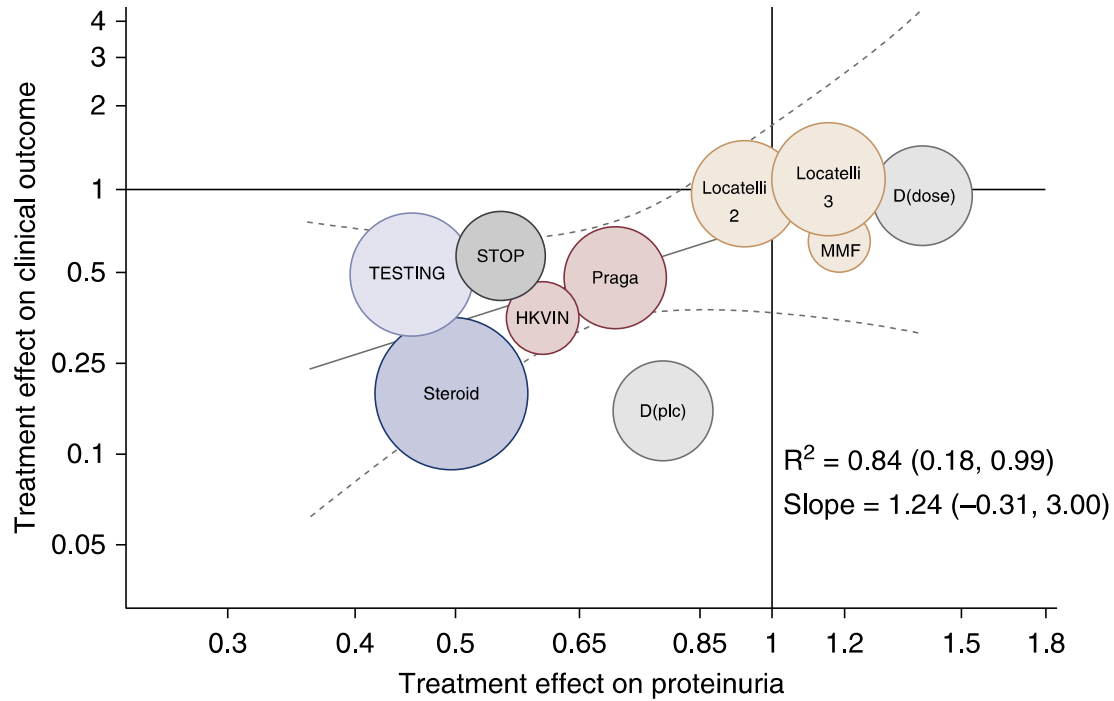
JAMA, August 2017

TESTING-2 low dose: N=10 out of 24 Canadian patients

# New therapeutic approaches in IgAN

Current clinical trials in BC







# Nefecon: targeted release budesonide

- Proprietary capsule targets release at Peyer's patches in ileum
- Affects local immunity in gut mucosa thought be related to production of Gd-IgA1
- High first-pass metabolism theoretically limits systemic corticosteroid toxicity

# NEFIGAN phase 2 trial

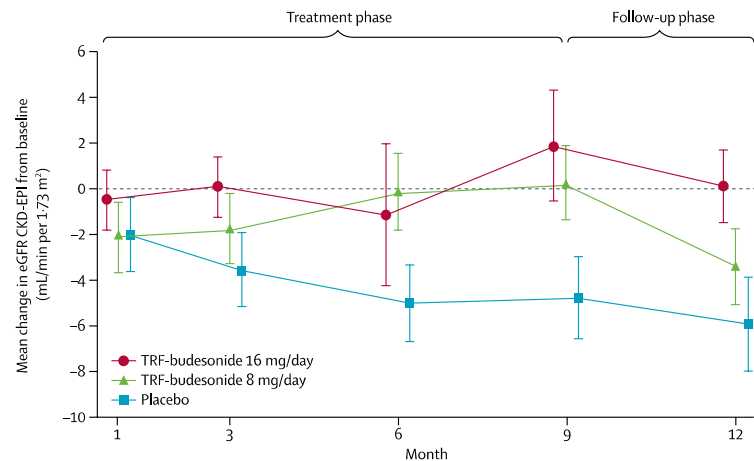
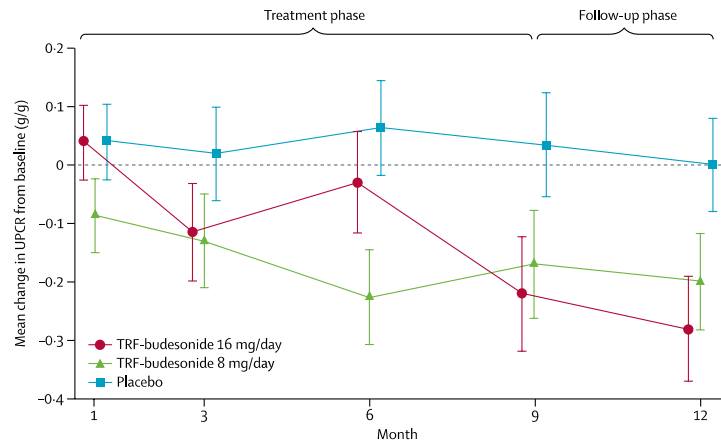
European double blind RCT

N=149, IgAN, eGFR>45, proteinuria  
>0.75g/d after RASB

Randomized to:

- Targeted release budesonide 16mg/d or 8mg/d x 9 months
- Placebo

Systemic exposure similar to prednisone  
8mg/day



# NeflgArd *Phase 3* trial

- Inclusion criteria:
  - IgAN on biopsy within 10 years
  - On maximum RASB with BP control
  - Proteinuria  $\geq 1\text{g/day}$  and eGFR  $\geq 35\text{mL/min/1.73m}^2$ , on max RASB
- Prior steroids/immunosuppression acceptable
- Randomized to:
  - Targeted release budesonide 16mg/day x 9 months
  - Placebo
- Primary outcome: 9-month proteinuria, and eGFR decline over 6 years

# OMS721: monoclonal Ab to MASP-2

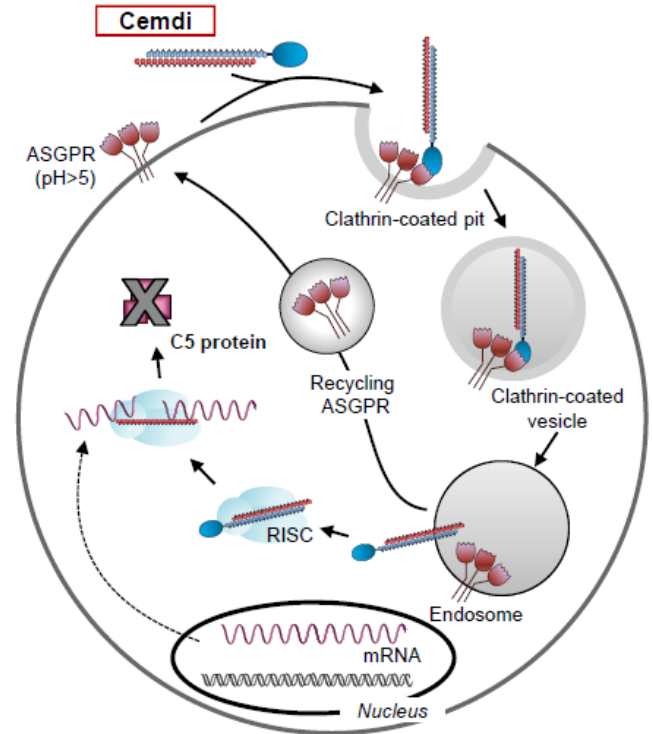
- Inhibits MASP-2, which is major effector enzyme of lectin pathway
  - MBL recognized galactose deficient hinge region in Gd-IgA1
  - MBL → MASP-2 → activates C3 convertase (C4bC2a)
  - Ab to MASP-2 selectively inhibits lectin pathway
  - Strong translational data suggests the lectin pathway drives disease activity in IgAN
- No risk of meningococcal infections
- Has been given to health volunteers, TMA patients, and C3G patients with few side effects

# ARTEMIS-IGAN *Phase 3* trial

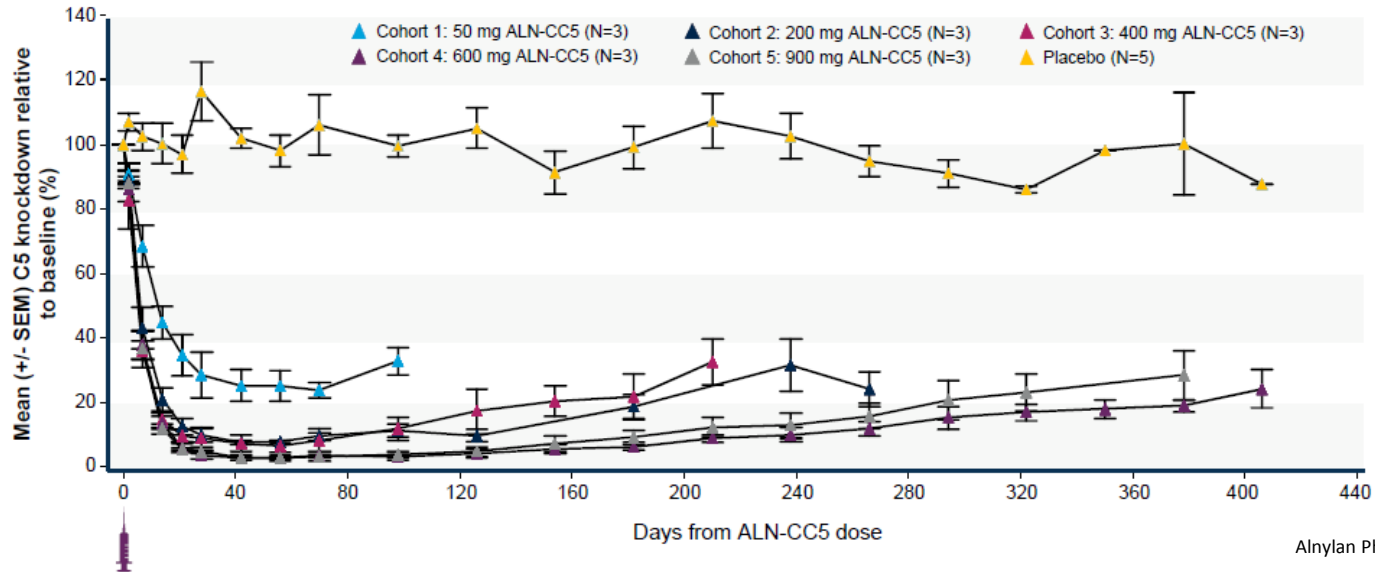
- Inclusion criteria:
  - IgAN on biopsy within 10 years
  - Proteinuria  $\geq 1\text{g/day}$  and  $\text{eGFR} \geq 30\text{mL/min/1.73m}^2$ , on max RASB
- Prior steroids and immunosuppression acceptable
- Randomized to:
  - OMS721 370mg IV weekly x 12 weeks, with repeat dosing based on proteinuria response/relapse for up to 3 years
  - Placebo, dosed similarly
- Primary outcome: 6-month proteinuria, and eGFR reduction over 3 years

# Cemdisiran: C5 gene knockdown

- siRNA targeted to hepatocytes
- siRNA: interferes with mRNA translation of C5 protein
- C5 produced exclusively in hepatocytes
- Administered SC
- C5 knockdown inhibits terminal C5b-9 formation
  - Inhibits both alternate and lectin pathways
  - Both implicated in disease activity in IgAN



# Cemdisiran: C5 gene knockdown



Sustained suppression of C5 levels for up to 120 days after a single dose

Presumed risk of meningococcal infection similar to eculizumab

Been given to healthy volunteers with no serious AEs

# Cemdisiran in IgAN *Phase 2* trial

- Inclusion criteria:
  - IgAN on biopsy within 5 years, with microscopic hematuria  $\geq 10$  RBC/hpf
  - Proteinuria  $\geq 1\text{g/day}$  and eGFR  $\geq 30\text{mL/min/1.73m}^2$ , on max RASB
  - Willing to receive meningococcal vaccine
- Prior steroids and immunosuppression acceptable
- Randomized to cemdisiran 600mg SC monthly x 8 months vs placebo
  - Followed by open-label cemdisiran x 1 year for all patients
- Primary outcome 8-month proteinuria, phase 2 trial not for drug approval



# Summary of clinical trials in IgAN

- Exciting time for drug development in IgAN
  - Target specific pathways of disease pathogenesis
- Clinical trials offer patients:
  - Access to novel treatments
  - Treatment for those previously treated with immunosuppression, or who aren't suitable for corticosteroids
- All are **industry sponsored trials**
  - No financial arrangement with any of the companies

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- Use the BC GN Registry to screen for potentially eligible patients
  - Information letter will be sent to nephrologists
  - Consider referring interested patients to the GN Clinic
  - Discuss different trial options
  - Protocol intensity may determine geographic feasibility
- Recruitment strategy successful in previous clinical trials, leverages unique BC resources:
  - Population-level data capture in the GN Registry
  - Small, collaborative nephrology community



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- BC Renal
- Kidney Foundation of Canada

## Statistical and data analysis:

- Sophia Zheng
- Lee Er
- Brian Savage
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## PROMIS data team:

- Support BC GN Registry and GN Atlas

## BC renal pathologists

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- Mei Lin Bissonnette
- Maziar Riaz

## GN Committee

- Committee members
- Yuriy Melnyk (project support)
- Brenda Lee (admin support)

## UBC nephrology research team

- Katy Vela
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- Mark Canney

