APOL1 Diagnostics and Therapeutics

Kirk Campbell, MD
Icahn School of Medicine at Mount Sinai
New York, NY

DISCLOSURES

- Consultant: AstraZeneca, Maze, Travere, Sanofi

Case 1

- 35 yo wor try w uterine fibroids, g gular physician. She no his D (eG
- The patie A test

to kidney cells called podocytes.

Read more at NCBI

You have both of the genetic variants we tested.

Variants Detected

Marker Tested	Genoty
G1	A
Gene: APOL1	Typical copy from one of your parents
Marker: rs73885319	V from your other parent
See all information	
G2	(–) TTATA A
Gene: AP	

Fit Width Fit to Window

The APOL1 gene contains instructions for making a protein that is found in the blood and in multiple organs, including the kidneys. The APOL1 protein plays a role in the immune system, helping the body fight certain parasites called trypanosomes. Although the mechanism is still unknown, certain variants in the APOL1 gene increase the risk for chronic kidney disease, perhaps by causing injury to kidney cells called podocytes.

Read more at NCBI

You have both of the genetic variants we tested.

Case 1 – Summer of 2021

- 35 yo woman of recent African ancestry with a history of hypothyroidism, uterine fibroids, gastroesophageal reflux is regularly followed by her primary care physician. She has no history of hypertension or CKD.
- The patient performs a 23andMe DNA test and uploads the findings
- The Primary Care Doctor refers the patient to a nephrologist
- The nephrologist reaches out with the following questions before seeing the patient:
  - Do these findings confirm a G1/G2 genotype?
  - Is this patient at higher risk for CKD
  - How should this patient be managed

Case 1

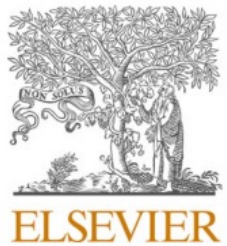
- 35 yo woman of recent African ancestry with a history of hypothyroidism, uterine fibroids, gastroesophageal reflux is regularly followed by her primary care physician. She has no history of hypertension or CKD.
- The patient had been getting annual eGFR tests (consistently > 90 ml/min) with most recent Cr 0.72 mg/dl
- She never had urine protein or albumin quantification, though a urinalysis 3 years prior had 1+ protein
- Nephrology visit:
  - Family history: no known kidney disease, but information not complete
  - BP: 101/55
  - Urine protein/creatinine ratio: 99 mg/g; **wnl**
  - CT Abd/pelvis: Normal size/structure of kidneys
- ***The patient was reassured and encouraged to follow up for annual kidney testing***

Case 2 – GUARDD Study and KPMP

- 65 yo African American Woman with a history of Hypertension and hyperlipidemia

- Participant in the GUARDD Study

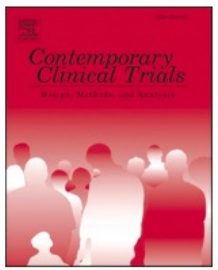
Contemporary Clinical Trials 119 (2022) 106813



Contents lists available at ScienceDirect

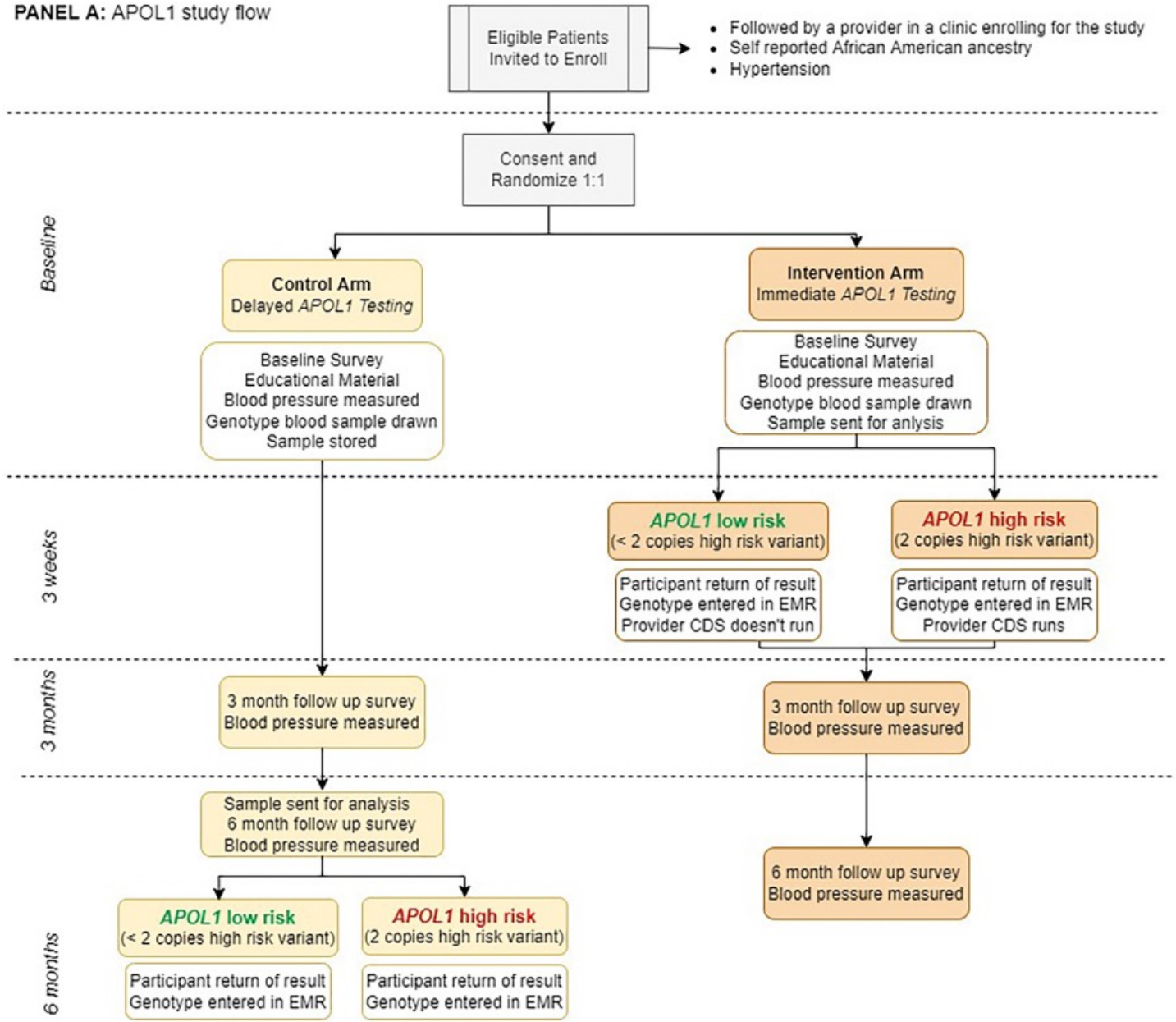
Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

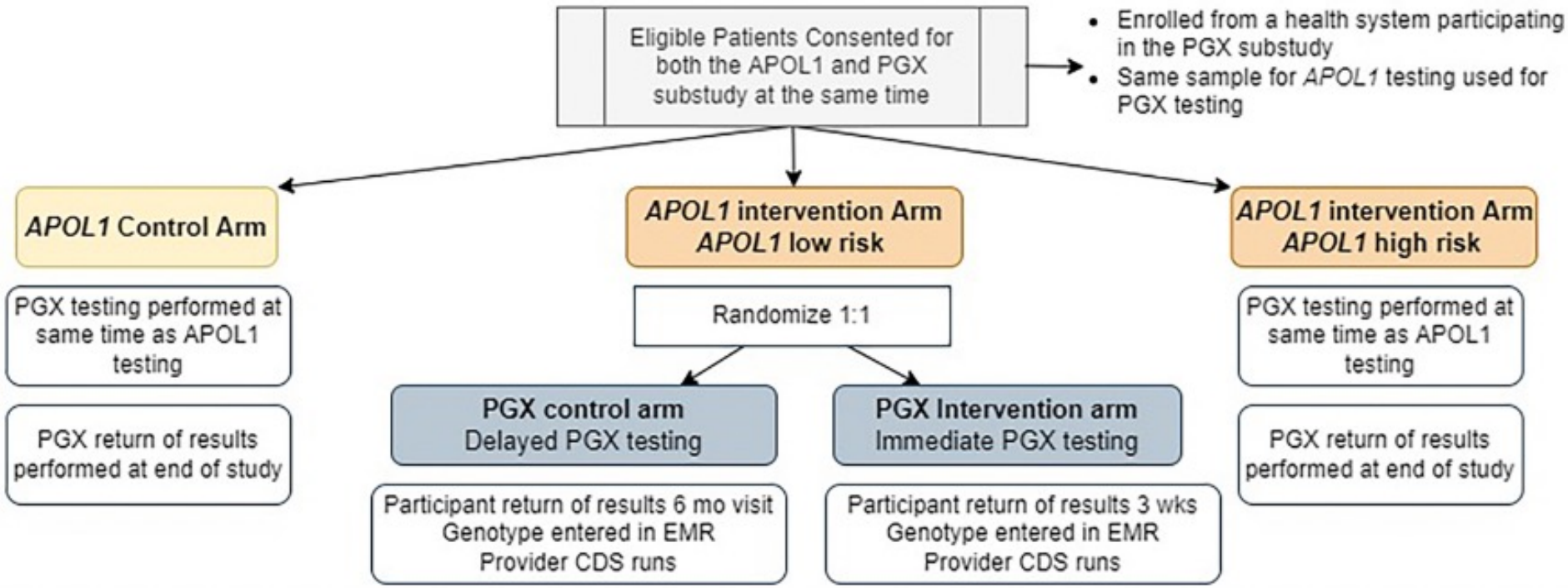


Design and rationale of GUARDD-US: A pragmatic, randomized trial of genetic testing for APOL1 and pharmacogenomic predictors of antihypertensive efficacy in patients with hypertension

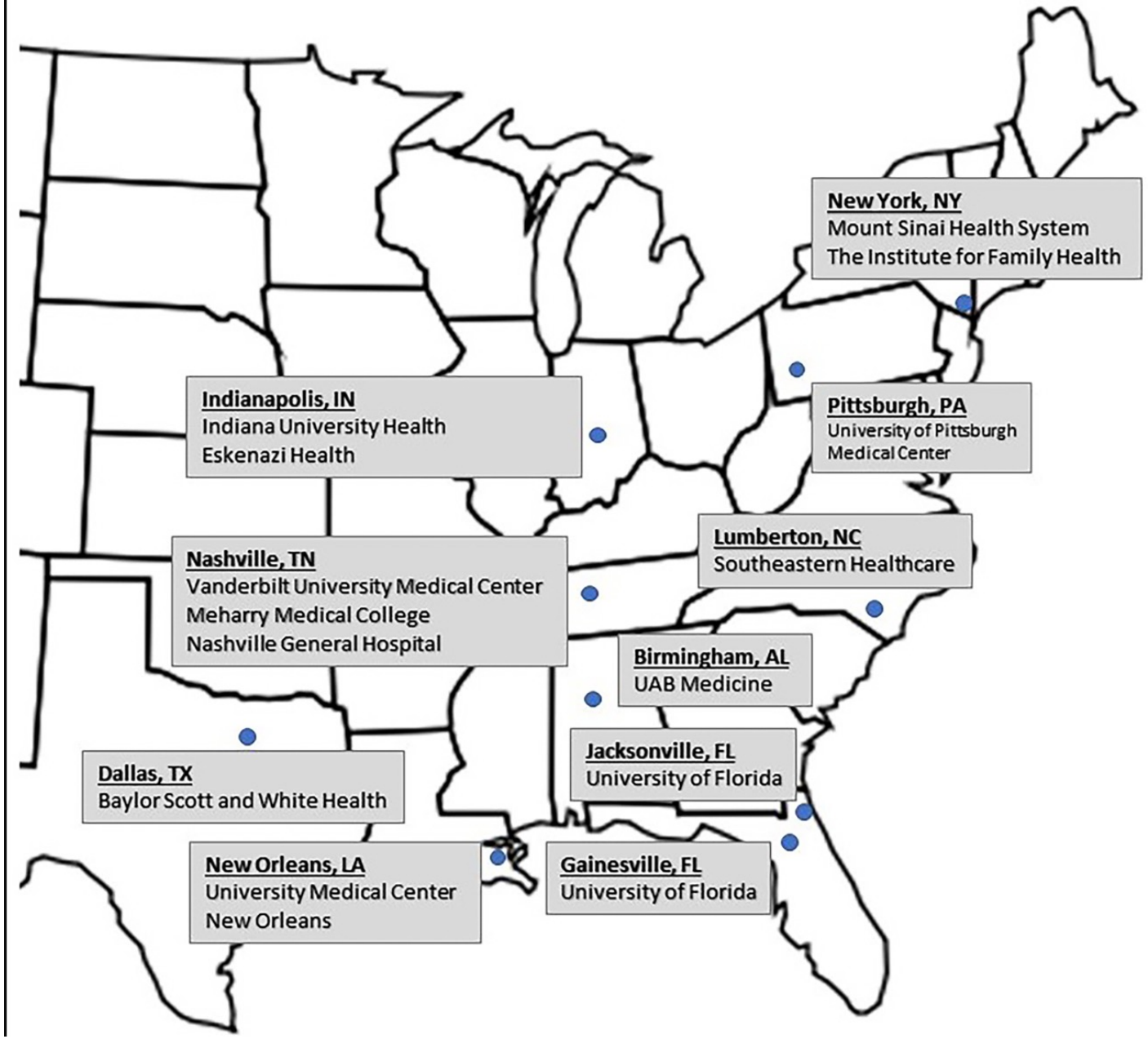
Michael T. Eadon [a,1], Kerri L. Cavanaugh [b,1], Lori A. Orlando [c,1], David Christian [d,1], Hrishikesh Chakraborty [c,e], Kady-Ann Steen-Burrell [e], Peter Merrill [e], Janet Seo [d], Diane Hauser [d,f], Rajbir Singh [g], Cherry Maynor Beasley [h], Jyotsna Fuloria [i], Heather Kitzman [j], Alexander S. Parker [k], Michelle Ramos [d], Henry H. Ong [b], Erica N. Elwood [l], Sheryl E. Lynch [a], Sabrina Clermont [d], Emily J. Cicali [l], Petr Starostik [m], Victoria M. Pratt [a], Khoa A. Nguyen [l], Marc B. Rosenman [n], Neil S. Calman [d,f], Mimsie Robinson [o], Girish N. Nadkarni [p], Ebony B. Madden [q], Natalie Kucher [q], Simona Volpi [q], Paul R. Dexter [a], Todd C. Skaar [a], Julie A. Johnson [l], Rhonda M. Cooper-DeHoff [l,**], Carol R. Horowitz [d,p,*], For the GUARDD-US Investigators


PANEL A: APOL1 study flow
Eligible Patients Invited to Enroll
Followed by a provider in a clinic enrolling for the study
Self reported African American ancestry
Hypertension
Consent and Randomize 1:1
Baseline
Control Arm
Delayed APOL1 Testing
Intervention Arm
Immediate APOL1 Testing
Baseline Survey
Educational Material
Blood pressure measured
Genotype blood sample drawn
Sample stored
Baseline Survey
Educational Material
Blood pressure measured
Genotype blood sample drawn
Sample sent for anlysis
3 weeks
APOL1 low risk
(< 2 copies high risk variant)
APOL1 high risk
(2 copies high risk variant)
Participant return of result
Genotype entered in EMR
Provider CDS doesn't run
Participant return of result
Genotype entered in EMR
Provider CDS runs
3 months
3 month follow up survey
Blood pressure measured
3 month follow up survey
Blood pressure measured
Sample sent for analysis
6 month follow up survey
Blood pressure measured
6 months
APOL1 low risk
(< 2 copies high risk variant)
APOL1 high risk
(2 copies high risk variant)
Participant return of result
Genotype entered in EMR
Participant return of result
Genotype entered in EMR
6 month follow up survey
Blood pressure measured

PANEL B: Pharmacogenomic (PGX) substudy



The pharmacogenomic sub-study will evaluate the relationship of pharmacogenomic genotype and change in systolic BP between baseline and 3 months.


New York, NY
Mount Sinai Health System
The Institute for Family Health
Indianapolis, IN
Indiana University Health
Eskenazi Health
Pittsburgh, PA
University of Pittsburgh
Medical Center
Lumberton, NC
Southeastern Healthcare
Nashville, TN
Vanderbilt University Medical Center
Meharry Medical College
Nashville General Hospital
Birmingham, AL
UAB Medicine
Jacksonville, FL
University of Florida
Dallas, TX
Baylor Scott and White Health
New Orleans, LA
University Medical Center
New Orleans
Gainesville, FL
University of Florida

Case 2 – GUARDD Study and KPMP

- 65 yo African American Woman with a history of Hypertension and hyperlipidemia
- Participant in the GUARDD Study
- BP 117/76 on Losartan 100 mg daily and Amlodipine 10 mg daily
- CKD stage 3 (eGFR 56-59 ml/min). UPCR 60 mg/g, UACR 18 mg/g
- APOL1 G1/G1
- Kidney Precision Medicine Project Research Biopsy

What is KPMP?

- A multi-year collaboration of leading research institutions to study patients with kidney disease
- Better understand the mechanisms of acute kidney injury (AKI) and chronic kidney disease (CKD)

Goals of the KPMP

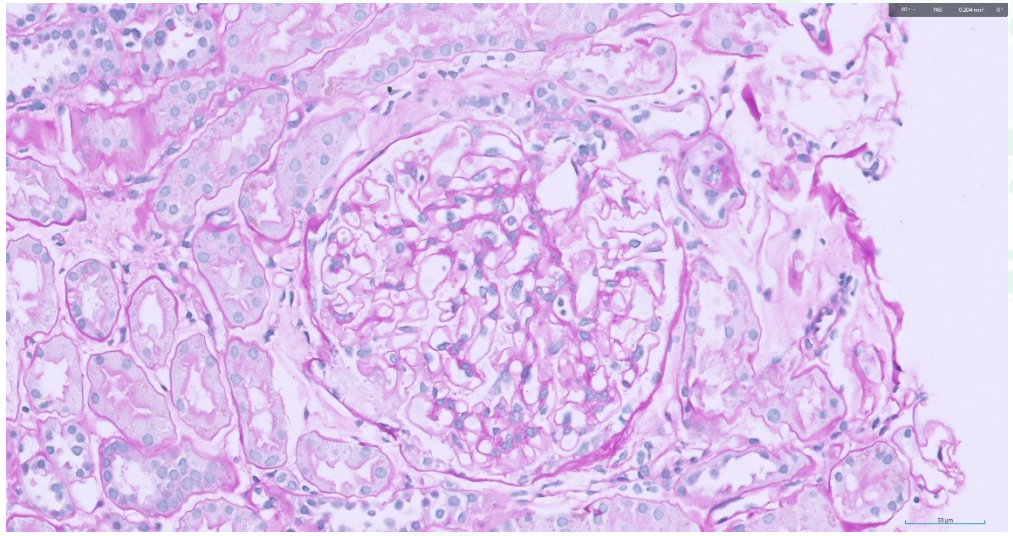
1. Identify new treatments for kidney disease
2. Ethically collect kidney biopsies from participants with acute kidney injury or chronic kidney disease
3. Create a Kidney Tissue Atlas
4. Define disease subgroups

Patient Engagement

Patient Engagement is at the core of KPMP. Patients sit on all KPMP committees and working groups.

Case 2 – GUARDD Study and KPMP

- - Focal Global Glomerulosclerosis (5% of Glomeruli; N = 22)
  - Mild Tubular Atrophy and Interstitial Fibrosis
  - Mild Arteriolar Sclerosis
- Representative glomeruli normal appearing



- ***Recommended continuing current antihypertensive regimen***

Case 3 – Spring of 2020

- A 53 year-old African-American female with a past medical history of hypertension, hypothyroidism, depression, obstructive sleep apnea, and obesity (BMI 31) was hospitalized with AKI and nephrotic-range proteinuria in the setting of confirmed COVID-19. Admission laboratory tests revealed elevated inflammatory markers including IL-6, IL-8, TNF-alpha, C-reactive protein, and Ferritin. Serologic work-up for alternate etiologies of glomerulonephritis was negative
- The patient required hemodialysis
- APOL1 genotyping performed using an in-house assay: G1/G1

The Journal of Molecular Diagnostics, Vol. 18, No. 2, March 2016

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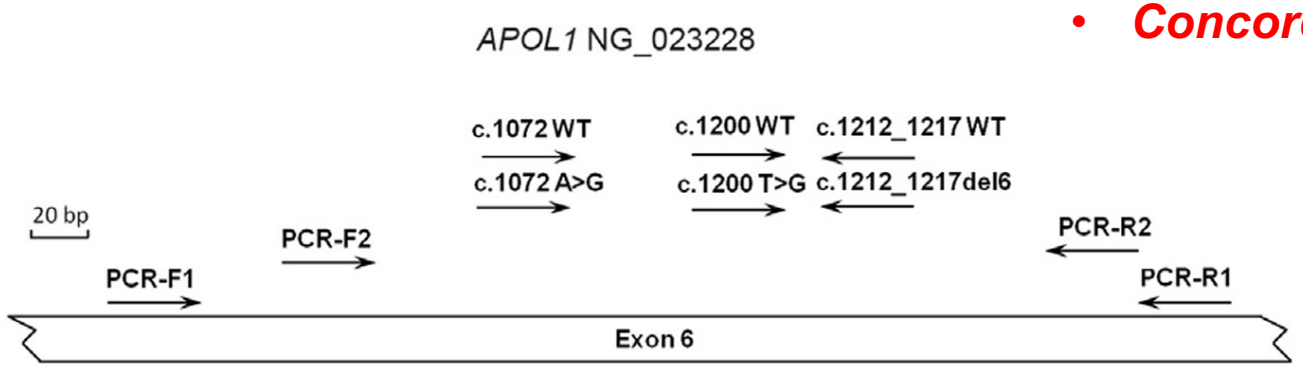
the Journal of Molecular Diagnostics
jmd.amjpathol.org

Analytical Validation of a Personalized Medicine *APOL1* Genotyping Assay for Nondiabetic Chronic Kidney Disease Risk Assessment

Jinglan Zhang,* Anastasia Fedick,* Stephanie Wasserman,* Geping Zhao,* Lisa Edelmann,* Erwin P. Bottinger,† Ruth Kornreich,* and Stuart A. Scott*

From the Department of Genetics and Genomic Sciences and the Institute for Personalized Medicine,† Icahn School of Medicine at Mount Sinai, New York, New York*

- ***PCR/allele specific primer extension***
- ***Validated with 48 positive and 10 negative controls***
- ***Concordant with Sanger sequencing***



Zhan et al J. Mol Diag 2016

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7059 DNA samples were used for the multiethnic APOL1 allele and genotype frequency screen

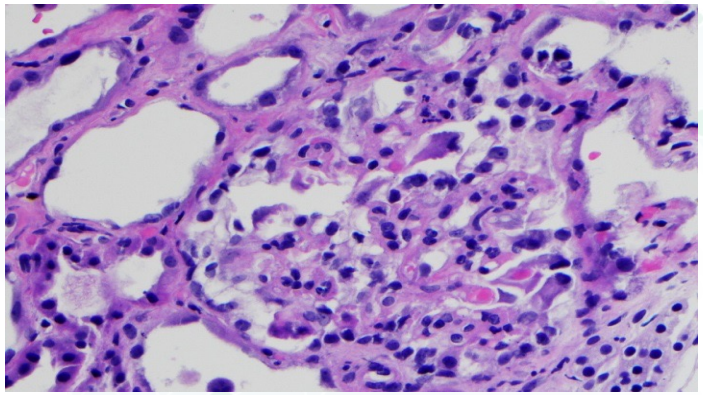
Zhang et al

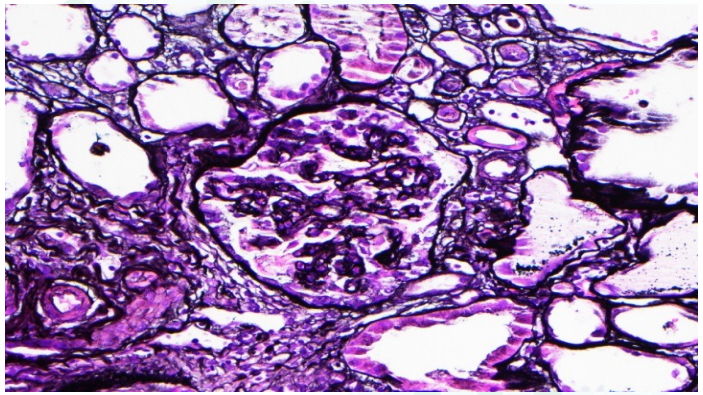
Table 5 Multiethnic *APOL1* G1 and G2 Diplotype Frequencies by Renal Disease Risk

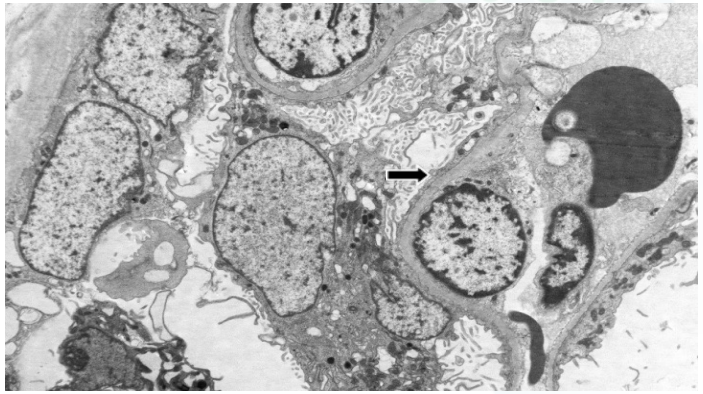
APOL1 diplotype*	African American, % (N = 5453)	Hispanic, % (N = 1146)	Asian, % (N = 460)
Normal risk			
WT/WT	44.6 (n = 2430)	87.8 (n = 1006)	97.0 (n = 446)
G1/WT	25.6 (n = 1398)	7.1 (n = 81)	2.2 (n = 10)
G2/WT	16.0 (n = 874)	4.9 (n = 56)	0.4 (n = 2)
Total	86.2 (n = 4702)	99.8 (n = 1143)	99.6 (n = 458)
Increased risk			
G1/G1	5.7 (n = 310)	0.1 (n = 1)	0.0 (n = 0)
G1/G2	6.1 (n = 334)	0.1 (n = 1)	0.4 (n = 2)
G2/G2	2.0 (n = 107)	0.1 (n = 1)	0.0 (n = 0)
Total	13.8 (n = 751)	0.3 (n = 3)	0.4 (n = 2)

*The G1 risk haplotype includes both the $G1^{GM}$ and $G1^{G}$ allele configurations.

High risk alleles present in 14% of African American individuals





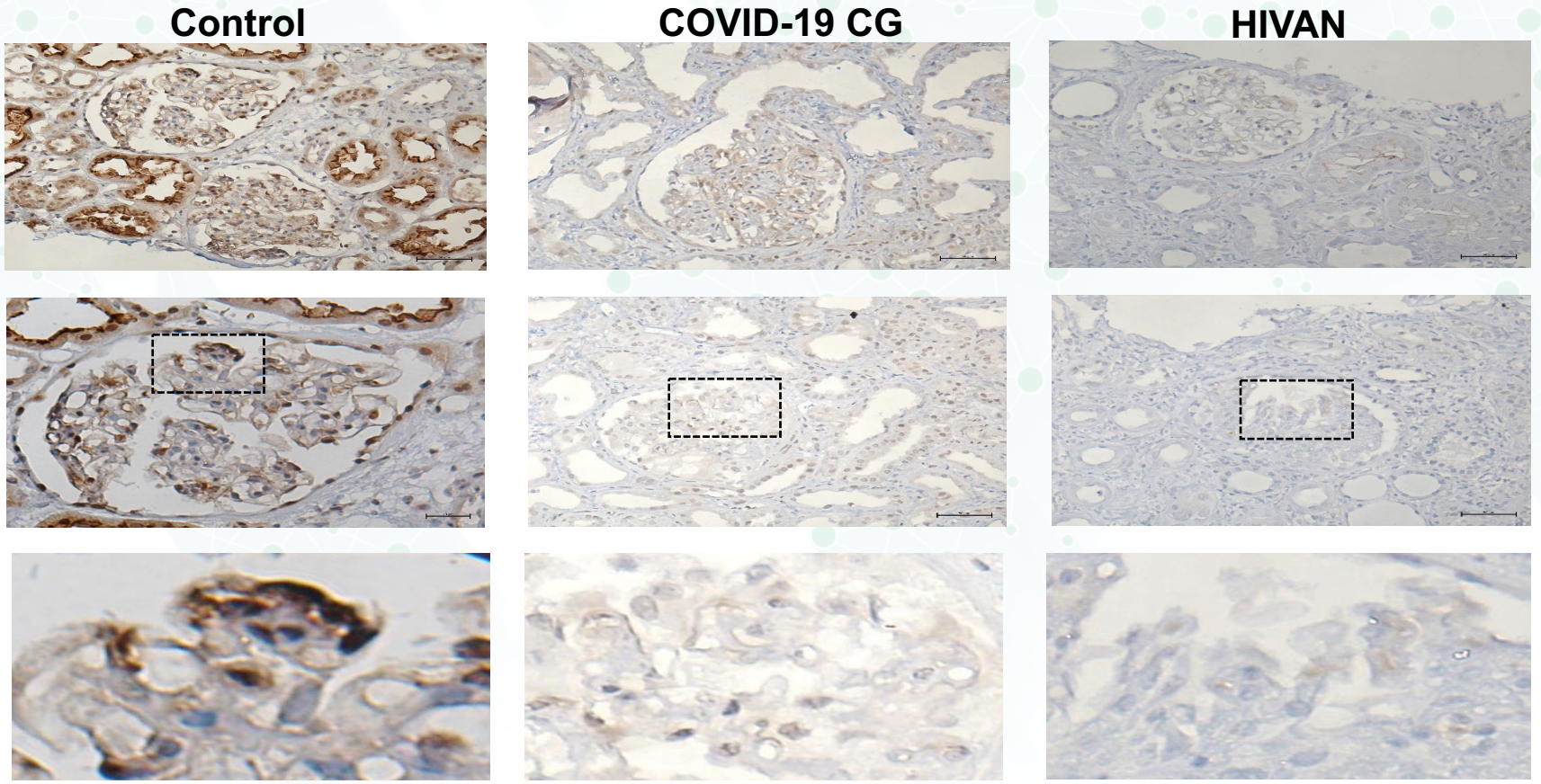


- Representative light microscopy demonstrates collapse of the glomerular tufts with hyperplasia of epithelial cells (hematoxylin-eosin; original magnification x400

- Another glomerulus shows collapse of capillary loops with proliferation of overlying epithelial cells (Jones methenamine silver stain; original magnification x200).

- Electron microscopy reveals diffuse effacement of foot processes (arrow) and hypertrophy of podocytes with tubulovillous transformation (TEM, original magnification x2000).

APOL1



*

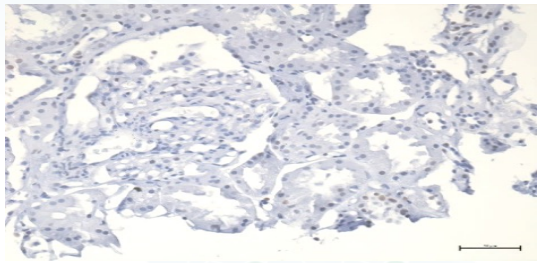
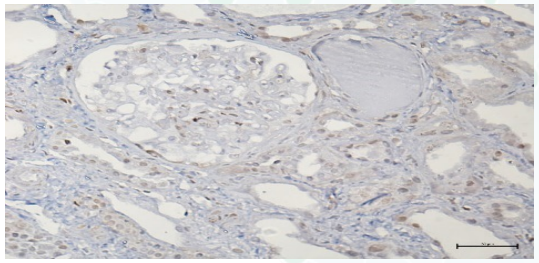
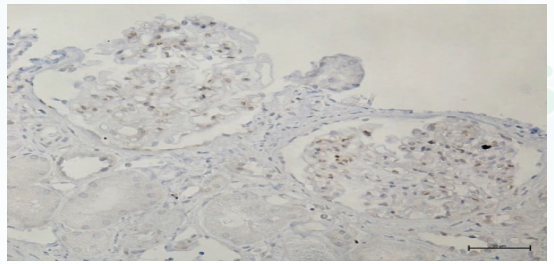
*

Case Report

Kidney Medicine

Molecular Analysis of the Kidney From a Patient With COVID-19–Associated Collapsing Glomerulopathy

Kristin Meliambro, Xuezhu Li, Fadi Salem, Zhengzi Yi, Zeguo Sun, Lili Chan, Miriam Chung, Jorge Chancay, Ha My T. Vy, Girish Nadkarni, Jenny S. Wong, Jia Fu, Kyung Lee, Weijia Zhang, John C. He, and Kirk N. Campbell

	Control	COVID-19 CG	HIVAN
Phospho-STAT3			

Phospho-STAT3 expression is significantly increased in podocytes and proximal tubular cells in COVID-19-associated CG and HIVAN as compared to normal kidney tissue

Kidney Med 2021

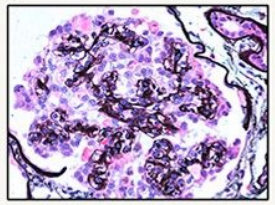
Acute Kidney Injury and Collapsing Glomerulopathy Associated with COVID-19 and APOL1 Risk Alleles

METHODS

6 black patients with COVID-19, AKI and proteinuria

Underwent kidney biopsy

Collapsing glomerulopathy



Key Lab Values

Serum Cr: **6.5** (2.9 – 11.4) mg/dL

UPCR: **11.5** (3.6 – 25.0) g/g

Genetic testing & RNA expression analysis

OUTCOMES

APOL1 alleles

4/6 – G1/G1
1/6 – G1/G2
1/6 – G2/G2

"Cytokine storm"

- Chemokines
- Immunoglobulins
- Fc receptors
- MHC II

No direct infection

- No virions by EM
- Neg SARS-CoV2 ISH
- Neg SARS NanoString

1/6 recovered

2/6 death

4/6 required dialysis

CONCLUSION SARS-CoV-2 infection can trigger collapsing glomerulopathy in patients with 2 APOL1 risk alleles, causing AKI and nephrotic-range proteinuria in patients of African ancestry with COVID-19.

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

- ***DNA extracted from peripheral blood or renal biopsy tissue***
- ***PCR genotyping***

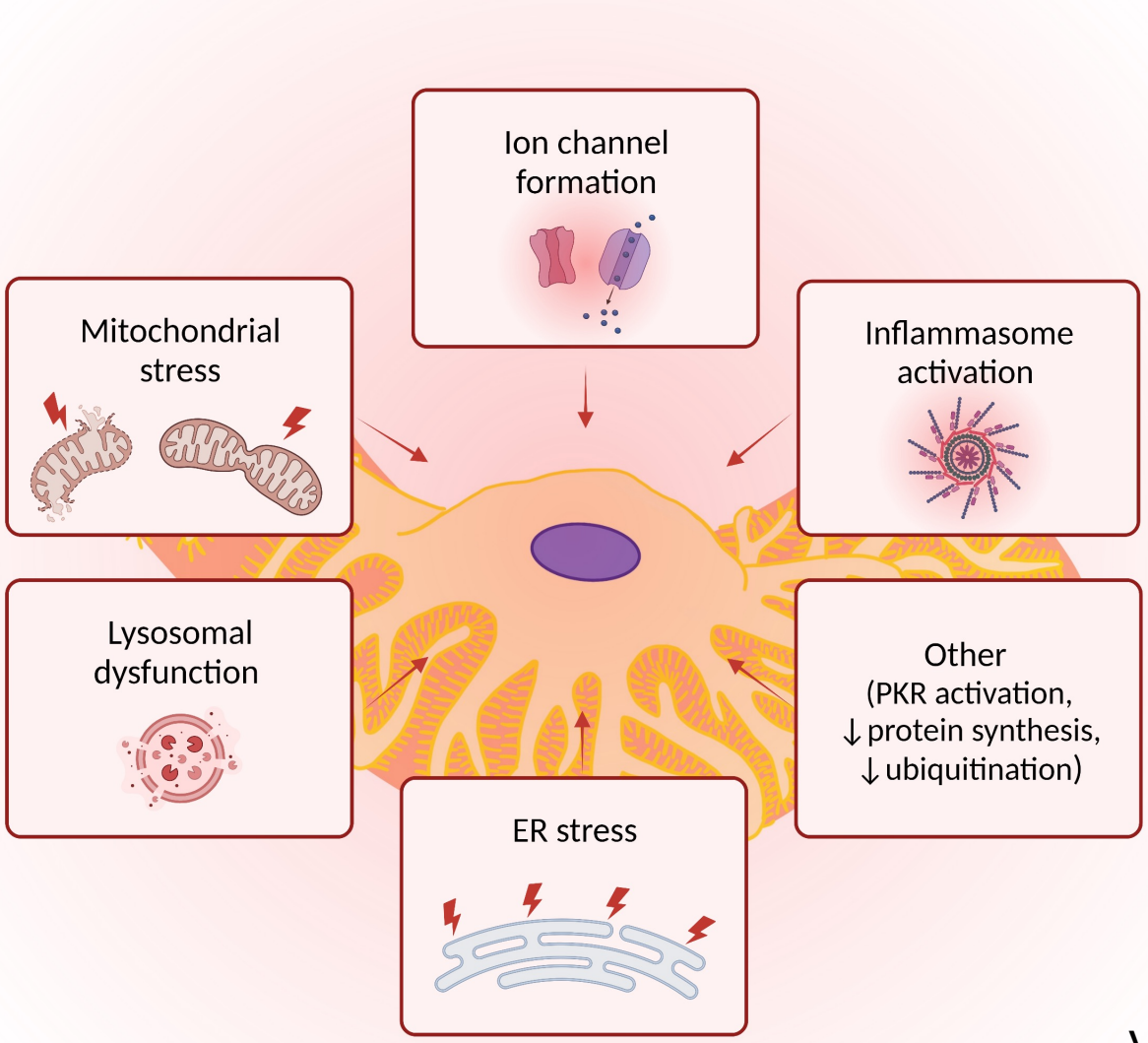
Velez et al. JASN 2020

- Most laboratories perform APOL1 variant analysis using DNA sequencing that identifies the nucleotide polymorphisms that code for the different phenotypes
- However, the LabCorp method employs Liquid chromatography–mass spectrometry (LC-MS/MS) to determine the APOL1 phenotype by detecting expressed mature proteins.
- *Results can differ from DNA sequencing (e.g. patient specific transcription/translation differences)*

Case 4 - Treatment

- 64 yo African American woman with HTN, DM, hyperlipidemia referred to nephrology after proteinuria discovered by PCP (the patient had complained of “foamy urine”
- Her baseline Cr was 1.2-1.4 mg/dl but increased recently to 2.1 after a hospitalization for COVID-19
- APOL1 G1/G2
- At biopsy: Cr 1.53 mg/dl, eGFR 41 ml/min, UPCR 3,363 mg/g
- Kidney biopsy:
  - Focal global (13/35) and focal segmental glomerulosclerosis with collapsing features in 4 gloms
  - Interstitial fibrosis and tubular atrophy, moderate
  - Arterio- and arteriolosclerosis, moderate to severe

Putative mechanisms of APOL1 induced injury



Vasquez KI Reports 2023

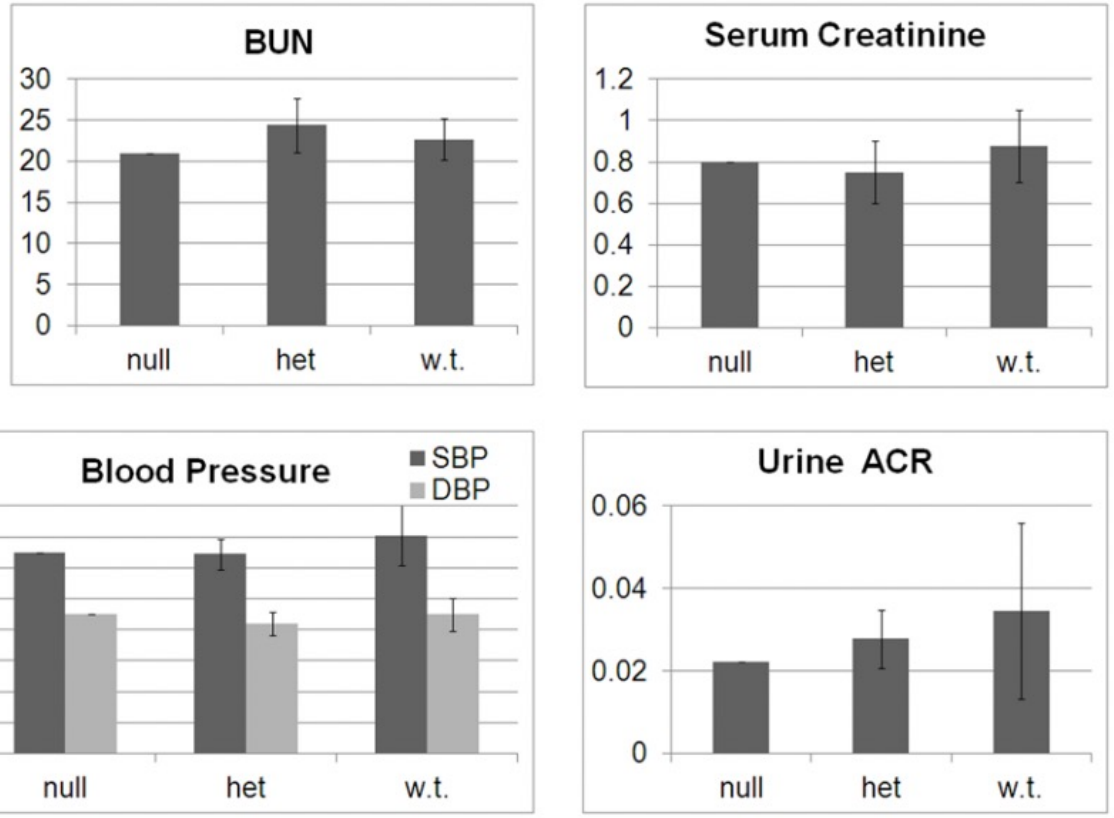
OPEN ACCESS Freely available online

PLOS ONE

APOL1 Null Alleles from a Rural Village in India Do Not Correlate with Glomerulosclerosis

Duncan B. Johnstone[1*☯¤], Vijay Shegokar[2☯], Deepak Nihalani[1], Yogendra Singh Rathore[3], Leena Mallik[3], Ashish[3], Vasant Zare[4], H. Omer Ikizler[1], Rajaram Powar[2], Lawrence B. Holzman[2]

1 Renal-Electrolyte and Hypertension Division, University of Pennsylvania, Philadelphia, Pennsylvania, United States of America, **2** Department of Microbiology, Government Medical Hospital, Nagpur, Maharastra, India, **3** CSIR- Institute of Microbial Technology, Chandigarh, India, **4** Public Health Institute of Nagpur, Maharashtra, India

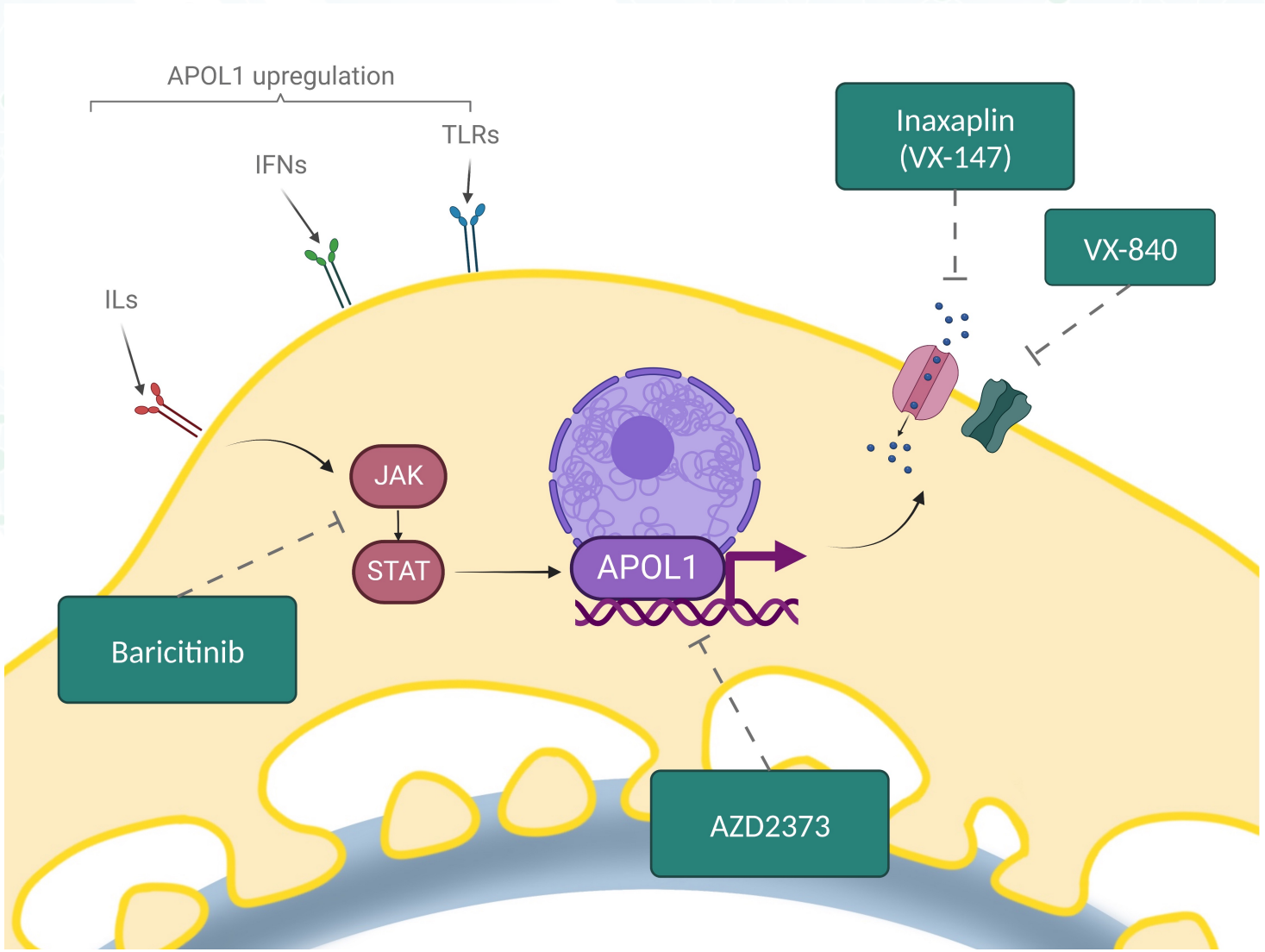


THERAPEUTIC TARGETS

Ongoing clinical trials for AMKD
https://clinicaltrials.gov/
Search term: APOL1;
Date accessed: 4/17/2024

Study ID	Title	Phase	Status	Target
NCT05237388	Janus Kinase-STAT Inhibition to Reduce APOL1 Associated Kidney Disease (JUSTICE)	2	Enrolling	JAK-STAT pathway inhibitor
NCT04340362	Phase 2a Study of VX-147 in Adults With APOL1-mediated Focal Segmental Glomerulosclerosis	2A	Completed	Compound inhibitor APOL1
NCT05312879	Phase 2/3 Adaptive Study of VX-147 in Adult and Pediatric Participants With APOL1- Mediated Proteinuric Kidney Disease Mediated Proteinuric Kidney Disease (AMPLITUDE)	2A/3	Enrolling	Compound inhibitor APOL1
NCT05324410	A Phase 1 Dose Escalation Study to Evaluate Safety and Pharmacokinetics (PK) of VX-840 in Healthy Participants	1	Completed	? Compound inhibitor
NCT05351047	A Study to Assess Safety, Tolerability, PK and PD of AZD2373 in Healthy Male Participants of Sub-Saharan West African Ancestry	1	Completed	Antisense oligonucleotide inhibitor (ASOI)

APOL1 therapies in development



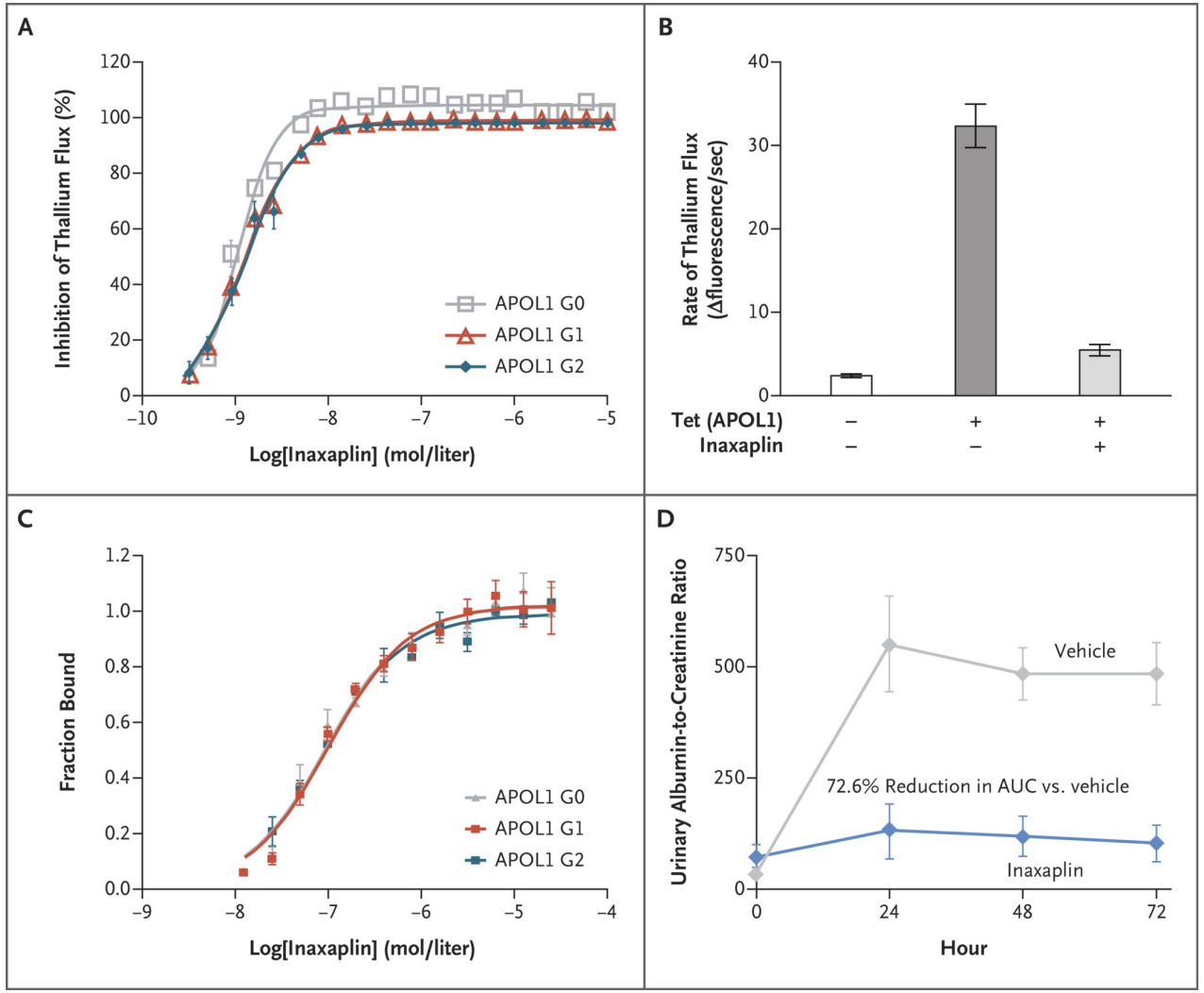
Preclinical Data

Percent inhibition of thallium ion flux

Inaxaplin inhibition of APOL1 induced thallium ion flux

Inaxaplin target binding

Inaxaplin reduction of UACR in APOL1 G2 mice

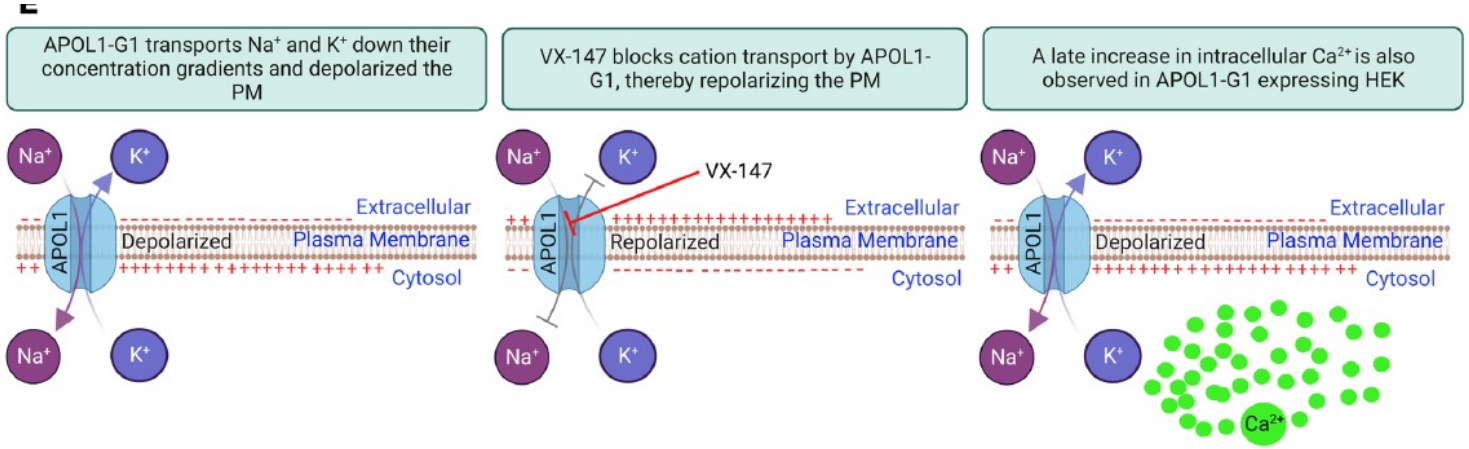


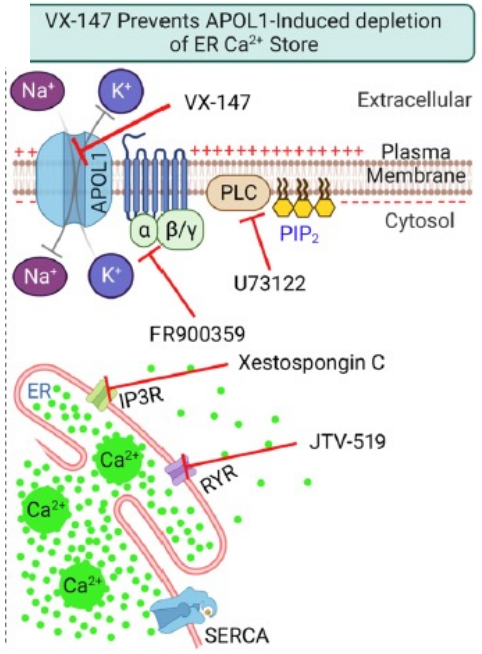
The NEW ENGLAND JOURNAL of MEDICINE

The Journal of Clinical Investigation RESEARCH ARTICLE

APOL1-mediated monovalent cation transport contributes to APOL1-mediated podocytopathy in kidney disease

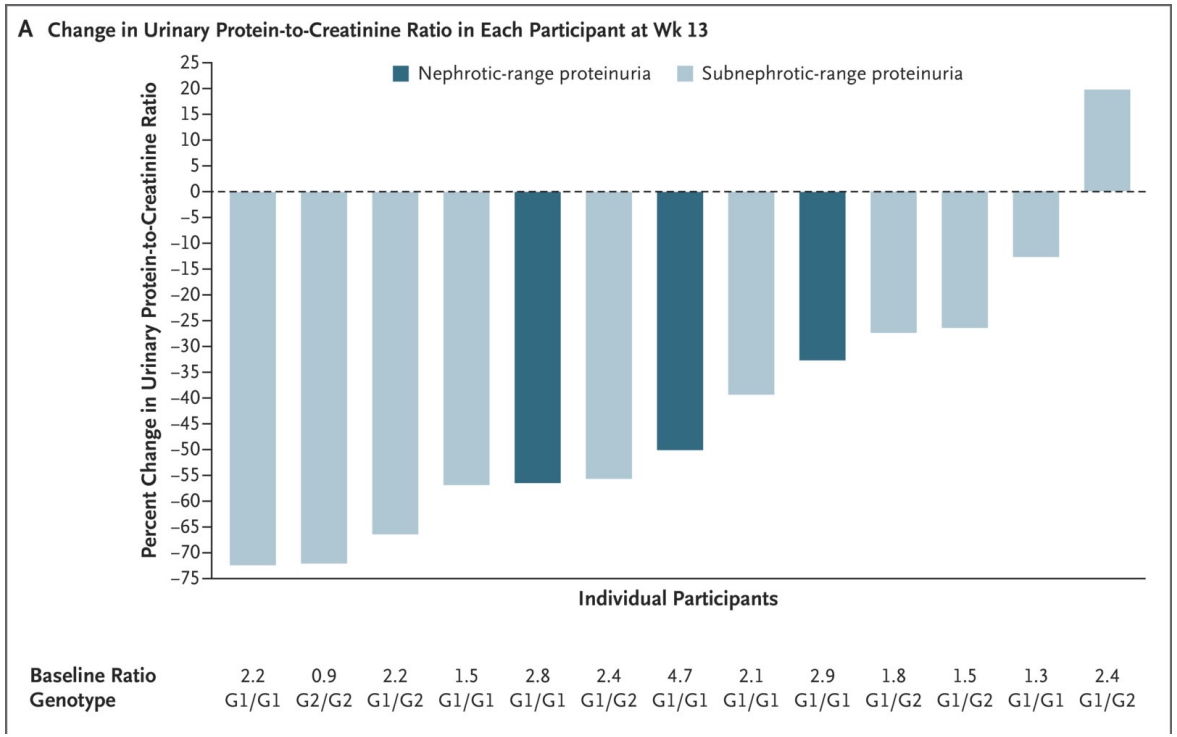
Somenath Datta,[1,2] Brett M. Antonio,[3] Nathan H. Zahler,[3] Jonathan W. Theile,[3] Doug Krafte,[3] Hengtao Zhang,[1,4] Paul B. Rosenberg,[1,4] Alec B. Chaves,[1] Deborah M. Muoio,[1,5,6] Guofang Zhang,[1,5] Daniel Silas,[1,2] Guojie Li,[1,2] Karen Soldano,[1,2] Sarah Nystrom,[1,2] Davis Ferreira,[7] Sara E. Miller,[7] James R. Bain,[1,5] Michael J. Muehlbauer,[1] Olga Ilkayeva,[1,5] Thomas C. Becker,[1,5] Hans-Ewald Hohmeier,[1,5] Christopher B. Newgard,[1,5,6] and Opeyemi A. Olabisi[1,2]

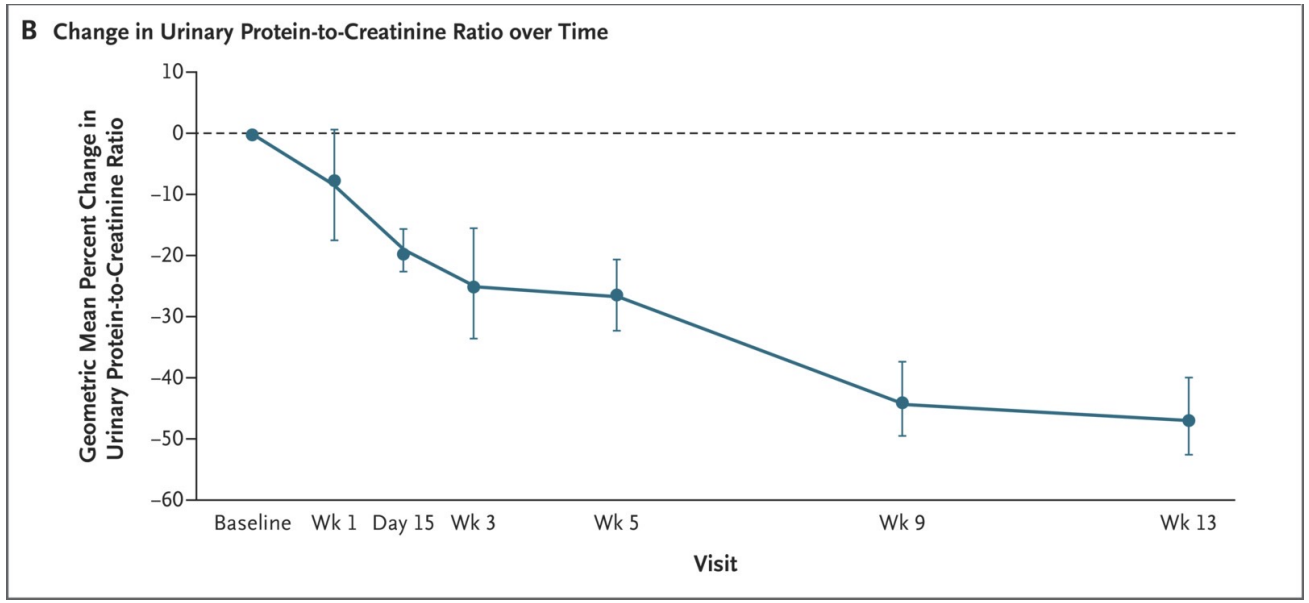




JCI 2024

Efficacy Outcomes in Ph2 Trial





The NEW ENGLAND JOURNAL of MEDICINE

Demographic and Clinical Characteristics of the Participants at Baseline

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Total (N = 16)	Participants with Nephrotic-Range Proteinuria (N=3)	Participants with Subnephrotic-Range Proteinuria (N=13)
Age — yr	38.8±14.5	45.0±10.5	37.3±15.2
Sex — no. (%)			
Male	7 (44)	1 (33)	6 (46)
Female	9 (56)	2 (67)	7 (54)
APOL1 genotype — no. (%)			
G1/G1	9 (56)	3 (100)	6 (46)
G2/G2	1 (6)	0	1 (8)
G1/G2	6 (38)	0	6 (46)
Body-mass index	29.6±6.4	32.7±6.4	28.9±6.4
Urinary protein-to-creatinine ratio†	2.08±0.90	3.47±1.07	1.77±0.49
Estimated GFR — ml/min/1.73 m^2	51.2±14.0	51.4±22.2	51.2±12.8
Standard-care medication			
ACE inhibitor			
≥28 days before day 1 — no. (%)	8 (50)	1 (33)	7 (54)
On day 1 — no./total no. (%)	8/8 (100)	1/1 (100)	7/7 (100)
Angiotensin-receptor blocker			
≥28 days before day 1 — no. (%)	7 (44)	3 (100)	4 (31)
On day 1 — no./ total no. (%)	6/7 (86)	2/3 (67)‡	4/4 (100)
Immunosuppressants§			
≥28 days before day 1 — no. (%)	4 (25)	1 (33)	3 (23)
On day 1 — no./ total no. (%)	4/4 (100)	1/1 (100)	3/3 (100)

* Plus–minus values are means ±SD. Data are shown for all the participants who received at least one dose of inaxaplin and who had at least one postbaseline efficacy assessment. Nephrotic-range proteinuria was defined as a urinary protein-to-creatinine ratio (with protein and creatinine both measured in grams) of at least 2.7 to less than 10 and an estimated glomerular filtration rate (GFR) of at least 27 ml per minute per 1.73 m^2 of body-surface area. Subnephrotic-range proteinuria was defined as a urinary protein-to-creatinine ratio of at least 0.7 to less than 2.7 and an estimated GFR of at least 27 ml per minute per 1.73 m^2. ACE denotes angiotensin-converting enzyme.

† For the urinary protein-to-creatinine ratio, the baseline value was the mean of the urinary protein-to-creatinine ratios from three urine samples obtained during screening.

‡ One participant had a reduction in the dose during the screening period, which was documented as a postenrollment eligibility deviation.

§ Immunosuppressants included systemic glucocorticoids. The following medications were taken by participants: prednisone (one participant), mycophenolate mofetil (one), and tacrolimus (two).

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Mean Percent Change from the Baseline Urinary Protein-to-Creatinine Ratio at Week 13

Table 2. Mean Percent Change from the Baseline Urinary Protein-to-Creatinine Ratio at Week 13.*

Variable	Total (N=13)	Participants with Nephrotic-Range Proteinuria (N=3)	Participants with Subnephrotic-Range Proteinuria (N=10)
Mean urinary protein-to-creatinine ratio			
At baseline	2.21±0.95	3.47±1.07	1.84±0.52
At wk 13	1.27±0.73	1.83±0.58	1.10±0.71
Geometric percent change from baseline at wk 13 (95% CI)	−47.6 (−60.0 to −31.3)	−47.7 (−70.1 to −8.5)	−47.5 (−63.4 to −24.6)

* Plus–minus values are means ±SD. Baseline and week 13 assessments of the urinary protein-to-creatinine ratio for each of the participants were calculated as the mean of three first-morning void measurements obtained within a 7-day window. The efficacy analysis set included all the participants who completed inaxaplin treatment and had at least 80% adherence to treatment. CI denotes confidence interval.

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Adverse Events

Table 3. Adverse Events.*

Event	Total (N=16)	Participants with Nephrotic-Range Proteinuria (N=3)	Participants with Subnephrotic-Range Proteinuria (N=13)
Any adverse event†	15 (94)	3 (100)	12 (92)
Adverse events according to severity			
Mild	7 (44)	1 (33)	6 (46)
Moderate	8 (50)	2 (67)	6 (46)
Severe	0	0	0
Life-threatening	0	0	0
Serious adverse event‡	1 (6)	0	1 (8)
Adverse event leading to treatment discontinuation	0	0	0
Adverse event occurring in ≥2 participants			
Headache	4 (25)	1 (33)	3 (23)
Back pain	3 (19)	0	3 (23)
Nausea	3 (19)	1 (33)	2 (15)
Decrease in blood bicarbonate level	2 (12)	0	2 (15)
Diarrhea	2 (12)	1 (33)	1 (8)
Dizziness	2 (12)	0	2 (15)
Dyspepsia	2 (12)	0	2 (15)
Fatigue	2 (12)	0	2 (15)

* The safety analysis included all the participants who received at least one dose of inaxaplin.
† Adverse events that were considered by the investigator as being possibly related to inaxaplin occurred in three participants: headache in one participant in the nephrotic-range group and in one in the subnephrotic-range group and headache, abdominal distension, dyspepsia, and back pain in one participant in the subnephrotic-range group.
‡ Two serious adverse events occurred in one participant: deep-vein thrombosis and uterine leiomyoma. Neither event was considered by the investigator to be related to inaxaplin.

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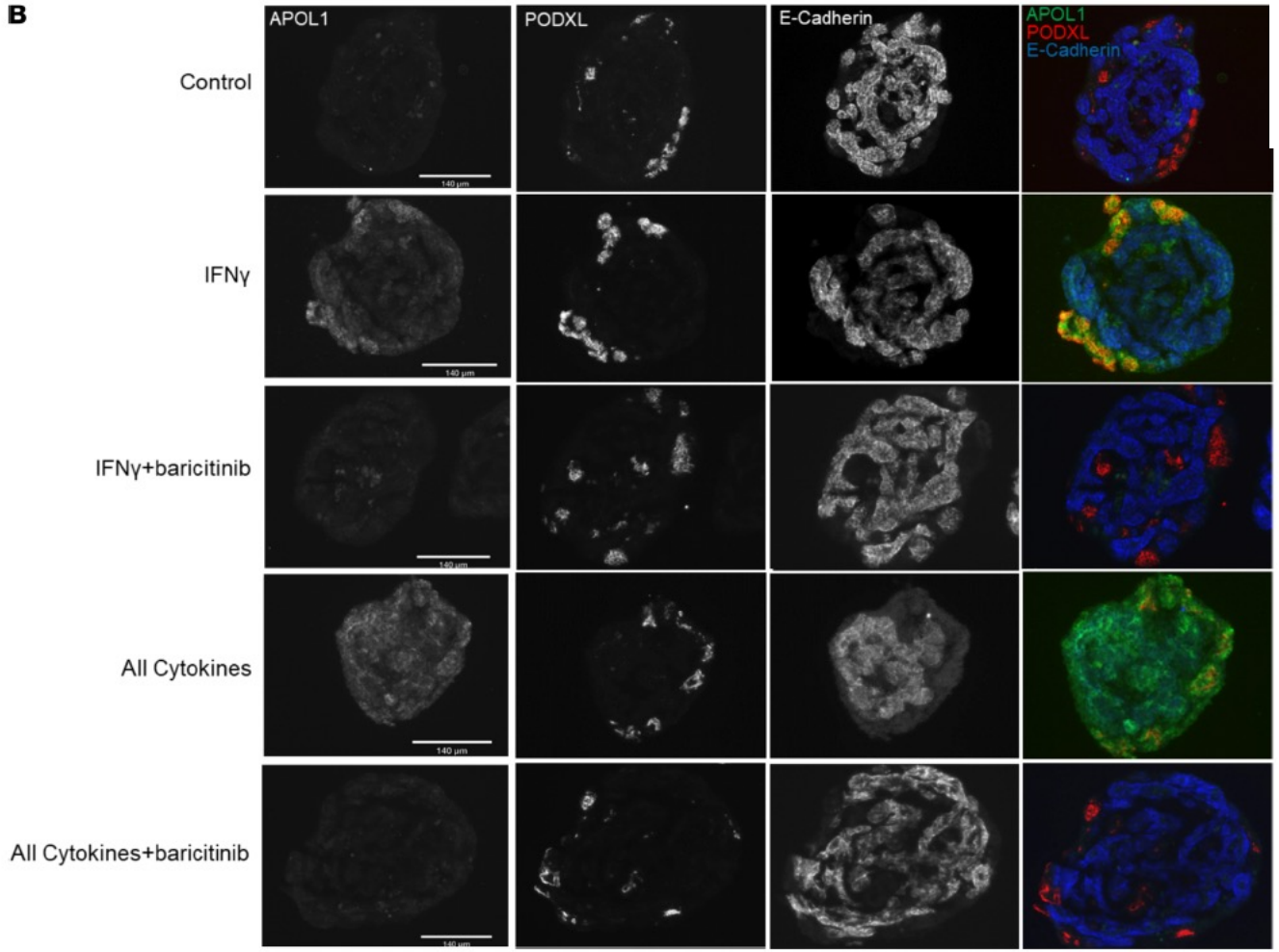
Other approaches to APOL1 inhibition



JCI insight

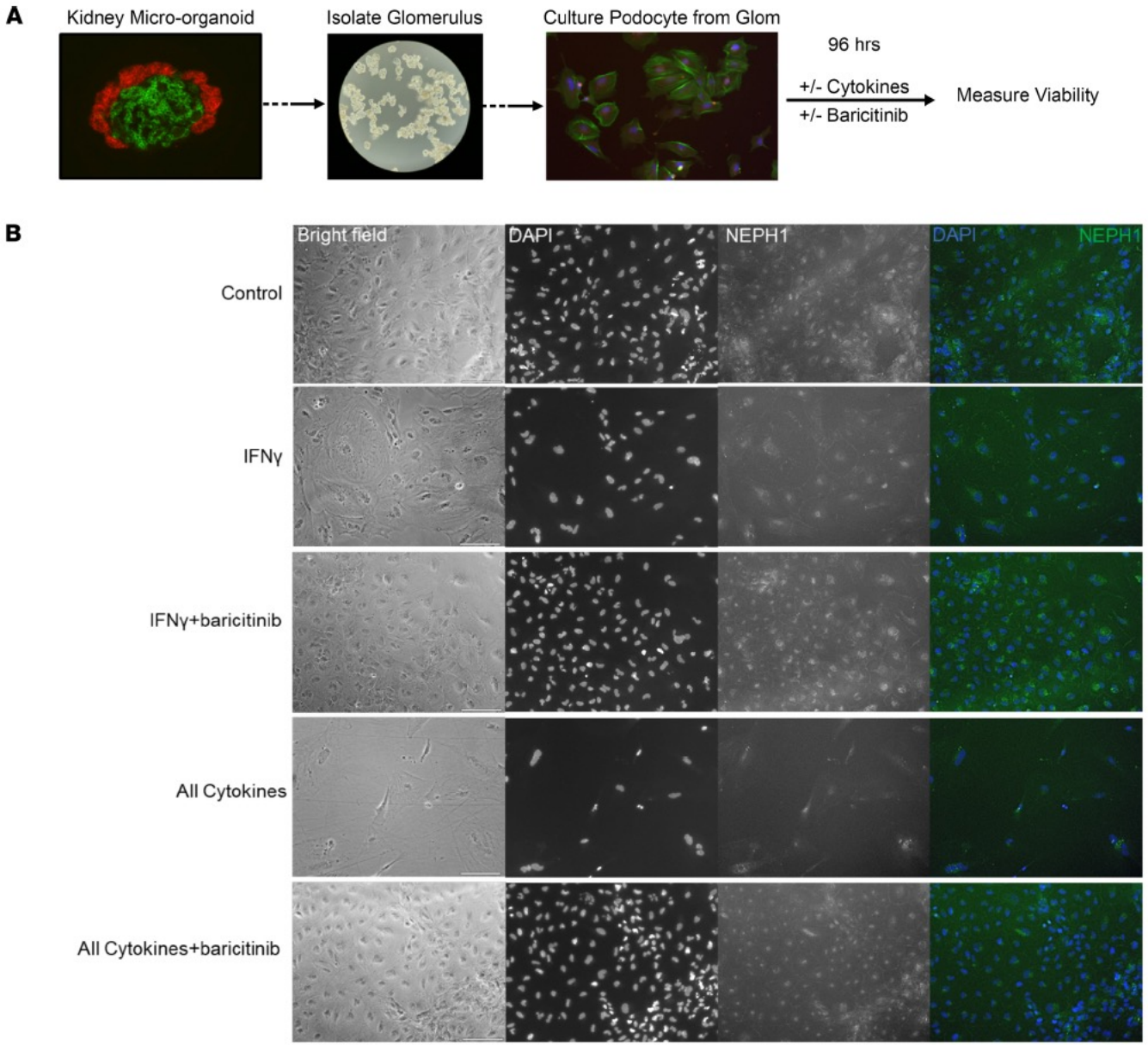
RESEARCH ARTICLE

JAK inhibitor blocks COVID-19 cytokine–induced JAK/STAT/APOL1 signaling in glomerular cells and podocytopathy in human kidney organoids

Sarah E. Nystrom,[1] Guojie Li,[1] Somenath Datta,[1] Karen L. Soldano,[1] Daniel Silas,[1] Astrid Weins,[2] Gentzon Hall,[1] David B. Thomas,[3] and Opeyemi A. Olabisi[1]

COVID-19 cytokines drive APOL1 expression in human iPSC organoids

Blocked by Baricitinib (JAK/STAT) inhibition



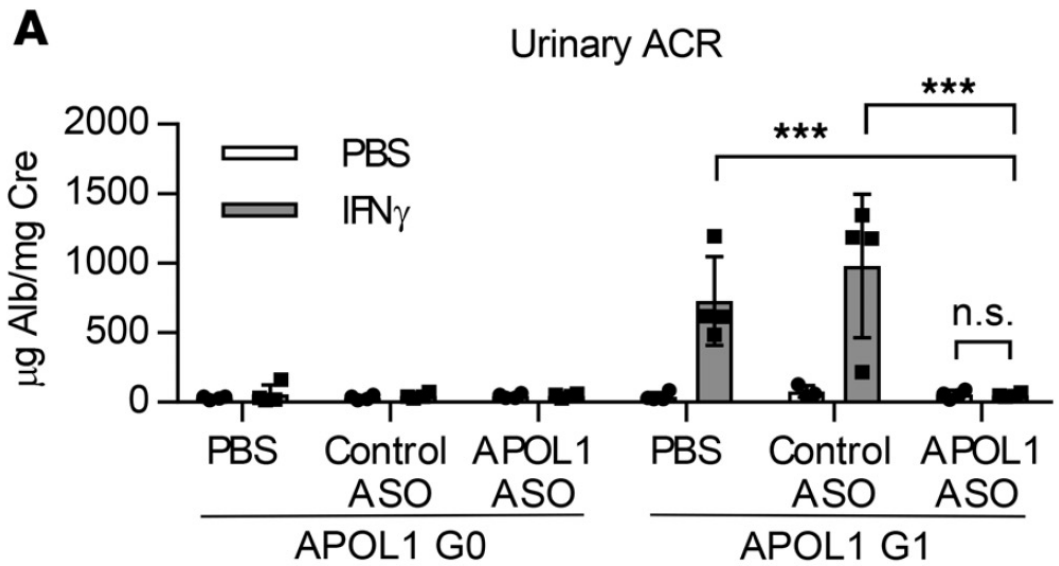
Viability of IFNα podocytes derived from organoids improved with JAK inhibition

JCI insight

Antisense oligonucleotide treatment ameliorates IFN-γ–induced proteinuria in *APOL1*-transgenic mice

Mariam Aghajan, … , Maria Chiara Magnone, Shuling Guo

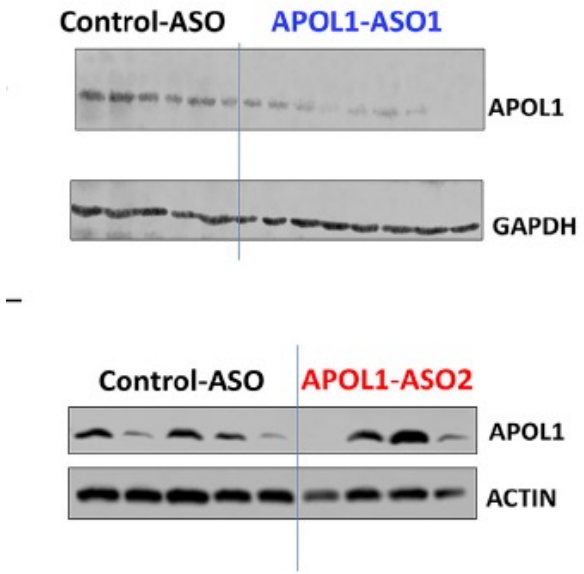
JCI Insight. 2019;4(12):e126124. https://doi.org/10.1172/jci.insight.126124.

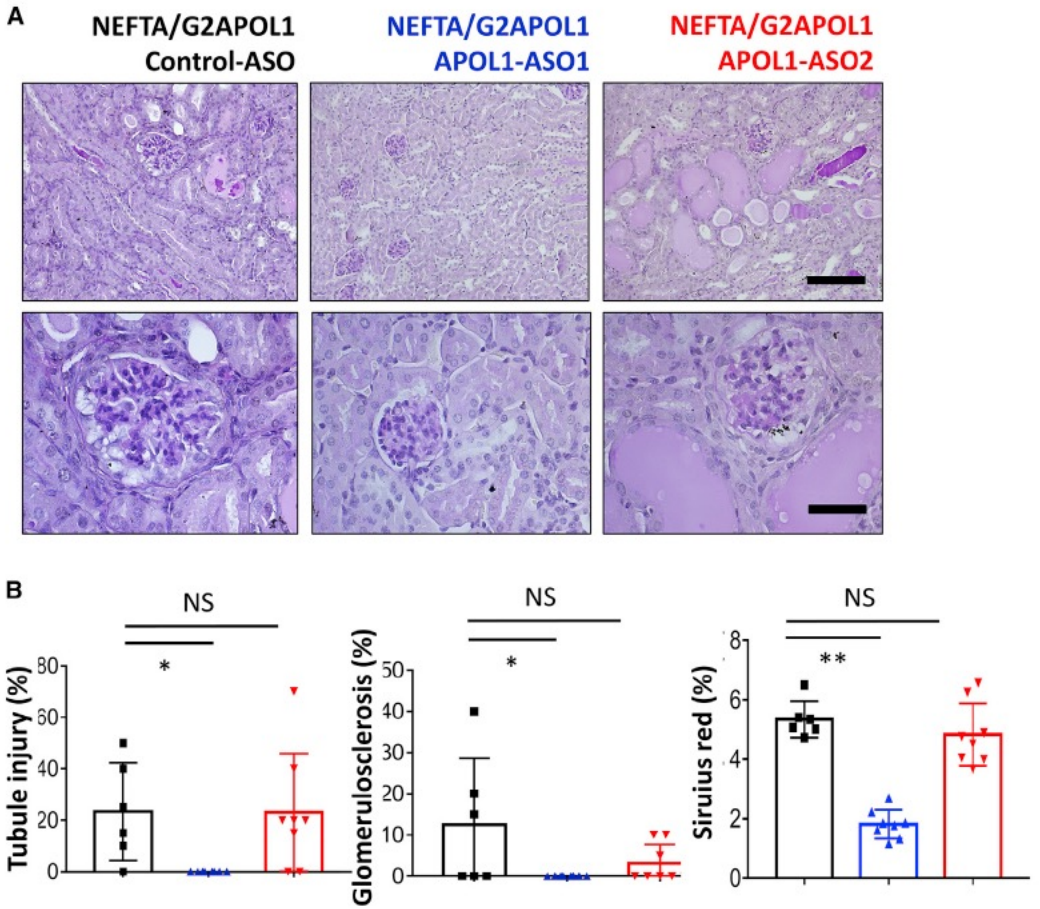


Molecular Therapy
Original Article

Antisense oligonucleotides ameliorate kidney dysfunction in podocyte-specific APOL1 risk variant mice

Ya-Wen Yang,[1,2,6] Bibek Poudel,[1,6] Julia Frederick,[1] Poonam Dhillon,[1] Rojesh Shrestha,[1] Ziyuan Ma,[1] Junnan Wu,[1] Koji Okamoto,[3] Jeffrey B. Kopp,[3] Sheri L. Booten,[4] Danielle Gattis,[4] Andrew T. Watt,[4] Matthew Palmer,[5] Mariam Aghajan,[4] and Katalin Susztak[1]





Mol Ther 2022

APOL1 N264K risk variant is protective

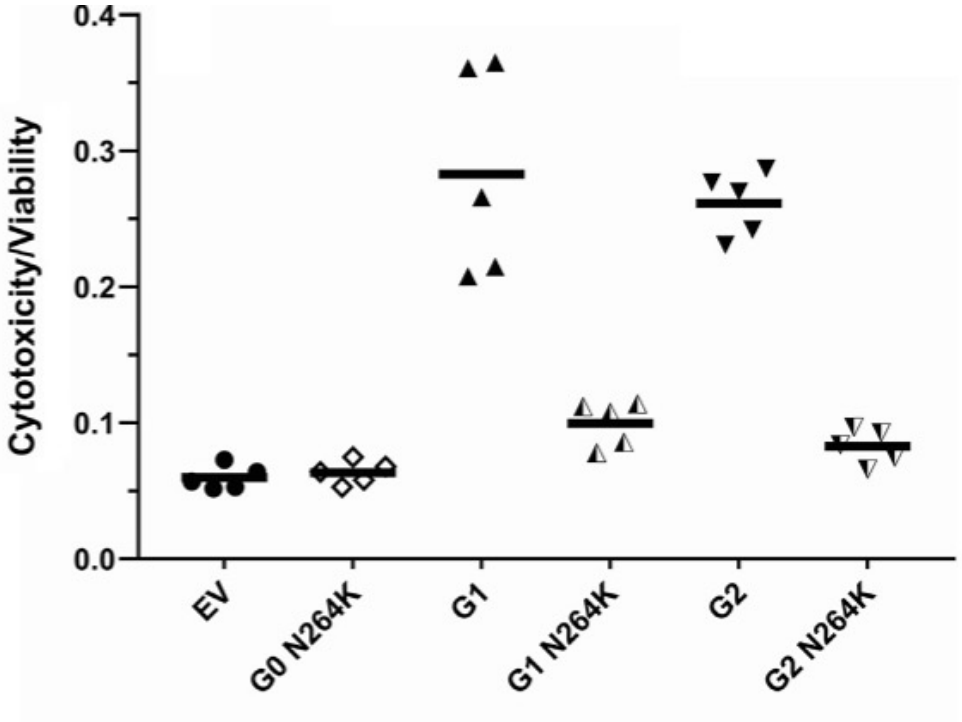
www.kidney-international.org brief report

Apolipoprotein L1 (APOL1) risk variant toxicity depends on the haplotype background

Check for updates

Herbert Lannon[1], Shrijal S. Shah[1], Leny Dias[1], Daniel Blackler[1], Seth L. Alper[1,2], Martin R. Pollak[1,2] and David J. Friedman[1]

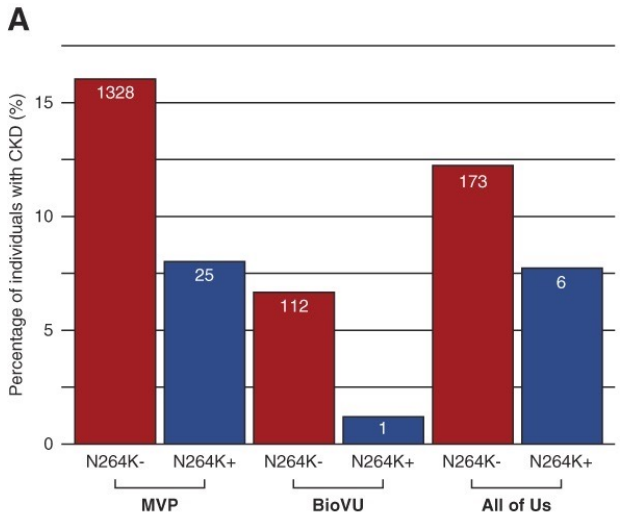
[1]Division of Nephrology, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA; and [2]Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA

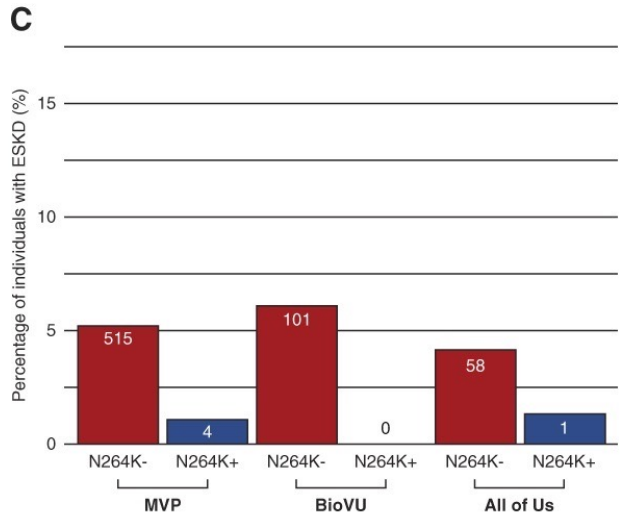


CLINICAL RESEARCH www.jasn.org OPEN

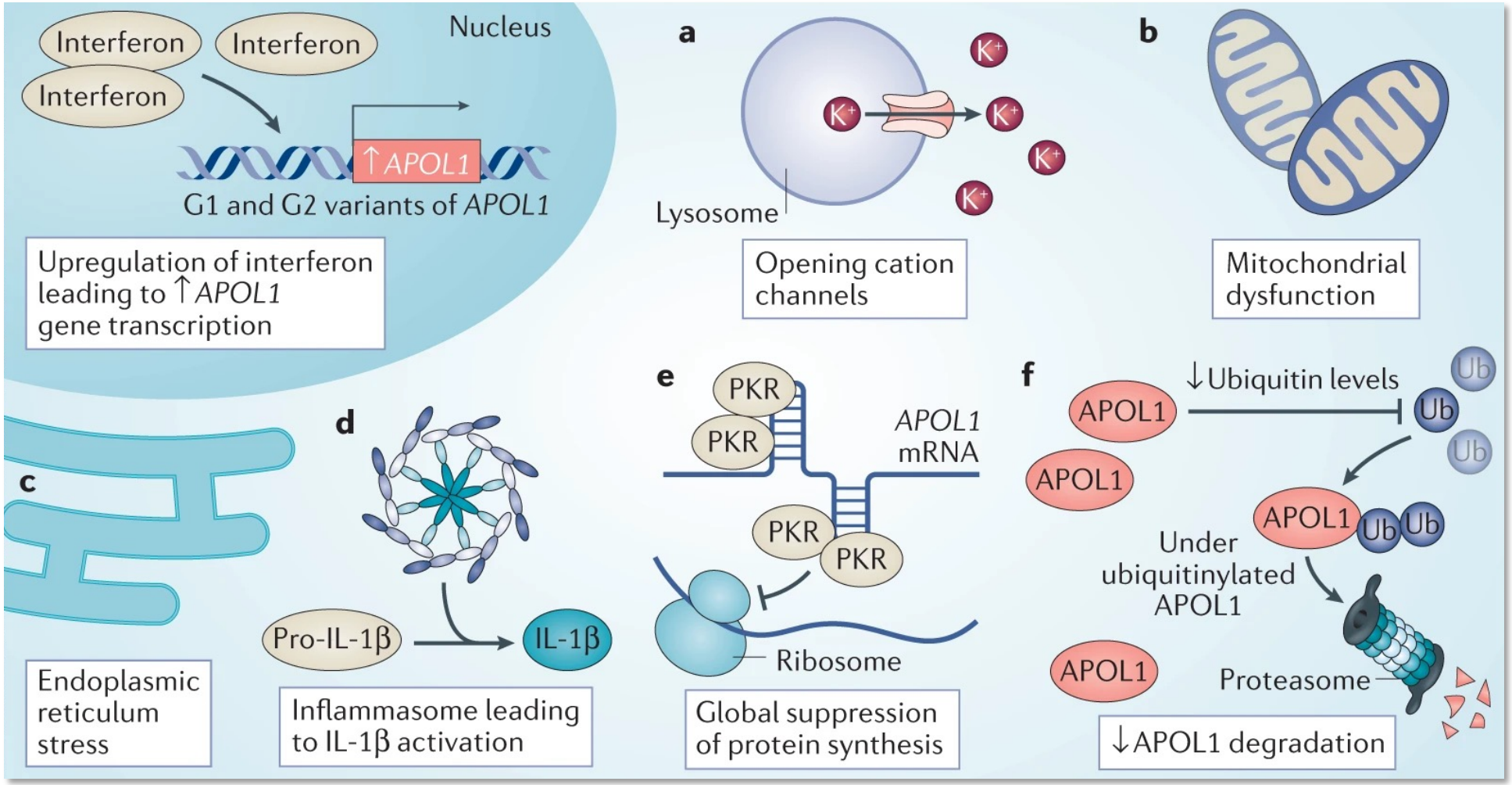
Genetic Inhibition of APOL1 Pore-Forming Function Prevents APOL1-Mediated Kidney Disease

Adriana M. Hung[1,2] Victoria A. Assimon,[3] Hua-Chang Chen[1,4] Zhihong Yu,[1,4] Caitlyn Vlasschaert,[5] Jefferson L. Triozzi[2] Helen Chan,[3] Lee Wheless[6] Otis Wilson,[1,2] Shailja C. Shah[7] Taralynn Mack[1,8] Trevor Thompson[2] Michael E. Matheny[1,4,9] Saranya Chandrasekar[3] Sahar V. Mozaffari[3] Cecilia P. Chung,[10] Philip Tsao[11,12] Katalin Susztak[13] Edward D. Siew[1,2] Karol Estrada,[3] J. Michael Gaziano,[14,15] Robert R. Graham[3] Ran Tao[1,4] Maarten Hoek[3] Cassianne Robinson-Cohen,[2] Eric M. Green[3] and Alexander G. Bick[8,14] for the Million Veteran Program*

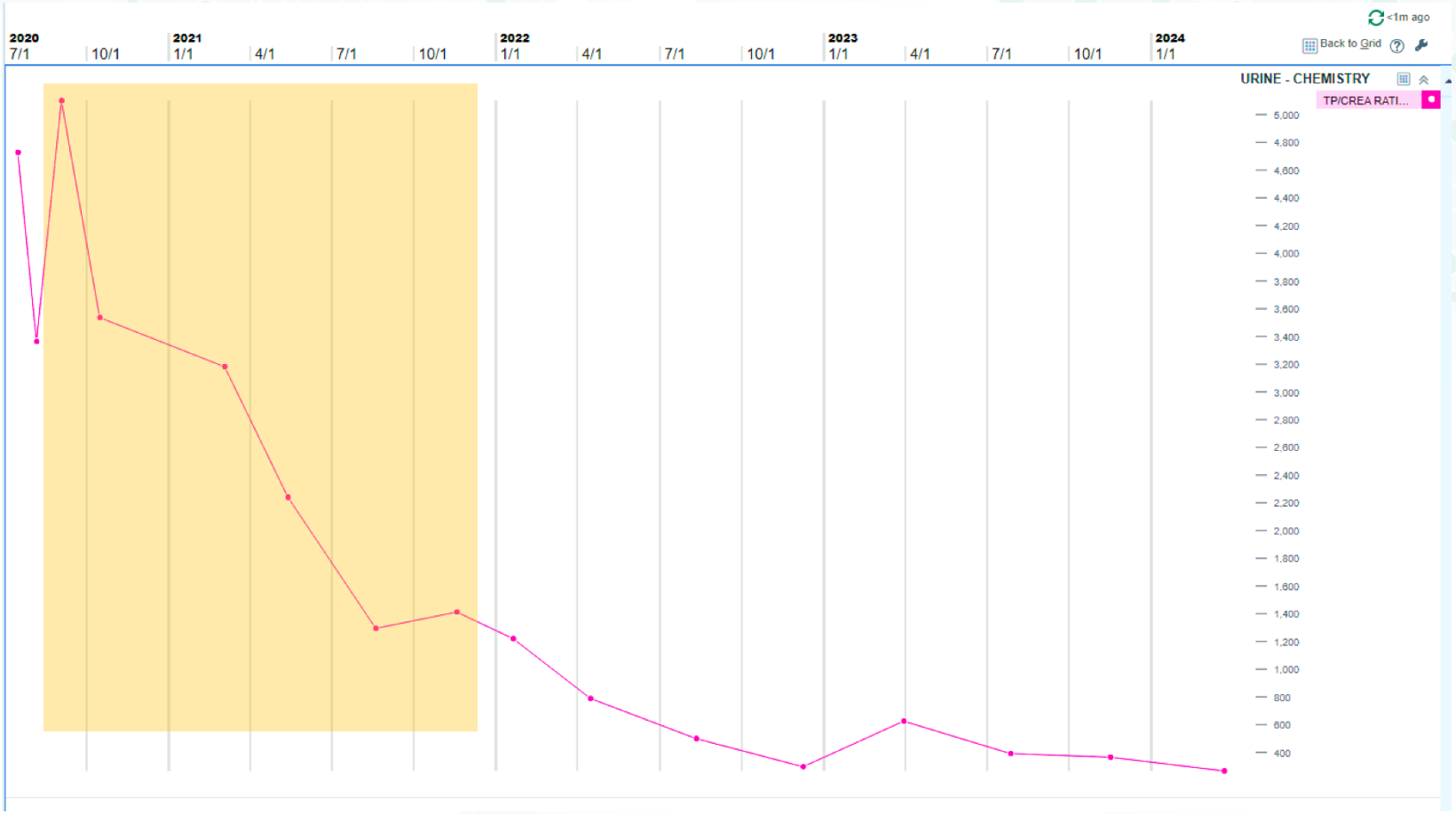




THERAPEUTIC TARGETING OF APOL1



Patient participated in the Vertex Phase 2 study



Study period

Last 12 months:
-UPCR < 0.4 g/g
-eGFR 30-35 ml/min

Taking:
-Losartan 100 mg daily
-Semaglutide 2mg weekly
-Spironolactone 25 mg daily

Conclusions

- APOL1 diagnostic approaches are expanding and would benefit from point of care, rapid result turnaround
- Therapeutic options with different mechanisms of action are being developed in the context of clinical trials
  - Channel modulators
  - Anti-sense oligonucleotides
  - Modulators of protective APOL1 variants
  - Other approaches
- Remaining questions exist around mechanism(s) of APOL1-induced injury, precision-based approach to treatment, and optimal supportive care