Elevated Circulating MMP-9 and Increased Exacerbation Risk in COPD: Results from SPIROMICS and COPDGene

(Data Supplement)

J. Michael Wells[1,2,3], Margaret M. Parker[4], Robert A. Oster[5], Russ P. Bowler[6], Mark T. Dransfield[1,2,3], Surya P. Bhatt[1,2], Michael H. Cho[4], Victor Kim[7], Jeffrey L. Curtis[8,9], Fernando J. Martinez[10], Robert Paine III[11,12], Wanda O'Neal[13], Wassim W. Labaki[8], Robert J. Kaner[10], Igor Barjaktarevic[14], MeiLan K. Han[8], Edwin K. Silverman[4], James D. Crapo[6], R. Graham Barr[15], Prescott Woodruff[16], Peter J. Castaldi[4], Amit Gaggar[1,2,3] for the SPIROMICS and COPDGene Investigators[†]

Supplemental Table 1. Unadjusted associations with prospective COPD exacerbations using logistic regression models

	SPIROMICS			COPDGene		
	OR	95% CI	P-value	OR	95% CI	P-value
Age, years	0.97	0.96 – 0.99	<0.001	0.99	0.95 – 1.04	0.67
White race	0.96	0.69 – 1.32	0.79			
Male sex	0.70	0.54 – 0.89	0.004	0.73	0.34 – 1.57	0.42
BMI, kg/m^2	0.99	0.97 – 1.01	0.23	1.00	0.94 – 1.07	0.91
FEV$_1$, percent predicted	0.97	0.96 – 0.98	<0.001	1.01	0.99 – 1.03	0.45
FVC, percent predicted	0.98	0.97 – 0.99	<0.001	1.01	0.99 – 1.03	0.48
FEV1/FVC	0.01	0.003 – 0.02	<0.001	1.93	0.09 – 42.63	0.68
Current smoker	0.89	0.69 – 1.16	0.39	0.90	0.35 – 2.40	0.85
Pack-year history	1.00	1.00 – 1.01	0.27	0.99	0.97 – 1.00	0.032
Chronic bronchitis	3.13	2.31 – 4.22	<0.001	1.23	0.50 – 3.04	0.65
WBC, x10^9 cell/ml	1.07	1.10 – 1.13	0.025	0.92	0.78 – 1.09	0.34
Serum Neutrophil %	1.02	1.00 – 1.03	0.020	1.00	0.96 – 1.04	0.95
Serum Eosinophil %	0.97	0.91 – 1.02	0.25	1.05	0.85 – 1.29	0.65
Any AECOPD within previous 12 months	3.37	2.53 – 4.51	<0.001	2.36	1.08 – 5.14	0.031
Elevated MMP-9	1.92	1.23 – 2.99	0.004	2.13	0.85 – 5.37	0.108
TIMP-1, ng/ml	1.00	0.99 – 1.01	0.60	1.01	0.98 – 1.04	0.48

Data represented as odds ratio (OR) along with its corresponding 95% confidence interval (CI). Unadjusted logistic regression models were used to obtain these results. Abbreviations BMI = body mass index; FEV$_1$ = forced expiratory volume in 1-second; FVC = forced vital capacity; WBC = white blood cell count; AECOPD = acute exacerbation of COPD; MMP-9 = matrix metalloprotease 9

Supplemental Table 2. Associations with prospective COPD exacerbations

	Multivariable Model (SPIROMICS)			Multivariable Model (COPDGene)		
	OR	95% CI	P-value	OR	95% CI	P-value
Age, years	0.98	0.97 – 1.00	0.12	1.00	0.94 – 1.05	0.85
White race	0.96	0.65 – 1.40	0.82	- -	- -	- -
Male sex	0.74	0.56 – 0.99	0.041	0.88	0.38 – 1.03	0.77
FEV_1, percent predicted	0.98	0.97 – 0.98	<0.001	1.01	0.98 – 1.03	0.63
Current smoker	0.85	0.61 – 1.17	0.31	0.58	0.17 – 2.07	0.41
Chronic Bronchitis	1.88	1.35 – 2.62	<0.001	1.30	0.44 – 3.79	0.64
WBC, x 10^9 cell/ml	1.01	0.94 – 1.08	0.88	0.81	0.65 – 1.00	0.052
Any AECOPD within previous 12 months	2.13	1.52 – 3.00	<0.001	2.62	1.11 – 6.15	0.027
Elevated MMP-9	1.71	1.00 – 2.90	0.049	3.03	1.02 – 9.01	0.046

Results are obtained from multivariable logistic regression models. OR=odds ratio, CI=confidence interval. For SPIROMICS, Nagelkerke R^2 = 0.228; for COPDGene, Nagelkerke R^2 = 0.128.
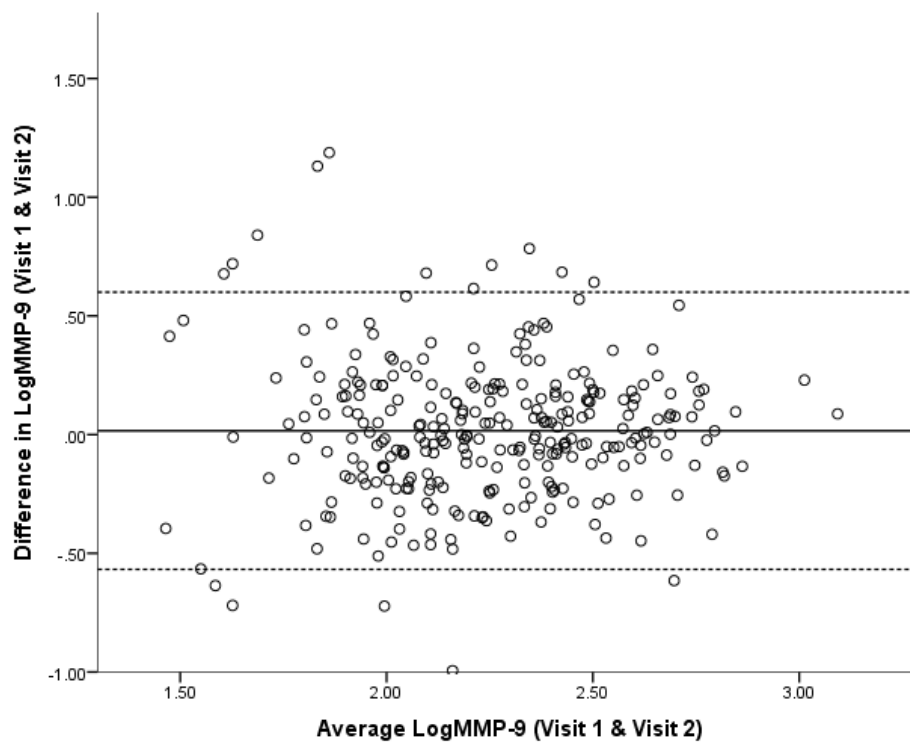
Supplemental Table 3. Associations with AECOPD Frequency

	Multivariable Model (SPIROMICS)			Multivariable Model (COPDGene)		
	IRR	95% CI	P-value	IRR	95% CI	P-value
Age, years	0.98	0.97 – 0.99	<0.001	0.99	0.98 –1.00	0.005
White race	0.93	0.81 – 1.07	0.27	- -	- -	- -
Male sex	0.65	0.59 – 0.73	<0.001	0.91	0.77 – 1.06	0.23
FEV_1, percent predicted	0.98	0.98 – 0.99	<0.001	1.00	1.00 – 1.01	0.35
Current smoker	0.94	0.83 – 1.07	0.35	0.88	0.70 – 1.12	0.30
Chronic Bronchitis	1.36	1.22 – 1.52	<0.001	0.92	0.76 – 1.12	0.42
WBC, x 10^9 cell/ml	0.99	0.97 – 1.01	0.40	1.01	0.97 – 1.05	0.75
Any AECOPD within previous 12 months	2.00	1.78 – 2.23	<0.001	2.67	1.22 – 3.21	<0.001
Elevated MMP-9	1.45	1.23 – 1.71	<0.001	1.24	1.03 – 1.49	0.024

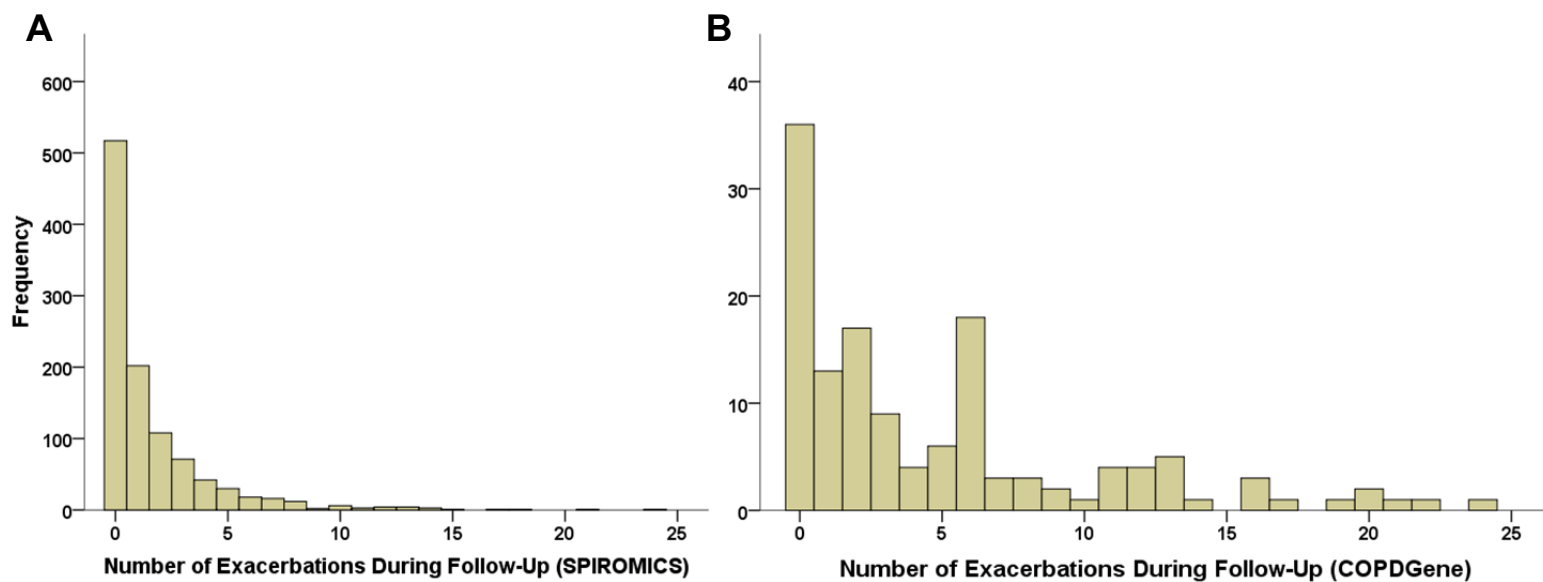Results are obtained from multivariable Poisson regression models. IRR=incidence rate ratio, CI=confidence interval.

Supplemental Table 4. Unadjusted associations with COPD exacerbation frequency using Poisson models

	SPIROMICS			COPDGene		
	IRR	95% CI	P-value	IRR	95% CI	P-value
Age, years	0.96	0.96-0.97	<0.001	0.97	0.97-0.99	<0.001
White race	0.87	0.77-0.99	0.029			
Male sex	0.61	0.55-0.67	<0.001	0.84	0.72-0.98	0.024
BMI, kg/m^2	1.00	0.99-1.01	0.58	1.00	0.98-1.01	0.56
FEV$_1$, percent predicted	0.98	0.97-0.98	<0.001	1.00	1.00-1.01	0.32
FVC, percent predicted	0.98	0.98-0.98	<0.001	1.00	1.00-1.00	0.64
FEV1/FVC	0.05	0.03-0.07	<0.001	1.67	0.88-3.17	0.11
Current smoker	0.98	0.88-1.09	0.70	1.19	0.98-1.45	0.077
Pack-year history	1.00	1.00-1.00	0.012	0.99	0.99-1.00	<0.001
Chronic bronchitis	2.24	2.02-2.48	<0.001	1.10	0.92-1.31	0.30
WBC, x10^9 cell/ml	1.04	1.03-1.07	<0.001	1.07	1.03-1.11	<0.001
Serum Neutrophil %	1.01	1.00-1.01	<0.001	1.02	1.02-1.03	<0.001
Serum Eosinophil %	0.99	0.96-1.01	0.22	0.91	0.87-0.95	<0.001
Any AECOPD within previous 12 months	3.11	2.82-3.43	<0.001	2.87	2.40-3.42	<0.001
Elevated MMP-9	1.45	1.26-1.67	<0.001	1.43	1.23-1.68	<0.001
TIMP-1, ng/ml	1.00	1.00-1.00	0.078	0.99	0.99-1.01	0.64

Data represented as incidence rate ratio (IRR) along with its corresponding 95% confidence interval (CI). Unadjusted Poisson regression models with were used to obtain these results. Abbreviations BMI = body mass index; FEV$_1$ = forced expiratory volume in 1-second; FVC = forced vital capacity; WBC = white blood cell count; AECOPD = acute exacerbation of COPD; MMP-9 = matrix metalloprotease 9

Supplemental Figure 1. Bland-Altman Plot for plasma logMMP-9 values at Visit 1 and Visit 2 in SPIROMICS. The solid horizontal line represents the mean of the two values and dashed horizontal lines represent the 95%CI boundaries. The coefficient of variation of the logMMP-9 was 14.7% for Visit 1 and 14.8% for Visit 2. Cohen's kappa was 0.44 (P<0.001) for elevated MMP-9 at visit 1 and visit 2, suggesting moderate agreement between the two timepoints.

A

B

Supplemental Figure 2. Histogram for exacerbations during longitudinal follow-up in (A) SPIROMICS and (B) COPDGene.

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SPIROMICS Investigators:

Neil E. Alexis, Ph.D.; Wayne H. Anderson, Ph.D.; R. Graham Barr, M.D., Dr.P.H.; Eugene R. Bleecker, M.D.; Richard C. Boucher, M.D.; Russell P. Bowler, M.D., Ph.D.; Elizabeth E. Carretta, M.P.H.; Stephanie A. Christenson, M.D.; Alejandro P. Comellas, M.D.; Christopher B. Cooper, M.D., Ph.D.; David J. Couper, Ph.D.; Gerard J. Criner, M.D.; Ronald G. Crystal, M.D.; Jeffrey L. Curtis, M.D.; Claire M. Doerschuk, M.D.; Mark T. Dransfield, M.D.; Christine M. Freeman, Ph.D.; MeiLan K. Han, M.D., M.S.; Nadia N. Hansel, M.D., M.P.H.; Annette T. Hastie, Ph.D.; Eric A. Hoffman, Ph.D.; Robert J. Kaner, M.D.; Richard E. Kanner, M.D.; Eric C. Kleerup, M.D.; Jerry A. Krishnan, M.D., Ph.D.; Lisa M. LaVange, Ph.D.; Stephen C. Lazarus, M.D.; Fernando J. Martinez, M.D., M.S.; Deborah A. Meyers, Ph.D.; John D. Newell, Jr., M.D.; Elizabeth C. Oelsner, M.D., M.P.H.; Wanda K. O'Neal, Ph.D.; Robert Paine III, M.D.; Nirupama Putcha, M.D., M.H.S.; Stephen I. Rennard, M.D.; Donald P. Tashkin, M.D.; Mary Beth Scholand, M.D.; J. Michael Wells, M.D.; Robert A. Wise, M.D.; and Prescott G. Woodruff, M.D., M.P.H.

COPDGene Investigators:
Core Units

Administrative Center: James D. Crapo, MD (PI); Edwin K. Silverman, MD, PhD (PI); Barry J. Make, MD; Elizabeth A. Regan, MD, PhD

Genetic Analysis Center: Terri Beaty, PhD; Ferdouse Begum, PhD; Robert Busch, MD; Peter J. Castaldi, MD, MSc; Michael Cho, MD; Dawn L. DeMeo, MD, MPH; Adel R. Boueiz, MD; Marilyn G. Foreman, MD, MS; Eitan Halper-Stromberg; Nadia N. Hansel, MD, MPH; Megan E. Hardin, MD; Lystra P. Hayden, MD, MMSc; Craig P.

Hersh, MD, MPH; Jacqueline Hetmanski, MS, MPH; Brian D. Hobbs, MD; John E.

Hokanson, MPH, PhD; Nan Laird, PhD; Christoph Lange, PhD; Sharon M. Lutz, PhD;

Merry-Lynn McDonald, PhD; Margaret M. Parker, PhD; Dandi Qiao, PhD; Elizabeth A.

Regan, MD, PhD; Stephanie Santorico, PhD; Edwin K. Silverman, MD, PhD; Emily S.

Wan, MD; Sungho Won

Imaging Center: Mustafa Al Qaisi, MD; Harvey O. Coxson, PhD; Teresa Gray;

MeiLan K. Han, MD, MS; Eric A. Hoffman, PhD; Stephen Humphries, PhD; Francine L.

Jacobson, MD, MPH; Philip F. Judy, PhD; Ella A. Kazerooni, MD; Alex Kluiber; David A.

Lynch, MB; John D. Newell, Jr., MD; Elizabeth A. Regan, MD, PhD; James C. Ross,

PhD; Raul San Jose Estepar, PhD; Joyce Schroeder, MD; Jered Sieren; Douglas

Stinson; Berend C. Stoel, PhD; Juerg Tschirren, PhD; Edwin Van Beek, MD, PhD; Bram

van Ginneken, PhD; Eva van Rikxoort, PhD; George Washko, MD; Carla G. Wilson,

MS;

PFT QA Center, Salt Lake City, UT: Robert Jensen, PhD

Data Coordinating Center and Biostatistics, *National Jewish Health, Denver, CO*:

Douglas Everett, PhD; Jim Crooks, PhD; Camille Moore, PhD; Matt Strand, PhD; Carla

G. Wilson, MS

Epidemiology Core, *University of Colorado Anschutz Medical Campus, Aurora,*

CO: John E. Hokanson, MPH, PhD; John Hughes, PhD; Gregory Kinney, MPH, PhD;

Sharon M. Lutz, PhD; Katherine Pratte, MSPH; Kendra A. Young, PhD

Clinical Centers

Ann Arbor VA: Jeffrey L. Curtis, MD; Carlos H. Martinez, MD, MPH; Perry G. Pernicano, MD

Baylor College of Medicine, Houston, TX: Nicola Hanania, MD, MS; Philip Alapat, MD; Mustafa Atik, MD; Venkata Bandi, MD; Aladin Boriek, PhD; Kalpatha Guntupalli, MD; Elizabeth Guy, MD; Arun Nachiappan, MD; Amit Parulekar, MD;

Brigham and Women's Hospital, Boston, MA: Dawn L. DeMeo, MD, MPH; Craig Hersh, MD, MPH; Francine L. Jacobson, MD, MPH; George Washko, MD

Columbia University, New York, NY: R. Graham Barr, MD, DrPH; John Austin, MD; Belinda D'Souza, MD; Gregory D.N. Pearson, MD; Anna Rozenshtein, MD, MPH, FACR; Byron Thomashow, MD

Duke University Medical Center, Durham, NC: Neil MacIntyre, Jr., MD; H. Page McAdams, MD; Lacey Washington, MD

HealthPartners Research Institute, Minneapolis, MN: Charlene McEvoy, MD, MPH; Joseph Tashjian, MD

Johns Hopkins University, Baltimore, MD: Robert Wise, MD; Robert Brown, MD; Nadia N. Hansel, MD, MPH; Karen Horton, MD; Allison Lambert, MD, MHS; Nirupama Putcha, MD, MHS

Los Angeles Biomedical Research Institute at Harbor UCLA Medical Center, Torrance, CA: Richard Casaburi, PhD, MD; Alessandra Adami, PhD; Matthew Budoff,

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Michael E. DeBakey VAMC, Houston, *TX*: Amir Sharafkhaneh, MD, PhD; Charlie Lan, DO

Minneapolis VA: Christine Wendt, MD; Brian Bell, MD

Morehouse School of Medicine, Atlanta, GA: Marilyn G. Foreman, MD, MS; Eugene Berkowitz, MD, PhD; Gloria Westney, MD, MS

National Jewish Health, Denver, CO: Russell Bowler, MD, PhD; David A. Lynch, MB

Reliant Medical Group, Worcester, MA: Richard Rosiello, MD; David Pace, MD

Temple University, Philadelphia, PA: Gerard Criner, MD; David Ciccolella, MD; Francis Cordova, MD; Chandra Dass, MD; Gilbert D'Alonzo, DO; Parag Desai, MD; Michael Jacobs, PharmD; Steven Kelsen, MD, PhD; Victor Kim, MD; A. James Mamary, MD; Nathaniel Marchetti, DO; Aditi Satti, MD; Kartik Shenoy, MD; Robert M. Steiner, MD; Alex Swift, MD; Irene Swift, MD; Maria Elena Vega-Sanchez, MD

University of Alabama, Birmingham, AL: Mark Dransfield, MD; William Bailey, MD; Surya Bhatt, MD; Anand Iyer, MD; Hrudaya Nath, MD; J. Michael Wells, MD

University of California, San Diego, CA: Joe Ramsdell, MD; Paul Friedman, MD; Xavier Soler, MD, PhD; Andrew Yen, MD

University of Iowa, Iowa City, IA: Alejandro P. Comellas, MD; John Newell, Jr., MD; Brad Thompson, MD

University of Michigan, Ann Arbor, MI: MeiLan K. Han, MD, MS; Ella Kazerooni, MD; Carlos H. Martinez, MD, MPH

University of Minnesota, Minneapolis, MN: Joanne Billings, MD; Abbie Begnaud, MD; Tadashi Allen, MD

University of Pittsburgh, Pittsburgh, PA: Frank Sciurba, MD; Jessica Bon, MD; Divay Chandra, MD, MSc; Carl Fuhrman, MD; Joel Weissfeld, MD, MPH

University of Texas Health Science Center at San Antonio, San Antonio, TX: Antonio Anzueto, MD; Sandra Adams, MD; Diego Maselli-Caceres, MD; Mario E. Ruiz, MD