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Inherited Causes of Clonal Hematopoiesis of Indeterminate Potential in TOPMed Whole Genomes

Tuesday, 2019-08-27 21:21 America/New_York — ecterry

Current Status:

2019-09-09: Penultimate Draft MS received – undergoing expedited review

2019-09-09: Penultimate Draft approved by Steering Committee [How to Proceed](#)

BASICS

Penultimate Draft: Cover Note	
Submission not preceded by an approved paper proposal	<ul style="list-style-type: none"> It is a new meta-analysis that derives from a single “project” or “omnibus” proposal as part of a larger consortium of many cohorts in which CHS has agreed to participate and for which no new data are needed <p>Parent Proposal: Omnibus: The NHLBI Trans-Omics for Precision Medicine (TOPMed) Program</p>
First Author	Bick, Alexander (Massachusetts General Hospital)
CHS Sponsor Name	Psaty, Bruce (University of Washington)
Coauthors	Joshua Bis, Brian Cade, James Floyd, Susan Heckbert, Robert Kaplan, Bruce Psaty, Jerome Rotter, Russell Tracy
Additional authors	Alexander G Bick*, Joshua S Weinstock*, Satish K Nandakumar, Charles Fulco, Matthew J Leventhal, Erik L Bao, Joseph Nasser, Seyedeh M Zekavat, Mindy D Szeto, Cecelia Laurie, Braxton D Mitchell, Eric Boerwinkle, Kathleen C Barnes, Arden Moscati, Myriam Fornage, Susan Redline, Bruce M Psaty, Edwin K Silverman, Scott T Weiss, Nicholette D Palmer, Ramachandran S Vasam, Esteban G Burchard, Margaret A Taub, Sharon LR Kardia, Jiang He, Donna K Arnett, Robert C Kaplan, Nicholas L Smith, Donna K Arnett, David A Schwartz, Adolfo Correa, Mariza de Andrade,

	Xiuqing Guo, Barbara A Konkle, Brian Custer, Juan M Peralta, Esteban G Burchard, Hongsheng Gui, Deborah A Meyers, Stephen T McGarvey, Ida Yii-Der Chen, Benjamin C Shoemaker, Benjamin M Shoemaker, Eric A Whitsel, Patricia A Peyser, Jai G Broome, Stephanie M Gogarten, Fei Fei Wang, Quenna Wong, May E Montasser, Michelle Daya, Eimear E Kenny, Lenore J Launer, Brian E Cade, Joshua C Bis, Michael H Cho, Jessica Lasky-Su, Donald W Bowden, L Adrienne Cupples, Angel CY Mak, Lewis C Becker, Jennifer A Smith, Tanika N Kelly, Stella Aslibekyan, Susan R Heckbert, Hemant K Tiwari, Ivana V Yang, Paul L Auer, John A Heit, Stephen S Rich, Jill M Johnsen, Joanne E Curran, Angel CY Mak, Sally Wenzel, Daniel E Weeks, Dabeeru C Rao, Dawood Darbar, Dan M Roden, JoAnn E Manson, Russell P Tracy, Erin J Buth, Nicholas Rafaels, Ruth JF Loos, Lifang Hou, Jiwon Lee, Russell P Tracy, Priyadarshini Kachroo, Barry I Freedman, Daniel Levy, Rasika A Mathias, Lawrence F Bielak, James E Hixson, James S Floyd, Marguerite R Irvin, Tasha E Fingerlin, Laura M Raffield, Sebastian M Armasu, Jerome I Rotter, Marsha M Wheeler, Ester C Sabino, John Blangero, L. Keoki Williams, Bruce D Levy, Wayne Huey-Herng Sheu, Dan M Roden, Dawood Darbar, Pinkal Desai, Kent D Taylor, Charles Kooperberg, Cathy C Laurie, Thomas W Blackwell, Albert V Smith, Hongyu Zhao, Ethan Lange, Leslie Lange, James G Wilson, Eric Lander, Jesse M Engreitz, Benjamin L Ebert, Alexander P Reiner, Vijay G Sankaran, Sidd Jaiswal, Goncalo Abecasis, Pradeep Natarajan*, Sekar Kathiresan* on behalf of the NHLBI Trans-Omics for Precision (TOPMed) Consortium
Location of analysis	local (not at CC)
Analysts	Russell Tracy (University of Vermont)
CHS Working Group	
Consortium	<ul style="list-style-type: none"> ○ TOPMed
Type of Study	Main
Data/Analysis type	<ul style="list-style-type: none"> ○ Meta-analysis / Pooled analysis
Manuscript Keyword(s)	CHIP whole gene sequencing (WGS)

1. Assurances

This draft has been	Yes
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reviewed and approved by all coauthors	
Is CHS correctly represented?	Yes
When data are used from ancillary studies, are they included and credited?	Yes
Do you or any member of your Writing Group intend to patent any process, aspect or outcome of these analyses?	No
Are these analyses to involve a for-profit Corporation?	No
If genetic data are used, does the paper include the required genetic exclusions statement?	Yes
Is CMS data used?	No
If CMS data were used, does the paper include cell sizes greater than 10?	No CMS data were used in these analyses
I included the current (rev. 2018) CHS grant & contract numbers in the funding acknowledgement	Yes
As part of the CHS data use agreement, I will update this	Yes

<p>record when my manuscript has been accepted by a journal</p>	
<p>In accordance with the NIH public access policy, I will submit any resulting publication to PubMed Central & update this record with its PMCID within 6 month</p>	<p>Yes</p>

Abstract

Age is the dominant risk factor for most chronic human diseases; yet the mechanisms by which aging confers this risk are largely unknown.¹ Recently, the age-related acquisition of somatic mutations in regenerating hematopoietic stem cell populations was associated with both hematologic cancer incidence²⁻⁴ and coronary heart disease prevalence.⁵ Somatic mutations with leukemogenic potential may confer selective cellular advantages leading to clonal expansion, a phenomenon termed 'Clonal Hematopoiesis of Indeterminate Potential' (CHIP).⁶ Simultaneous germline and somatic whole genome sequence analysis now provides the opportunity to identify root causes of CHIP. Here, we analyze high-coverage whole genome sequences from 99,261 participants of diverse ancestries in the NHLBI TOPMed program and identify 4,229 individuals with CHIP. We identify associations with blood cell, lipid, and inflammatory traits specific to different CHIP genes. Association of a genome-wide set of germline genetic variants identified three genetic loci associated with CHIP status, including one locus at TET2 that was African ancestry specific. In silico-informed in vitro evaluation of the TET2 germline locus identified a causal variant that disrupts a TET2 distal enhancer. Aggregates of rare germline loss-of-function variants in CHEK2, a DNA damage repair gene, predisposed to CHIP acquisition. Overall, we observe that germline genetic variation altering hematopoietic stem cell function and the fidelity of DNA-damage repair increase the likelihood of somatic mutations leading to CHIP.

2. Review Method

Paper includes NHLBI author	No
Review method	Expedited – this is a meta-analysis (includes pooled) (1-2 weeks)

3. File

Uploaded Supplemental File(s)	<p>Bick TOPMed CHIP v7.docx</p> <p>Description: Penultimate draft</p> <p>TOPMED CHIP 100k Figures v7.pdf</p> <p>Description: Figures</p>
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PUBLICATION STATUS

Publication	
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ABSTRACT & PRESENTATIONS

PP manuscript proposal/penultimate manuscript vote

SC manuscript proposal/penultimate manuscript vote

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**MULTI-ETHNIC STUDY OF ATHEROSCLEROSIS
MEMORANDUM**

Date: September 9, 2019
To: Alexander Bick & Jerry Rotter
From: MESA Genetics P&P Committee
Re: MESA Genetics Manuscript #G 704 (Inherited Causes of Clonal Hematopoiesis of Indeterminate Potential in TOPMed Whole Genomes)

The MESA Genetics P&P Committee has reviewed and approved the penultimate draft of your manuscript referenced above. **With this approval memo you can now submit your manuscript to a journal.**

Publication information requested by P&P Committee:

Please inform the MESA Genetics P&P Coordinator when the manuscript is accepted at a journal (date of acceptance and journal name). Please also notify the Coordinator when the manuscript has been published (complete citation and a PDF of the manuscript).

Publication information requested by the NHLBI:

The NHLBI no longer reviews MESA manuscripts (except those that include NHLBI staff members as authors), but to stay informed of findings from large studies and to prepare for press queries, the NHLBI Project Office would like authors to send them a courtesy copy of manuscript at or before the time of journal acceptance, particularly for “high-profile” papers. These generally include the following:

- Main results papers or key secondary results papers from clinical trials
- Papers with direct clinical implications, particularly if they impact NHLBI policies
- Papers on potentially sensitive topics
- Papers published in prestige high-impact journals, such as *Nature*, *Nature Genetics*, *Science*, *PLoS*, *NEJM*, *JAMA*, and *Lancet*.

Most importantly, please inform Lorraine Silsbee (silsbeel@nhlbi.nih.gov), NHLBI Project Officer, as soon as you are notified that your manuscript has been accepted for publication at one of the high-profile journals mentioned above. For **MESA SHARe** papers, please notify Dr. George Papanicolaou (gjp@nhlbi.nih.gov), MESA SHARe Project Officer.

PubMed

Please note that as of April 7, 2008, all peer-reviewed manuscripts arising from NIH funds are subject to the NIH Public Access Policy and must be submitted to PubMed Central (PMC) upon acceptance. When you submit your paper for consideration for publication, you must inform the journal of the need to comply with this policy. For details about what you need to do with submission, please go to <http://publicaccess.nih.gov/>.

If you have any questions, please contact the MESA Genetics P&P Coordinator (genpp@uw.edu).



**Research
with Heart.**

Memorandum

To: Alexander Bick
From: Richey Sharrett, for the ARIC Publications Committee
CC: ARIC Publications Committee; Hunter Holbrook
Subject: Review of ARIC MS # TOPmed06
Title: Inherited Causes of Clonal Hematopoiesis of Indeterminate Potential in TOPMed Whole Genomes
Date: Monday, September 9, 2019

On behalf of the ARIC Steering Committee, I am happy to inform you that the above-referenced paper has been approved.

ARIC Publication Policies Require:

1. To comply with NIH Public Access Policy, all ARIC manuscripts are required to be submitted to PubMed Central upon acceptance for publication. If your paper is accepted for publication in a journal that deposits all final published articles in PubMed Central, no author involvement is required. If the journal does not automatically deposit all final manuscripts into PubMed Central, you (or a co-author) **MUST** deposit the final peer-reviewed manuscript in PubMed Central via the NIH Manuscript Submission System (NIHMS): <http://www.nihms.nih.gov/>. More information regarding NIH Public Access Policy can be found here: <http://publicaccess.nih.gov/>
2. Enclosed are the instructions to authors, per our policy, as well as a sentence acknowledging ARIC staff, which should be added to the paper.
3. Please remember to add reference to “ARIC,” in either the title of the paper or the abstract, so that the study can be identified by reference searches. In addition, when the paper has been published, please email the citation and pdf to both Hunter Holbrook (aricpub@unc.edu) and Kendra Hay (aricjhu@jhu.edu).
4. Please follow procedures local to your center for archiving a copy of the programs which created this paper. At Johns Hopkins provide a copy to Natalie Daya (ndaya1@jhu.edu).

Congratulations and good luck with this interesting paper’s submission.



MEMORANDUM

Date: August 23, 2019

To: Alexander Bick

From: Lindsey Bull
P&P Committee Coordinator

Subject: Manuscript 3988 – Inherited causes and clinical consequences of clonal hematopoiesis from 100,002 whole genomes

Congratulations! The Publications and Presentations (P&P) Committee has approved this paper with recommended changes. Please see the review at the end of this memo for details.

You may now submit your manuscript for publication. It is important to keep WHI updated of your manuscript's status on an ongoing basis. Please notify P&P when your manuscript is submitted to a journal and accepted for publication by e-mailing (p&p@whi.org). As they become available, please send (1) a copy of the manuscript as accepted by the journal, (2) the published manuscript in PDF form, and (3) the NIH Manuscript Submission number/PubMed Central number. Authors are required to submit their published manuscript to PubMed Central; see <http://publicaccess.nih.gov> if you are unfamiliar with the NIH Public Access Policy.

Please be aware that lead authors are responsible for identifying and reporting any conflicts of interest among co-authors and noting these in the final manuscript, per journal requirements. Please ensure that all authors complete and report their conflicts on this paper. In addition, please be sure to keep all co-authors informed of your manuscript's progress. If a journal requires revisions, please solicit and incorporate co-author input and inform the P&P Chairs of any major disagreements among the writing group.

Please be reminded that, in accordance with the data use agreement you signed to obtain WHI data for this paper, the data may only be used for this approved analysis and may not be shared with anyone without authorization from WHI.

At a minimum, consortia/pooling papers must include the following acknowledgements statement: *“The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts HHSN268201600018C, HHSN268201600001C, HHSN268201600002C, HHSN268201600003C, and HHSN268201600004C.”* The authors thank the WHI investigators and staff for their dedication, and the study participants for making the program possible. A full listing of WHI investigators can be found at: <http://www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Log%20List.pdf>”

Review 1:

Recommended changes:

Approve, please note there is a reference missing in the "fine mapping" section.

Bick, Alexander G.

From: Bick, Alexander G.
Sent: Tuesday, July 30, 2019 1:07 PM
To: 'snandaku@broadinstitute.org'; 'Jesse Engreitz'; 'ebao@broadinstitute.org'; 'Matthew Leventhal'; 'Maryam Zekavat'; 'mindy.szeto@ucdenver.edu'; 'hongyu.zhao@yale.edu'; 'ETHAN.LANGE@UCDENVER.EDU'; 'LESLIE.LANGE@UCDENVER.EDU'; Ebert, Benjamin Levine, M.D., Ph.D.; 'James G. Wilson'; 'Matthew Leventhal'; 'Alexander Reiner'; Sankaran, Vijay Ganesh; 'Jaiswal, Sidd'; 'Cecelia Laurie'; 'Cathy C. Laurie'; 'Thomas W. Blackwell'; 'Braxton Mitchell'; 'Eric Boerwinkle'; 'KATHLEEN.BARNES@ucdenver.edu'; 'ruth.loos@mssm.edu'; 'eimear.kenny@mssm.edu'; 'Myriam Fornage'; Redline, Susan, M.D., M.P.H.; 'Bruce M Psaty'; 'Ed Silverman'; Scott Weiss; Weiss, Scott T., M.D.; 'Nicholette Allred'; 'Ramachandran, Vasani'; 'Esteban Burchard'; 'RASIKA Mathias'; 'skardia@umich.edu'; 'jhe@tulane.edu'; 'Donna Arnett'; 'Robert Kaplan'; 'Susan R Heckbert'; 'htiwari@uab.edu'; 'irvinr@uab.edu'; 'David Schwartz'; 'Adolfo Correa'; 'mandrade@mayo.edu'; 'Rotter, Jerome'; 'Rich, Stephen S (ssr4n)'; 'BarbaraK@bloodworksnw.org'; 'bcuster@bloodsystems.org'; 'john.blangero@utrgv.edu'; Silverman, Edwin; 'joanne.curran@utrgv.edu'; 'kwillia5@hfhs.org'; 'dameyers@email.arizona.edu'; 'Stephen McGarvey'; 'DC Rao'; 'moore.b.shoemaker@vanderbilt.edu'; 'darbar@uic.edu'; 'Charles Kooperberg'; 'Taylor, Kent'; 'albertvs@umich.edu'; 'tblackw@umich.edu'; 'bmitchel@som.umaryland.edu'; 'mmontass@som.umaryland.edu'; 'arden.moscati@mssm.edu'; 'eimear.kenny@mssm.edu'; 'ruth.loos@mssm.edu'; 'joshbis@uw.edu'; Silverman, Edwin; 'remhc@channing.harvard.edu'; Scott Weiss; 'rejas@channing.harvard.edu'; 'reprk@channing.harvard.edu'; 'nallred@wakehealth.edu'; 'dbowden@wakehealth.edu'; 'bfreedma@wakehealth.edu'; 'esteban.burchard@ucsf.edu'; 'chiyan.mak@ucsf.edu'; 'esteban.burchard@ucsf.edu'; 'chiyan.mak@ucsf.edu'; 'mtaub@jhsp.h.edu'; 'rmathias@jhmi.edu'; 'lbecker@jhmi.edu'; 'donna.arnett@uky.edu'; 'saslibek@uab.edu'; 'robert.kaplan@einstein.yu.edu'; 'heckbert@uw.edu'; 'jfloyd@uw.edu'; 'donna.arnett@uky.edu'; 'htiwari@uab.edu'; 'irvinr@uab.edu'; 'acorrea@umc.edu'; 'pauer@uwm.edu'; 'laura_raffield@unc.edu'; 'mandrade@mayo.edu'; 'Heit.John@mayo.edu'; 'armasu.sebastian@mayo.edu'; 'xguo@labiomed.org'; 'ssr4n@virginia.edu'; 'jrotter@labiomed.org'; 'juan.peralta@utrgv.edu'; 'joanne.curran@utrgv.edu'; 'john.blangero@utrgv.edu'; 'esteban.burchard@ucsf.edu'; 'chiyan.mak@ucsf.edu'; 'kwillia5@hfhs.org'; 'hgui@hfhs.org'; 'sxiao@hfhs.org'; 'eric_whitsel@med.unc.edu'; Manson, JoAnn Elisabeth, M.D., Dr.P.H.; 'pid9006@med.cornell.edu'; 'clk@fredhutch.org'; 'ppeyser@umich.edu'; 'russell.tracy@uvm.edu'; 'ktaylor@labiomed.org'
Cc: Joshua Weinstock; 'Pradeep Natarajan'; Sekar Kathiresan; Goncalo Abecasis
Subject: RE: Please review - TOPMed CHIP paper

Dear Colleagues,

Enclosed please find the TOPMED Clonal Hematopoiesis manuscript for your review. Please send any feedback with tracked changes to me by Friday August 9. We have had some positive preliminary communication with Nature regarding the manuscript and are targeting submission by the end of August.

Text: <https://www.dropbox.com/s/x3sbgdhn1woc38/Bick%20TOPMed%20CHIP%20v5.docx?dl=0>

Figures: <https://www.dropbox.com/s/7kwba17632ju8o4/TOPMED%20CHIP%20100k%20Figures%20v5.pdf?dl=0>

Supplemental

Tables: <https://www.dropbox.com/s/3wgumi9yv106fob/Bick%20TOPMed%20CHIP%20supplemental%20tables%20v5.xlsx?dl=0>

Authorship

table: <https://docs.google.com/spreadsheets/u/1/d/1uWZDdjn9Oc8Tz6oGAnuZUGZbeppmgVhkYFFkdBgblqQ/edit#gid=1571894054>

Thank you in advance for your feedback and your ongoing collaboration!

Alex

Alexander Bick, MD PhD

Resident in Medicine, MGH

Post-doctoral Fellow, Broad Institute

abick@mgh.harvard.edu

From: Pradeep Natarajan <pradeep@broadinstitute.org>

Sent: Wednesday, June 12, 2019 2:22 PM

Subject: Please review - TOPMed CHIP paper authorship

Dear colleagues,

We're making a strong push for the TOPMed CHIP paper to be circulated for your review next month. In the meantime, we wanted to sort out authorship. Please refer to the Google Sheet link below. We have allotted 3 authors per contributing study. We recognize that some TOPMed study labels do reflect multiple substudies justifying a change to this allocation; please email Sek and me for such instances.

<https://docs.google.com/spreadsheets/d/1uWZDdjn9Oc8Tz6oGAnuZUGZbeppmgVhkYFFkdBgblqQ/edit?usp=sharing>

Important: If your study requires its own P&P approval process, please indicate so in the Google Sheet.

And many thanks again for your collaboration!

Pradeep

Pradeep Natarajan, MD MMSc

Director of Preventive Cardiology, Massachusetts General Hospital

Assistant Professor of Medicine, Harvard Medical School

Associate Member, Broad Institute of Harvard and MIT

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natarajanlab.mgh.harvard.edu



August 12, 2019

Drs. Sekar Kathiresan and Pradeep Natarajan

Dear Sek and Pradeep,

We are pleased to hear about your plans to utilize data from the Outcome Modifying Genes in Sickle Cell Disease cohort (OMG SCD) in TOPMed cross-study analyses for the clonal hematopoiesis (CHIP) analysis. We are happy to share OMG SCD data with your group through dbGaP and the TOPMed dbGaP Exchange Area (phs001608) and to collaborate on the analysis and interpretation of results. We understand that your research falls within the scope of the "Research Use Statement" given below. We also understand that the OMG SCD data may be used in analyses for multiple publications and that we will be informed in advance, through the TOPMed manuscript proposal process, of each intended use and will have the opportunity to approve or disapprove the specific use cases. This permission is effective from now until February 28, 2021.

Sincerely,

A handwritten signature in black ink that reads "Allison Ashley-Koch". The signature is written in a cursive, flowing style.

Allison Ashley-Koch, Ph.D.
Professor
Department of Medicine, Div. of Nephrology
Duke Molecular Physiology Institute
Duke University Medical Center

A handwritten signature in black ink that reads "Marilyn J. Telen". The signature is written in a cursive, flowing style.

Marilyn J. Telen, M.D.
Wellcome Professor of Medicine
Department of Medicine, Div of Hematology
Duke Comprehensive Sickle Cell Center
Duke University Medical Center

Research Use Statement

Phenotypic and genomic data from TOPMed studies will be used for: (a) investigating genotype-phenotype associations; (b) variant summary statistics, (c) common controls in association tests, (d) reference panels to impute into un-sequenced individuals from TOPMed; and (e) population genetic studies.

TOPMed data will not be used to investigate individual identity. Consent type and other Data Use Limitations (DUL) for each study will be respected in all analyses. Data from an individual with disease-specific consent will not be used in analyses outside of that restriction, including indirect uses such as imputation reference panels, common controls for association studies and variant summary statistics. For example, an individual with consent restricted to lung function studies will not be used to impute data intended for analyses of diseases not clearly related to lung function. When an individual's DUL prohibits investigation of population genetics, population history or related issues, their data will be excluded from studies that address those issues. We intend to publish or otherwise broadly share any findings from this study with the scientific community.

This application anticipates collaboration among TOPMed investigators from multiple institutions, who are named in a master list appended to the IRB document uploaded with this application. Within a set of applicants approved for access to the TOPMed Exchange Areas, data may be shared in a cloud environment or by direct transfer, provided that they all agree among themselves to allow such sharing, and that all have approved TOPMed Data Access Requests for the specific data sets to be shared. Otherwise, data will be shared only among Internal Collaborators – i.e. within an institution. Data from TOPMed may be combined with non-TOPMed data from the same or other studies (obtained from dbGaP or other sources), to improve the power for novel genetic discoveries, while respecting the consent of all participants. We expect that this activity creates no additional risks to participants.

Bick, Alexander G.

From: Raffield, Laura <laura_raffield@unc.edu>
Sent: Monday, September 9, 2019 10:19 AM
To: jhspub
Cc: Bick, Alexander G.
Subject: RE: TOPMed consortia manuscript for review

External Email - Use Caution

Just wanted to check back in to see if you had heard anything back on the expedited review of this consortium manuscript (proposal 6282). Sorry to be a pain, it's just almost ready to submit once we hear from JHS and a few other cohorts.

Thanks for any information!
Laura

From: Raffield, Laura
Sent: Monday, August 26, 2019 5:47 PM
To: jhspub <jhspub@umc.edu>
Subject: RE: TOPMed consortia manuscript for review

I am a co-author so I cannot review.... Otherwise I'd be happy to! If you could send for expedited review that would be great.

Thanks so much,
Laura

From: jhspub <jhspub@umc.edu>
Sent: Monday, August 26, 2019 5:38 PM
To: Raffield, Laura <laura_raffield@unc.edu>
Subject: RE: TOPMed consortia manuscript for review

Hi Laura,

I apologize but I completely missed this. Would you have a conflict of interest in reviewing this manuscript? If not, I will send it to you for expedited review.

Regards,
The PPS Administrative Team

From: Raffield, Laura [mailto:laura_raffield@unc.edu]
Sent: Monday, August 26, 2019 1:46 PM
To: jhspub <jhspub@umc.edu>
Cc: Bick, Alexander G. <ABICK@MGH.HARVARD.EDU>; Alexander Reiner <apreiner@uw.edu>
Subject: [EXTERNAL] RE: TOPMed consortia manuscript for review

Hi Erica,

Sorry to bother you with two in one day... but any status updates on this consortium manuscript (proposal 6282)?

Best wishes,
Laura

From: Raffield, Laura
Sent: Wednesday, July 31, 2019 1:51 PM
To: jhspub <jhspub@umc.edu>
Cc: Bick, Alexander G. <ABICK@MGH.HARVARD.EDU>; Alexander Reiner <apreiner@uw.edu>
Subject: TOPMed consortia manuscript for review

Please see the attached consortium manuscript for review under TOPMed manuscript proposal 6282. The JHS acknowledgements are in the linked spreadsheet, but we will make sure the text below is included in the submitted paper.

Thanks! Please let me know if there are any questions.
Laura

The Jackson Heart Study (JHS) is supported and conducted in collaboration with Jackson State University (HHSN268201800013I), Tougaloo College (HHSN268201800014I), the Mississippi State Department of Health (HHSN268201800015I/HHSN26800001) and the University of Mississippi Medical Center (HHSN268201800010I, HHSN268201800011I and HHSN268201800012I) contracts from the National Heart, Lung, and Blood Institute (NHLBI) and the National Institute for Minority Health and Health Disparities (NIMHD). The authors also wish to thank the staffs and participants of the JHS.

Whole genome sequencing (WGS) for the Trans-Omics in Precision Medicine (TOPMed) program was supported by the National Heart, Lung and Blood Institute (NHLBI). WGS for "NHLBI TOPMed: The Jackson Heart Study" (phs000964) was performed at the University of Washington Northwest Genomics Center (HHSN268201100037C).

Postdoctoral Fellow, Department of Genetics
5100 Genetic Medicine Building
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120 Mason Farm Road
Chapel Hill, NC, 27599
laura_raffield@unc.edu

Individuals who have received this information in error or are not authorized to receive it must promptly return or dispose of the information and notify the sender. Those individuals are hereby notified that they are strictly prohibited from reviewing, forwarding, printing, copying, distributing or using this information in any way.

Bick, Alexander G.

Subject: Please review - TOPMed CHIP paper authorship

From: Robert Kaplan <Robert.Kaplan@einstein.yu.edu>

Sent: Wednesday, September 4, 2019 12:17 PM

To: Bick, Alexander G. <ABICK@MGH.HARVARD.EDU>; Pradeep Natarajan <pradeep@broadinstitute.org>

Cc: kari_north@unc.edu; Jee-Young Moon <jee-young.moon@einstein.yu.edu>

Subject: RE: Please review - TOPMed CHIP paper authorship

External Email - Use Caution

Dear Alexander,

Additional coauthors from the Hispanic cohort are copied here:

Kari North

Jee-Young Moon

If you have a template for the 3 of us to provide author information, please let me know.

We submitted your MS to our committee.

Robert

Robert C Kaplan, PhD
Albert Einstein College of Medicine
718-430-4076 (New York)
206-667-6913 (Seattle)

From: Bick, Alexander G. [ABICK@MGH.HARVARD.EDU]

Sent: Wednesday, September 04, 2019 6:26 AM

To: Robert Kaplan; Pradeep Natarajan

Cc: kari_north@unc.edu

Subject: RE: Please review - TOPMed CHIP paper authorship

Thank you Robert! Very much appreciate the feedback. We will incorporate your feedback on the blood traits and other markers. The differential prevalence of CHIP by ancestry was adjusted for age ... we will clarify this in the text.

Alex

From: Robert Kaplan <Robert.Kaplan@einstein.yu.edu>

Sent: Wednesday, September 4, 2019 9:17 AM

To: Bick, Alexander G. <ABICK@MGH.HARVARD.EDU>; Pradeep Natarajan <pradeep@broadinstitute.org>

Cc: kari_north@unc.edu

Subject: RE: Please review - TOPMed CHIP paper authorship

External Email - Use Caution

Dear Pradeep and Alexander,

Great work on this MS. I have a few comments.

Page 3 (counting sequentially from title page): The analyses in relation to blood cell traits, inflammation, lipids, etc read like very trivial correlations because you do not indicate any adjustment variables were considered. I would suggest to add this information about covariates at least to the legend of Figure 2, and better yet also note in the text that you controlled for age and other things. Adjustment for smoking status ideally would have been done, but at least you might want to check to see if that made a difference.

Likewise, the Ns are not given for subjects with these traits, so why not add this to the Figure 2 legend.

You might want to look at IGF-1 and IGFBP-3, available in some TM cohorts as additional aging relating traits that have prior evidence for association with ASXL2 (not ASXL1). See: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5013013/>

Comparisons across ancestry (lower in Hispanic and east Asian) might be explained by differences in the age ranges or age distribution of the European, African American, Hispanic, Asian etc. Did you repeat these analyses after restricting to a similar age distribution across the ancestries? Was the statement of lower CHIP in Hispanic/Asian adjusted for age?

I will send your MS on to the HCHS/SOL cohort for review.

Robert

Robert C Kaplan, PhD
Albert Einstein College of Medicine
718-430-4076 (New York)
206-667-6913 (Seattle)

From: Bick, Alexander G. [ABICK@MGH.HARVARD.EDU]
Sent: Tuesday, August 27, 2019 5:25 AM
To: Robert Kaplan; Pradeep Natarajan
Cc: kari_north@unc.edu
Subject: RE: Please review - TOPMed CHIP paper authorship

Dear Robert,

The manuscript and figures are attached for committee review.

Thank you in advance for your assistance!

Alex

Alexander Bick, MD PhD
Massachusetts General Hospital
Pager: 28942 | Cell: 973-886-2291
email: abick@partners.org

From: Robert Kaplan <Robert.Kaplan@einstein.yu.edu>
Sent: Tuesday, August 27, 2019 12:49 AM
To: Pradeep Natarajan <pradeep@broadinstitute.org>
Cc: kari_north@unc.edu; Bick, Alexander G. <ABICK@MGH.HARVARD.EDU>
Subject: RE: Please review - TOPMed CHIP paper authorship

External Email - Use Caution

Dear Pradeep,

Please re-send, I did not find an attachment. We would like to be able to have committee review before it is submitted.

Thank you
Robert

Robert C Kaplan, PhD
Albert Einstein College of Medicine
718-430-4076 (New York)
206-667-6913 (Seattle)

From: Pradeep Natarajan [pradeep@broadinstitute.org]
Sent: Monday, August 26, 2019 7:13 PM
To: Robert Kaplan
Cc: kari_north@unc.edu; Bick, Alexander G.
Subject: FW: Please review - TOPMed CHIP paper authorship

Hi Robert and Kari,

We only used HCHS_SOL for demographics, blood cell count, lipid, and CRP analyses.

Also, does this need to go through HCHS_SOL P&P review (in addition to TOPMed P&P)? Here's the near final version of the manuscript.

Pradeep

Pradeep Natarajan, MD MMSc
Director of Preventive Cardiology, Massachusetts General Hospital
Assistant Professor of Medicine, Harvard Medical School
Associate Member, Broad Institute of Harvard and MIT
pnatarajan@mgh.harvard.edu
pradeep@broadinstitute.org
185 Cambridge St, CPZN 3.184, Boston, MA 02114
[@pnatarajanmd](https://twitter.com/pnatarajanmd)
natarajanlab.mgh.harvard.edu

Bick, Alexander G.

From: Bick, Alexander G.
Sent: Wednesday, August 7, 2019 8:21 PM
To: Weeks, Daniel E
Cc: Stephen McGarvey
Subject: RE: Please review - TOPMed CHIP paper

Thanks Dan and Stephen! We very much appreciate your feedback and collaboration and will incorporate into the next version.

Alex

From: Weeks, Daniel E <weeks@pitt.edu>
Sent: Wednesday, August 7, 2019 5:21 PM
To: Bick, Alexander G. <ABICK@MGH.HARVARD.EDU>
Cc: Stephen McGarvey <Stephen_McGarvey@brown.edu>
Subject: RE: Please review - TOPMed CHIP paper

External Email - Use Caution

Dear Alex,

Very interesting and comprehensive paper representing an immense amount of work!

I have used the Box comment feature to make comments/suggestions.

Main suggestion: Add a Sup Table that indicates which cohorts were used in which analyses. I suspect the Samoans were only used in a small subset of them, due to missing phenotypes, etc.

Thanks,
-- Dan --

From: [Bick, Alexander G.](#)
To: uerickson@som.umaryland.edu
Cc: [Pradeep Natarajan](#)
Subject: TOPMed Manuscript -- Amish cohort
Date: Monday, August 26, 2019 1:37:00 PM

Dear Ugur,

Enclosed please find a near final draft of our manuscript on clonal hematopoiesis in the TOPMed project that included data from the Amish cohort for your review.

Manuscript:

<https://www.dropbox.com/s/x75wu5303degg39/Bick%20TOPMed%20CHIP%20v7.docx?dl=0>

Figures:

<https://www.dropbox.com/s/7iqynn24wyfpt3p/TOPMED%20CHIP%20100k%20Figures%20v7.pdf?dl=0>

Many thanks!

Alex

Alexander Bick, MD PhD

Resident in Medicine, PGY-3

Department of Medicine

Massachusetts General Hospital

Pager: 28942 | Cell: 973-886-2291

email: abick@partners.org

TOPMed Manuscript Approval by Sponsoring Working Group

Working Group name: Hematology & Hemostasis

Working Group convener(s) name(s) & affiliations: Alex Reiner (WHI, JHS), Andrew Johnson (FHS), Rasika Mathias (GeneSTAR)

Date: August 26, 2019

Re Manuscript: # 3551, Alex Bick/Pradeep Natarajan, Association of clonal hematopoiesis with cardiovascular disease

Dear TOPMed Publications Committee,

The TOPMed Hematology & Hemostasis Working Group has considered the manuscript cited above and approves its submission for publication, provided that it passes administrative review. We have considered the following factors:

1. Scientific rigor
2. Appropriate authorship, including coauthor(s) from each contributing study (unless the study declined authorship), the sequencing centers, IRC and DCC, as well as TOPMed banner authorship when appropriate.
3. Scope of the manuscript being consistent with the proposal and not infringing on other proposals from this Working Group
4. Potential for stigmatization

We understand that administrative review will be performed by the DCC and will consist of the following checks:

1. Data set use approvals by study PIs are in place.
2. TOPMed and study-specific acknowledgments are included

Sincerely,



Alex Reiner

Bick, Alexander G.

From: Pradeep Natarajan <pradeep@broadinstitute.org>
Sent: Wednesday, June 12, 2019 2:22 PM
To: snandaku@broadinstitute.org; Jesse Engreitz; ebao@broadinstitute.org; Matthew Leventhal; Maryam Zekavat; Ebert, Benjamin Levine, M.D., Ph.D.; James G. Wilson; Alexander Reiner; Vijay G. Sankaran; Jaiswal, Sidd; Cecelia Laurie; Cathy C. Laurie; Thomas W. Blackwell; Braxton Mitchell; Eric Boerwinkle; KATHLEEN.BARNES@ucdenver.edu; ruth.loos@mssm.edu; eimear.kenny@mssm.edu; Myriam Fornage; Redline, Susan, M.D., M.P.H.; Bruce M Psaty; Ed Silverman; Scott Weiss; Weiss, Scott T., M.D.; Nicholette Allred; Ramachandran, Vasani; Esteban Burchard; RASIKA Mathias; skardia@umich.edu; jhe@tulane.edu; Donna Arnett; Robert Kaplan; Susan R Heckbert; htiwari@uab.edu; irvinr@uab.edu; David Schwartz; Adolfo Correa; mandrade@mayo.edu; Rotter, Jerome; Rich, Stephen S (ssr4n); BarbaraK@bloodworksnw.org; bcuster@bloodsystems.org; john.blangero@utrgv.edu; ed.silverman@channing.harvard.edu; joanne.curran@utrgv.edu; kwillia5@hfhs.org; dameyers@email.arizona.edu; Stephen McGarvey (stephen_mcgarvey@brown.edu); DC Rao; moore.b.shoemaker@vanderbilt.edu; darbar@uic.edu; Charles Kooperberg; Taylor, Kent
Cc: Bick, Alexander G.; Joshua Weinstock; Sekar Kathiresan; Goncalo Abecasis
Subject: Please review - TOPMed CHIP paper authorship

External Email - Use Caution

Dear colleagues,

We're making a strong push for the TOPMed CHIP paper to be circulated for your review next month. In the meantime, we wanted to sort out authorship. Please refer to the Google Sheet link below. We have allotted 3 authors per contributing study. We recognize that some TOPMed study labels do reflect multiple substudies justifying a change to this allocation; please email Sek and me for such instances.

<https://docs.google.com/spreadsheets/d/1uWZDdjn9Oc8Tz6oGAnuZUGZbepmgVhkYFFkdBgbIqQ/edit?usp=sharing>

Important: If your study requires its own P&P approval process, please indicate so in the Google Sheet.

And many thanks again for your collaboration!

Pradeep

Pradeep Natarajan, MD MMSc
Director of Preventive Cardiology, Massachusetts General Hospital
Assistant Professor of Medicine, Harvard Medical School
Associate Member, Broad Institute of Harvard and MIT
pnatarajan@mgh.harvard.edu
pradeep@broadinstitute.org
185 Cambridge St, CPZN 3.184, Boston, MA 02114
[@pnatarajanmd](https://twitter.com/pnatarajanmd)
natarajanlab.mgh.harvard.edu

Bick, Alexander G.

From: Bick, Alexander G.
Sent: Monday, August 26, 2019 1:56 PM
To: lsellers@uabmc.eu
Cc: Pradeep Natarajan
Subject: TOPMED manuscript with CARDIA data
Attachments: Bick TOPMed CHIP v7.docx; TOPMED CHIP 100k Figures v7.pdf

Dear Ms. Sellers,

Attached for your records is a manuscript entitled “**Inherited Causes of Clonal Hematopoiesis of Indeterminate Potential in TOPMed Whole Genomes**” that incorporates data from CARDIA. Dr. Fornage has already reviewed the manuscript (and is a co-author), but I realized I had not sent it to you per the TOPMed P&P instructions.

Thanks!

Alex

Alexander Bick, MD PhD
Massachusetts General Hospital
Pager: 28942 | Cell: 973-886-2291
email: abick@partners.org

Bick, Alexander G.

Subject: FW: time sensitive -- Action required NHBLI-EBDOC -Levy FW: TOPMed paper with FHS data Inherited Causes of Clonal Hematopoiesis of Indeterminate Potential in TOPMed Whole Genomes

Attachments: Bick TOPMed CHIP v7.docx; TOPMED CHIP 100k Figures v7.pdf

From: Levy, Daniel (NIH/NHLBI) [E] <levyd@nhlbi.nih.gov>
Sent: Monday, August 26, 2019 3:03 PM
To: Walsh, Ann (NIH/NHLBI) [E] <walshac@nhlbi.nih.gov>
Subject: RE: Action required NHBLI-EBDOC -Levy FW: TOPMed paper with FHS data

Hi Ann,

Thank you. Yes, please submit to NHLBI.

I will answer the questions after I've had a chance to read through the manuscript.

Best,

Dan

From: Walsh, Ann (NIH/NHLBI) [E] <walshac@nhlbi.nih.gov>
Sent: Monday, August 26, 2019 3:01 PM
To: Levy, Daniel (NIH/NHLBI) [E] <levyd@nhlbi.nih.gov>
Subject: Action required NHBLI-EBDOC -Levy FW: TOPMed paper with FHS data

Dear Dan,

Have you submitted this manuscript to NHLBI EBDOC? If not, I would be happy to send it – kindly answer the following.

NHLBI requires the following verifications from the author and the assembly of manuscript documents. Your responses will be included with the request to NHLBI to review the manuscript-

- 1) Before submitting papers for review, please have the NHLBI author(s) reply to the items below:
 - A. Verify the funding source is acknowledged, if appropriate.
 - B. Verify the disclaimer statement is present. ("The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute; the National Institutes of Health; or the U.S. Department of Health and Human Services.")
 - C. Verify that there are no critical problems with the clarity of the writing.
 - D. Verify that there are no critical problems with the conclusions. They are supported by the data.
 - E. Verify there are no policy-related issues or anything else that would raise any red flags.
 - F. Verify that notification of our press office is not a priority (not newsworthy).
- 2) If there are supplemental docs for a paper, please consolidate them into one doc. (So there would be 2 attachments: the main paper and the supplemental information doc.)
- 3) Which journal will this manuscript be submitted to?

Thank you for your consideration,
Ann Walsh

From: Bick, Alexander G. <ABICK@MGH.HARVARD.EDU>

Sent: Monday, August 26, 2019 2:15 PM

To: Walsh, Ann (NIH/NHLBI) [E] <walshac@nhlbi.nih.gov>; kmutalik@bu.edu

Subject: TOPMed paper with FHS data

Dear Ann and Karen,

Attached for your records is the penultimate draft of a manuscript entitled “**Inherited Causes of Clonal Hematopoiesis of Indeterminate Potential in TOPMed Whole Genomes**” that incorporates data from FHS for your records and feedback.

Many thanks in advance for your assistance!

Alex

Alexander Bick, MD PhD

Massachusetts General Hospital

Pager: 28942 | Cell: 973-886-2291

email: abick@partners.org

The information in this e-mail is intended only for the person to whom it is addressed. If you believe this e-mail was sent to you in error and the e-mail contains patient information, please contact the Partners Compliance Helpline at <http://www.partners.org/complianceline> . If the e-mail was sent to you in error but does not contain patient information, please contact the sender and properly dispose of the e-mail.

Bick, Alexander G.

From: RASIKA Mathias <rmathias@jhmi.edu>
Sent: Monday, August 26, 2019 2:54 PM
To: Bick, Alexander G.
Cc: Pradeep Natarajan
Subject: Re: TOPMed CHIP paper for GeneSTAR review

External Email - Use Caution

Thanks Alex - looks good, you have two thumbs up from GeneSTAR.

Rasika Mathias, ScD.

Associate Professor of Medicine,
Johns Hopkins University.
Director of Genomics, GeneSTAR Research program, General Internal Medicine.
Director, Data Analysis Unit, Allergy and Clinical Immunology.
5501 Hopkins Bayview Circle, 3A.62A
Baltimore, MD 21224
Tel: 410-550-2487

From: Bick, Alexander G. <ABICK@MGH.HARVARD.EDU>
Sent: Monday, August 26, 2019 2:18 PM
To: RASIKA Mathias
Cc: Pradeep Natarajan
Subject: TOPMed CHIP paper for GeneSTAR review

Dear Rasika,

I hope you are well! Enclosed please find the penultimate draft of the TOPMed CHIP paper for the GeneSTAR P&P/Steering committee review (if you have not already distributed it to the GeneSTAR group). We're hoping to submit in the next two weeks.

Many thanks!

Alex

PS: My admiration for all of the administrative hoops you and Margaret jumped through for the Telomere paper is increasing with every one of these P&P emails ...

Alexander Bick, MD PhD
Massachusetts General Hospital
Pager: 28942 | Cell: 973-886-2291
email: abick@partners.org

The information in this e-mail is intended only for the person to whom it is addressed. If you believe this e-mail was sent to you in error and the e-mail contains patient information, please contact the Partners Compliance HelpLine at <http://www.partners.org/complianceline> . If the e-mail was sent to you in error

but does not contain patient information, please contact the sender and properly dispose of the e-mail.

Bick, Alexander G.

From: Bick, Alexander G.
Sent: Monday, August 26, 2019 2:21 PM
To: steven.claas@uky.edu
Subject: FW: TOPMed manuscript with GOLDN data
Attachments: Bick TOPMed CHIP v7.docx; TOPMED CHIP 100k Figures v7.pdf

Dear Mr. Claas,

Attached for your records is a manuscript entitled “**Inherited Causes of Clonal Hematopoiesis of Indeterminate Potential in TOPMed Whole Genomes**” that incorporates data from GOLDN. Dr. Arnett has already reviewed the manuscript (and is a co-author), but I realized I had not sent it to you per the TOPMed Publication committee instructions.

Thank you in advance for your assistance!

Alex

Alexander Bick, MD PhD
Massachusetts General Hospital
Pager: 28942 | Cell: 973-886-2291
email: abick@partners.org

Bick, Alexander G.

From: Bick, Alexander G.
Sent: Wednesday, September 4, 2019 12:49 PM
To: Robert Kaplan; Pradeep Natarajan
Cc: kari_north@unc.edu; Jee-Young Moon
Subject: RE: Please review - TOPMed CHIP paper authorship

Fantastic!

The authorship template is here:

<https://docs.google.com/spreadsheets/d/1uWZDdjn9Oc8Tz6oGAnuZUGZbepmgVhkYFFkdBgbLqQ/edit#gid=1571894054>

I've added Kari North and Jee-Young Moon to the listing for HCHS_SOL

Thanks!

Alex

From: Robert Kaplan <Robert.Kaplan@einstein.yu.edu>
Sent: Wednesday, September 4, 2019 12:17 PM
To: Bick, Alexander G. <ABICK@MGH.HARVARD.EDU>; Pradeep Natarajan <pradeep@broadinstitute.org>
Cc: kari_north@unc.edu; Jee-Young Moon <jee-young.moon@einstein.yu.edu>
Subject: RE: Please review - TOPMed CHIP paper authorship

External Email - Use Caution

Dear Alexander,

Additional coauthors from the Hispanic cohort are copied here:

Kari North

Jee-Young Moon

If you have a template for the 3 of us to provide author information, please let me know.

We submitted your MS to our committee, so please check back in 2-3 weeks about the status.

Robert

Robert C Kaplan, PhD
Albert Einstein College of Medicine
718-430-4076 (New York)
206-667-6913 (Seattle)

From: Bick, Alexander G. [ABICK@MGH.HARVARD.EDU]
Sent: Wednesday, September 04, 2019 6:26 AM
To: Robert Kaplan; Pradeep Natarajan
Cc: kari_north@unc.edu
Subject: RE: Please review - TOPMed CHIP paper authorship

Thank you Robert! Very much appreciate the feedback. We will incorporate your feedback on the blood traits and other markers. The differential prevalence of CHIP by ancestry was adjusted for age ... we will clarify this in the text.

Alex

From: Robert Kaplan <Robert.Kaplan@einstein.yu.edu>
Sent: Wednesday, September 4, 2019 9:17 AM
To: Bick, Alexander G. <ABICK@MGH.HARVARD.EDU>; Pradeep Natarajan <pradeep@broadinstitute.org>
Cc: kari_north@unc.edu
Subject: RE: Please review - TOPMed CHIP paper authorship

External Email - Use Caution

Dear Pradeep and Alexander,

Great work on this MS. I have a few comments.

Page 3 (counting sequentially from title page): The analyses in relation to blood cell traits, inflammation, lipids, etc read like very trivial correlations because you do not indicate any adjustment variables were considered. I would suggest to add this information about covariates at least to the legend of Figure 2, and better yet also note in the text that you controlled for age and other things. Adjustment for smoking status ideally would have been done, but at least you might want to check to see if that made a difference.

Likewise, the Ns are not given for subjects with these traits, so why not add this to the Figure 2 legend.

You might want to look at IGF-1 and IGFBP-3, available in some TM cohorts as additional aging relating traits that have prior evidence for association with ASXL2 (not ASXL1). See: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5013013/>

Comparisons across ancestry (lower in Hispanic and east Asian) might be explained by differences in the age ranges or age distribution of the European, African American, Hispanic, Asian etc. Did you repeat these analyses after restricting to a similar age distribution across the ancestries? Was the statement of lower CHIP in Hispanic/Asian adjusted for age?

I will send your MS on to the HCHS/SOL cohort for review.

Robert

Robert C Kaplan, PhD
Albert Einstein College of Medicine
718-430-4076 (New York)
206-667-6913 (Seattle)

From: Bick, Alexander G. [ABICK@MGH.HARVARD.EDU]
Sent: Tuesday, August 27, 2019 5:25 AM
To: Robert Kaplan; Pradeep Natarajan
Cc: kari_north@unc.edu
Subject: RE: Please review - TOPMed CHIP paper authorship

Dear Robert,

The manuscript and figures are attached for committee review.

Thank you in advance for your assistance!

Alex

Alexander Bick, MD PhD
Massachusetts General Hospital
Pager: 28942 | Cell: 973-886-2291
email: abick@partners.org

From: Robert Kaplan <Robert.Kaplan@einstein.yu.edu>
Sent: Tuesday, August 27, 2019 12:49 AM
To: Pradeep Natarajan <pradeep@broadinstitute.org>
Cc: kari_north@unc.edu; Bick, Alexander G. <ABICK@MGH.HARVARD.EDU>
Subject: RE: Please review - TOPMed CHIP paper authorship

External Email - Use Caution

Dear Pradeep,

Please re-send, I did not find an attachment. We would like to be able to have committee review before it is submitted.

Thank you
Robert

Robert C Kaplan, PhD
Albert Einstein College of Medicine
718-430-4076 (New York)
206-667-6913 (Seattle)

From: Pradeep Natarajan [pradeep@broadinstitute.org]
Sent: Monday, August 26, 2019 7:13 PM
To: Robert Kaplan
Cc: kari_north@unc.edu; Bick, Alexander G.
Subject: FW: Please review - TOPMed CHIP paper authorship

Hi Robert and Kari,

We only used HCHS_SOL for demographics, blood cell count, lipid, and CRP analyses.

Also, does this need to go through HCHS_SOL P&P review (in addition to TOPMed P&P)? Here's the near final version of the manuscript.

Pradeep

Pradeep Natarajan, MD MMSc
Director of Preventive Cardiology, Massachusetts General Hospital
Assistant Professor of Medicine, Harvard Medical School
Associate Member, Broad Institute of Harvard and MIT
pnatarajan@mg.harvard.edu
pradeep@broadinstitute.org
185 Cambridge St, CPZN 3.184, Boston, MA 02114
[@pnatarajanmd](https://twitter.com/pnatarajanmd)
natarajanlab.mgh.harvard.edu

Begin forwarded message:

From: Robert Kaplan <Robert.Kaplan@einstein.yu.edu>
Subject: RE: Please review - TOPMed CHIP paper authorship
Date: June 12, 2019 at 3:02:31 PM EDT
To: Pradeep Natarajan <pradeep@broadinstitute.org>
Cc: "North, Kari E" <kari_north@unc.edu>

Dear Pradeep,

Thank you. I would like to ask more information because it is not clear to me what phenotypes you plan to include for SOL (this has relevance to who we will add as coauthor). The only "CVD" measure that we have available in your list of variables is ABI. Metabolomics data are available on a subset but they are under the auspices of ongoing R01 and other funding, therefore if you plan to include those data we will need to discuss in more detail.

Robert

Robert C Kaplan, PhD
Albert Einstein College of Medicine
718-430-4076 (New York)
206-667-6913 (Seattle)

From: Pradeep Natarajan [pradeep@broadinstitute.org]
Sent: Wednesday, June 12, 2019 11:48 AM
To: Robert Kaplan
Cc: North, Kari E
Subject: Re: Please review - TOPMed CHIP paper authorship

Hi Robert,

This in reference to this proposal: <https://www.nhlbiwgs.org/paperproposals/3551-association-clonal-hematopoiesis-cardiovascular-disease>

Working title for the paper is: "Inherited causes and clinical consequences of clonal hematopoiesis from 100,002 whole genomes"

Pradeep

Pradeep Natarajan, MD MMSc
Director of Preventive Cardiology, Massachusetts General Hospital
Assistant Professor of Medicine, Harvard Medical School
Associate Member, Broad Institute of Harvard and MIT
pnatarajan@mgh.harvard.edu
pradeep@broadinstitute.org
185 Cambridge St, CPZN 3.184, Boston, MA 02114
@pnatarajanmd
natarajanlab.mgh.harvard.edu

On Jun 12, 2019, at 2:29 PM, Robert Kaplan <Robert.Kaplan@einstein.yu.edu> wrote:

Dear Pradeep,

We in SOL will look forward to participating. Please can you clarify what is the title and topic of this manuscript (there are so many in TOPMed and your email did not make this clear).

Thanks,
Robert

Robert C Kaplan, PhD
Albert Einstein College of Medicine
718-430-4076 (New York)
206-667-6913 (Seattle)

From: Pradeep Natarajan [pradeep@broadinstitute.org]
Sent: Wednesday, June 12, 2019 11:22 AM
To: snandaku@broadinstitute.org; engreitz@broadinstitute.org; ebao@broadinstitute.org; Matthew Leventhal; Maryam Zekavat; Ebert, Benjamin Levine, M.D., Ph.D.; James G. Wilson; Alexander Reiner; Vijay G. Sankaran; Jaiswal, Sidd; Cecelia Laurie; Cathy C. Laurie; Thomas W. Blackwell; Braxton Mitchell; Eric Boerwinkle; KATHLEEN.BARNES@ucdenver.edu; ruth.loos@mssm.edu; eimear.kenny@mssm.edu; Myriam Fornage; Redline, Susan, M. D. , M. P. H.; Bruce M Psaty; Ed Silverman; Scott Weiss; Weiss, Scott T. , M. D.; Nicholette Allred; Ramachandran, Vasana; Esteban Burchard; RASIKA Mathias; skardia@umich.edu; jhe@tulane.edu; Donna Arnett; Robert Kaplan; Susan R Heckbert; htiwari@uab.edu; irvin@uab.edu; David Schwartz; Adolfo Correa; mandrade@mayo.edu; Rotter, Jerome; Rich, Stephen S (ssr4n); BarbaraK@bloodworksnw.org; bcuster@bloodsystems.org; john.blangero@utrgv.edu; ed.silverman@channing.harvard.edu; joanne.curran@utrgv.edu; kwillia5@hfhs.org; dameyers@email.arizona.edu; Stephen McGarvey (stephen_mcgarvey@brown.edu); DC Rao; moore.b.shoemaker@vanderbilt.edu; darbar@uic.edu; Charles Kooperberg; Taylor, Kent
Cc: Bick, Alexander G.; Joshua Weinstock; Sekar Kathiresan; Goncalo Abecasis
Subject: Please review - TOPMed CHIP paper authorship

Dear colleagues,

We're making a strong push for the TOPMed CHIP paper to be circulated for your review next month. In the meantime, we wanted to sort out authorship. Please refer to the Google Sheet link below. We have allotted 3 authors per contributing study. We recognize that some TOPMed study labels do reflect multiple substudies justifying a change to this allocation; please email Sek and me for such instances.

<https://docs.google.com/spreadsheets/d/1uWZDdjn9Oc8Tz6oGAnuZUGZbeppmgVhkYFFkdBgbIqQ/edit?usp=sharing>

Important: If your study requires its own P&P approval process, please indicate so in the Google Sheet.

And many thanks again for your collaboration!

Pradeep

Pradeep Natarajan, MD MMSc
Director of Preventive Cardiology, Massachusetts General Hospital
Assistant Professor of Medicine, Harvard Medical School
Associate Member, Broad Institute of Harvard and MIT
pnatarajan@mgh.harvard.edu
pradeep@broadinstitute.org
185 Cambridge St, CPZN 3.184, Boston, MA 02114
@pnatarajanmd

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Bick, Alexander G.

From: Nicholas L. Smith <nsmith@uw.edu>
Sent: Monday, August 26, 2019 7:16 PM
To: Bick, Alexander G.
Cc: Alexander Reiner; Pradeep Natarajan; Susan R Heckbert; Bruce M Psaty
Subject: RE: TOPMed manuscript with HVH data

External Email - Use Caution

Alex:

The HVH study does not have a review process for TOPMed outside a review by the HVH PIs.

In the acknowledgements, you list the HVH grants twice (see page 13). FYI.

Good luck with the submission!

Nick

Nicholas L. Smith, PhD
Professor, Department of Epidemiology, University of Washington
Director, Seattle Epidemiologic Research and Information Center, VA Cooperative Studies Program

From: Bick, Alexander G. [mailto:ABICK@MGH.HARVARD.EDU]
Sent: Monday, August 26, 2019 11:41 AM
To: Nicholas L. Smith <nsmith@uw.edu>
Cc: Alexander Reiner <apreiner@uw.edu>; Pradeep Natarajan <pradeep@broadinstitute.org>
Subject: TOPMed manuscript with HVH data

Dear Dr. Smith,

Attached for your records is the penultimate draft of a manuscript entitled “**Inherited Causes of Clonal Hematopoiesis of Indeterminate Potential in TOPMed Whole Genomes**” that incorporates data from HVH-VTE. I believe you’ve already received a copy of the manuscript, but wanted to be sure. Please let me know if there is any further process needed to obtain HVH study-specific manuscript review.

Thank you in advance for your assistance!

Alex

Alexander Bick, MD PhD
Massachusetts General Hospital
Pager: 28942 | Cell: 973-886-2291
email: abick@partners.org

Bick, Alexander G.

From: Bick, Alexander G.
Sent: Monday, August 26, 2019 2:43 PM
To: mandrade@mayo.edu
Cc: Pradeep Natarajan; Alexander Reiner
Subject: TOPMed manuscript with Mayo VTE data
Attachments: Bick TOPMed CHIP v7.docx; TOPMED CHIP 100k Figures v7.pdf

Dear Dr. de Andrade,

Attached for your records is the penultimate draft of a manuscript entitled “**Inherited Causes of Clonal Hematopoiesis of Indeterminate Potential in TOPMed Whole Genomes**” that incorporates data from Mayo-VTE. I believe you’ve already received a copy of the manuscript, but wanted to be sure. Please let me know if there is any further process needed to obtain study-specific manuscript approval.

Thank you in advance for your assistance!

Alex

Alexander Bick, MD PhD
Massachusetts General Hospital
Pager: 28942 | Cell: 973-886-2291
email: abick@partners.org

Bick, Alexander G.

From: Dr. Barbara Konkle <BarbaraK@BloodWorksNW.org>
Sent: Sunday, September 1, 2019 9:44 AM
To: Bick, Alexander G.
Subject: RE: TOPMed manuscript with MLOF data

External Email - Use Caution

Alex,
What you have written for MLOF is correct. Nothing else is needed.

Best wishes, Barbraa

Barbara A. Konkle, M.D., **A pos**
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From: Bick, Alexander G. <ABICK@MGH.HARVARD.EDU>
Sent: Monday, August 26, 2019 11:37 AM
To: Dr. Barbara Konkle <BarbaraK@BloodWorksNW.org>
Subject: TOPMed manuscript with MLOF data

This email originated from outside Bloodworks' email system. Do NOT click links or open attachments unless you recognize the sender and know the content is safe.

Dear Dr. Konkle

Attached for your records is the penultimate draft of a manuscript entitled “**Inherited Causes of Clonal Hematopoiesis of Indeterminate Potential in TOPMed Whole Genomes**” that incorporates data from MLOF. I believe you’ve already received a copy of the manuscript, but wanted to be sure. Please let me know if there is any further process needed to obtain MLOF study-specific manuscript review.

Thank you in advance for your assistance!

Alex

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