Clonal Hematopoiesis of Indeterminate Potential and Kidney Function Decline in the General Population

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Rationale & Objective: Clonal hematopoiesis of indeterminate potential (CHIP), defined by the age-related ontogenesis of expanded leukemic variants indicative of a genetically distinct clonal leukocyte population, is associated with risk of hematologic malignancy and cardiovascular disease. In experimental models, recapitulation of CHIP promotes kidney interstitial fibrosis with direct tissue infiltration of donor macrophages. We tested the hypothesis that CHIP is associated with kidney function decline in the general population.

Study Design: Cohort study.

Setting & Participants: 12,004 individuals from 3 community-based cohorts in the TOPMed Consortium.

Exposure: CHIP status from whole-genome sequences obtained from DNA extracted from peripheral blood.

Outcome: Risk of 30% decline in estimated glomerular filtration rate (eGFR) and percent eGFR decline per year during the follow-up period.

Analytical Approach: Cox proportional hazards models for 30% eGFR decline end point and generalized estimating equations for annualized relative change in eGFR with meta-analysis.

Study-specific estimates were combined using fixed-effect meta-analysis.

Results: The median baseline eGFR was 84 mL/min/1.73 m². The prevalence of CHIP was 6.6%, 9.0%, and 12.2% in persons aged 50-60, 60-70, and >70 years, respectively. Over a median follow-up period of 8 years, for the 30% eGFR outcome 205 events occurred among 1,002 CHIP carriers (2.1 events per 100 person-years) and 2,041 events in persons without CHIP (1.7 events per 100 person-years). In meta-analysis, CHIP was associated with greater risk of a 30% eGFR decline (17% [95% CI, 1%-36%] higher; \( P = 0.04 \)). Differences were not observed between those with baseline eGFR above or below 60 mL/min/1.73 m², of age above or below 60 years, or with or without diabetes.

Limitations: Small number of participants with moderate-to-advanced kidney disease and restricted set of CHIP driver variants.

Conclusions: We report an association between CHIP and eGFR decline in 3 general population cohorts without known kidney disease. Further studies are needed to investigate this novel condition and its potential impact among individuals with overt kidney disease.

Clonal hematopoiesis of indeterminate potential (CHIP) is an age-related disorder among asymptomatic adults defined by the ontogenesis of leukemic variants indicative of a genetically distinct clonal leukocyte population. CHIP is caused by somatic variants within a restricted set of cancer driver genes in hematopoietic stem cells (primarily DNMT3A, TET2, ASXL1, JAK2, and TP53). The resulting progeny propagate through the hematopoietic system to produce a resilient clonal population with a selective survival advantage. By definition, CHIP is not overtly malignant; however, clonal leukocytes harboring CHIP variants increase the risk of future hematologic malignancy presumably through a second genetic hit. In addition to cancer, CHIP is also associated with cardiovascular diseases, including myocardial infarction, stroke, and heart failure. In murine models, Tet2-deficient hematopoietic stem cells accelerate atherosclerosis and promote cardiac and kidney interstitial fibrosis with direct tissue infiltration of donor macrophages.

Kidney function declines progressively with aging. The rate of decline is variable across individuals and is associated with multiple risk factors including hypertension, diabetes, and inflammatory markers. The pathologic hallmark of progressive chronic kidney disease (CKD) is tubulointerstitial fibrosis, which is characterized by the accumulation of inflammatory infiltrates and fibroblasts within the kidney interstitium and permanent loss of tubular epithelial cells.

Given mechanistic links connecting CHIP with both atherosclerosis and tubulointerstitial fibrosis, we hypothesized that in the general population CHIP would be associated with greater kidney function decline compared to those without CHIP. To test this hypothesis, we ascertained the CHIP status of 12,004 individuals from 3 community-based cohort studies, and we delineated the associations with the decline in the estimated glomerular filtration rate (eGFR) over the follow-up period.

Methods

Study Populations

The NHLBI Trans-Omics for Precision Medicine (TOPMed) program was designed to facilitate research in precision
medicine by integrating whole-genome genetic sequencing and molecular data across established epidemiology studies. For the current analysis, we studied participants from 3 community-based cohort studies in the freeze 8 release of TOPMed. The included studies were the Atherosclerosis Risk in Communities Study (ARIC, n = 6,575), the Cardiovascular Health Study (CHS, n = 1,701), and the Multi-Ethnic Study of Atherosclerosis (MESA, n = 3,728). We selected participants who were ≥50 years old due to the rarity of CHIP in younger persons; the additional inclusion criteria were valid ascertainment of CHIP status from the TOPMed genomic data and at least 2 longitudinal measurements of serum creatinine to assess changes in eGFR. The participants provided written consent per each study’s institutional review board–approved protocol.

**Ascertainment of CHIP**

Using GATK MuTect2 as described elsewhere, we derived CHIP genotypes from TOPMed whole genome sequences obtained from DNA extracted from peripheral blood samples. Several quality control steps were applied to identify and remove sequencing artifacts and germline mutations from the call set. At present, a universal standard for CHIP driver variants definition does not exist. However, many groups, including ours, employ the criteria defined by Jaiswal et al in their seminal work describing CHIP. Samples were assigned CHIP carriers status were identified based on the presence of a leukemogenic driver variant at an allele frequency > 2% in 74 prespecified genes known to promote clonal expansion of hematopoietic stem cells (see Table S1). For 23 of these genes, only truncating (frameshifting/ nonsense/splicing) variants are permitted; for another 26, only select missense variants are permitted (mostly gain-of-function); and for the remaining 25 genes, truncating and select missense variants are permitted. These gene-specific criteria were curated to minimize the number of germline and passenger variants as well as sequencing artifacts. The median variant allele frequency for CHIP carriers was 16%. To test for associations between clonal hematopoiesis due to specific variants and eGFR decline, in secondary analyses we categorized CHIP driver gene variants into those in DNMT3A (the most common driver gene) and those not in DNMT3A.

**Ascertainment of eGFR Decline and Albuminuria Outcomes**

We estimated the eGFR at each study visit from serum creatinine concentrations, age, and sex using the 3-variable 2021 CKD-EPI equation. The kidney function decline outcome was defined as a ≥30% decrease in eGFR from the baseline value. This definition was selected to balance a clinically meaningful change in eGFR with a sufficient number of events for analysis. Moreover, relative changes in eGFR are less dependent on the baseline value than absolute changes. As secondary outcomes, we assessed a ≥40% decline in eGFR, the percent eGFR decline per year over the follow-up period, and incident eGFR < 60 mL/min/1.73 m². We defined the albuminuria outcome as a spot urinary albumin-creatinine ratio (UACR) ≥30 mg/g.

**Statistical Analysis**

We tabulated the baseline characteristics within each study according to CHIP status. We estimated the cross-sectional associations of CHIP with baseline eGFR and albuminuria using linear, binary, and multinomial logistic regression with age adjustment and internal standardization. We constructed Cox proportional hazards models to delineate the associations of CHIP status at baseline with the first occurrence of a ≥30% decline in eGFR from the baseline value in each study cohort. The participants were censored due to death, loss to follow-up, or the end of the study data collection period, whichever came first. Regression models were adjusted for age, age squared, sex, baseline eGFR, self-reported race, and diabetes. Models in CHS and MESA were additionally adjusted for log-transformed UACR. UACR was not measured concomitantly with CHIP in the ARIC study. Study-specific hazard ratios were combined using fixed-effect meta-analysis. For secondary analyses of annualized relative change in log(eGFR), we used a mixed effects model with random intercept with adjustment for age, age squared, sex, self-reported race, diabetes, and log-transformed UACR. We tested for multiplicative interactions by age, baseline eGFR, and baseline diabetes using a Wald test on the product term. Analyses were conducted using Stata 17 (StataCorp).

**Results**

The mean age was 57 ± 4 (SD) years in the ARIC cohort, 72 ± 5 years in CHS, and 64 ± 8 years in MESA. The mean baseline eGFR among all cohorts was 84 ± 6 mL/min/1.73 m²; 7.3% of participants had a baseline eGFR < 60 mL/min/1.73 m². The prevalence of CHIP across all study cohorts was 6.6% in persons 50-60 years old, 9.0% in persons 60-70 years old, and 12.2% in persons greater than 70 years of age. The prevalence of CHIP was similar among men and women and in participants with and without diabetes (Table 1).

After age adjustment, the percentage of participants with a baseline eGFR < 45, 45-59, and ≥ 60 mL/min/1.73 m² was similar by CHIP status (Fig 1, left panel). The presence of CHIP was not associated with baseline eGFR < 60 mL/min/1.73 m² after adjustment for age and age-squared (13% [95% CI, −10% to 42%] higher odds; P = 0.3). Age-adjusted rates of UACR ≥ 30 mg/g were 12.5% in participants with CHIP and 10.6% in participants without CHIP (Fig 1, right panel). The presence of CHIP was associated with a 17% (95% CI, 3%-33%) higher UACR after age-adjustment (P = 0.02).
The median follow-up periods were 9 years in ARIC, 7 years in CHS, and 9 years in MESA (Table 2). The median number of eGFR assessments in these studies ranged from 2 to 4. In terms of 30% decline in eGFR over the follow-up period, there were 205 events in persons with CHIP (2.05 events per 100 person-years) and 2,041 events in persons without CHIP (1.71 events per 100 person-years). In meta-analysis, the presence of CHIP at baseline was associated with a 17% (95% CI, 1% to 36%) greater risk of 30% eGFR decline (Table 2), after adjustment for baseline age, age squared, sex, eGFR, UACR, and diabetes (Fig 1). After adjustment for the same covariates, CHIP was not associated with the outcome of a 40% decline in eGFR (Table S2), nor with incident eGFR <60 mL/min/1.73 m² (Table S3). The least-squares mean slope of eGFR was $-1.14 \text{ mL/min/1.73 m}^2$ per year in persons with CHIP and $-1.15 \text{ mL/min/1.73 m}^2$ per year in persons without CHIP (Table 3). After adjustment, there was no significant difference in the slope of eGFR by CHIP status.

The size of the association between CHIP and eGFR decline was similar among DNMT3A and non-DNMT3A gene driver variants (Fig 2; Tables S4-S5). Associations were also similar among participants with an eGFR <60 versus >60 mL/min/1.73 m² at baseline, and those aged <60 versus ≥60 years at baseline (Fig 2; Tables S6-S9). These distinctions were not statistically significant ($P$ for interactions > 0.5).

**Discussion**

In this study, we assessed the association between clonal hematopoiesis and eGFR decline and found CHIP was
associated with a 17% higher risk of 30% eGFR decline among adults with relatively intact kidney function. We observed nonsignificant results for outcomes of a 40% eGFR decline, incident eGFR < 60 mL/min/1.73 m², and continuous slope of decline. Heterogeneity in the results was seen across the studies, with numerically positive associations in the ARIC and CHS cohorts and null results in MESA. Taken together, these findings provide evidence for a link between CHIP and eGFR decline in the general population. However, wide confidence limits, low CHIP prevalence, and inherent methodologic limitations of these cohorts for assessing longitudinal changes in eGFR leave residual uncertainty regarding the potential kidney consequences of CHIP and support further studies of this question.

Three previous studies have examined the association of CHIP and kidney function in humans, with conflicting results. Among 190,487 participants in the UK Biobank, individuals with myeloid clonal hematopoiesis had lower eGFR as estimated from cystatin C but not from creatinine. Among those with CKD, CHIP was associated with higher odds of cardiovascular events and death. In a small study of patients with advanced CKD, Vlasschaert et al reported a high prevalence of CHIP (25%) and that those with the condition had a 2.2-fold greater risk of kidney failure within 5 years. In contrast, a recent study of individuals with diabetic kidney disease found no association of CHIP with incident or progressive decline in kidney function.

Evidence from animal models also suggests that clonal hematopoiesis could plausibly contribute to kidney function decline. In hypercholesterolemic mice, transplantation of hematopoietic stem cells genetically deficient for Tet2, one of the most commonly altered genes in CHIP, leads to accelerated age-related glomerulosclerosis. Transplantation of Tet2-deficient hematopoietic stem cells results in rapid infiltration of Tet2-deficient donor cells into the kidney interstitium, replacement of resident macrophages, and accelerated interstitial fibrosis. Moreover, transplantation of Tet2-deficient hematopoietic stem cells leads to the

### Table 2. Associations of Clonal Hematopoiesis of Indeterminate Potential with 30% Decline in eGFR

<table>
<thead>
<tr>
<th>Cohort</th>
<th>CHIP</th>
<th>No. of Participants</th>
<th>No. of eGFRs</th>
<th>FU Time, y</th>
<th>eGFR Decline, %/y</th>
<th>Adjusted Difference, %/y</th>
<th>eGFR Decline, mL/min/1.73 m²/y</th>
<th>Adjusted Difference, mL/min/1.73 m²/y</th>
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<td>584</td>
<td>3 [3-4]</td>
<td>9 [8-22]</td>
<td>−2.30 (3.08)</td>
<td>−0.25 (−0.51 to 0.01)</td>
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<td>−0.17 (−0.34 to −0.01)</td>
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<td></td>
<td>No</td>
<td>5,991</td>
<td>3 [3-4]</td>
<td>9 [8-23]</td>
<td>−2.02 (2.80)</td>
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<td>−1.69 (2.06)</td>
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<td>CHS</td>
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<td>3 [2-3]</td>
<td>7 [3-7]</td>
<td>−0.98 (4.60)</td>
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<td></td>
<td>No</td>
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<td>3 [2-3]</td>
<td>7 [4-8]</td>
<td>−0.85 (3.89)</td>
<td>Reference</td>
<td>−0.47 (2.29)</td>
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<tr>
<td>MESA</td>
<td>Yes</td>
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<td>9 [9-10]</td>
<td>−1.60 (2.60)</td>
<td>0.36 (−0.01 to 0.74)</td>
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<td>4 [4-4]</td>
<td>9 [9-10]</td>
<td>−1.71 (2.44)</td>
<td>Reference</td>
<td>−1.16 (1.49)</td>
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<tr>
<td>Meta-analysis</td>
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<td>1,002</td>
<td>3 [3-4]</td>
<td>9 [7-16]</td>
<td>−1.75 (1.82)</td>
<td>−0.02 (−0.40 to 0.38)</td>
<td>−1.14 (1.11)</td>
<td>−0.02 (−0.26 to 0.23)</td>
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<td></td>
<td>No</td>
<td>11,002</td>
<td>3 [3-4]</td>
<td>9 [8-17]</td>
<td>−1.66 (1.66)</td>
<td>Reference</td>
<td>−1.15 (1.07)</td>
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Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; CHIP, Clonal hematopoiesis of indeterminate potential; CHS, Cardiovascular Health Study; eGFR, estimated glomerular filtration rate; FU, follow up; MESA, Multi-Ethnic Study of Atherosclerosis; PY, person-years.

### Table 3. Associations of Clonal Hematopoiesis of Indeterminate Potential With Longitudinal Change in eGFR

<table>
<thead>
<tr>
<th>Cohort</th>
<th>CHIP</th>
<th>No. of Participants</th>
<th>No. of eGFRs</th>
<th>FU Time, y</th>
<th>eGFR Decline, %/y</th>
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<td>7 [3-7]</td>
<td>−0.98 (4.60)</td>
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<td>Reference</td>
<td>−1.15 (1.07)</td>
<td>Reference</td>
</tr>
</tbody>
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Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; CHIP, Clonal hematopoiesis of indeterminate potential; CHS, Cardiovascular Health Study; eGFR, estimated glomerular filtration rate; FU, follow up; MESA, Multi-Ethnic Study of Atherosclerosis; PY, person-years.

*Adjusted for age, age squared, sex, baseline eGFR, diabetes, and log(urinary albumin-creatinine ratio) if available at baseline. Values in parentheses are 95% CI.

**P = 0.9.

Values in parentheses are SDs.
expansion of atherosclerotic plaque size and stimulation of proinflammatory cytokines; these experimental results are corroborated by associations of CHIP with incident cardiovascular events in human populations.4,5

It is possible that CHIP accelerates eGFR decline in persons with established kidney disease but has smaller effects on eGFR in the absence of pre-existing disease or injury. We did not detect significant differences in the size of the association between CHIP and eGFR decline among participants with a baseline eGFR < 60 mL/min/1.73 m² and those with an eGFR ≥ 60 mL/min/1.73 m². However, the number of participants with CKD, particularly moderate-advanced disease, was too small to reliably address this question, motivating future studies in kidney disease populations. It is also possible that the study lacked sensitivity for detecting a true association between CHIP and eGFR decline. The included cohorts included relatively few serum creatinine measurements over time, which reduces the precision and increases the possibility for differential censoring. Most serum creatinine measurements were within the normal range, in which GFR estimating equations are least precise. The number of participants with CHIP who experienced a 30% decline in eGFR was relatively small, contributing to the wide confidence limits. Larger declines in eGFR are clinically meaningful and used as outcomes in randomized trials; however, such declines were rare in this study population.

In summary, we detected an association between CHIP and eGFR decline in 3 general population cohorts without known kidney disease. Further studies are needed to investigate this novel condition and its potential impact on kidney disease.

Table S2: Associations of clonal hematopoiesis with 40% decline in eGFR.
Table S3: Associations of clonal hematopoiesis with incident eGFR < 60.
Table S4: Associations of DNMT3A clonal hematopoiesis with 30% decline in eGFR and longitudinal change in eGFR.
Table S5: Associations of non-DNMT3A clonal hematopoiesis with 30% decline in eGFR and longitudinal change in eGFR.
Table S6: Associations of clonal hematopoiesis with 30% decline in eGFR and longitudinal change in eGFR among individuals with eGFR < 60 at baseline.
Table S7: Associations of clonal hematopoiesis with 30% decline in eGFR and longitudinal change in eGFR among individuals with diabetes at baseline.
Table S8: Associations of clonal hematopoiesis with 30% decline in eGFR and longitudinal change in eGFR among individuals without diabetes at baseline.
Table S9: Associations of clonal hematopoiesis with 30% decline in eGFR and longitudinal change in eGFR among individuals aged >60 years at baseline.

### Supplementary Material

**Table S1:** Leukemogenic driver variants used for CHIP variant calling.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. Events/Total</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
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<tr>
<td>eGFR &lt; 60</td>
<td>14 / 109</td>
<td>1.07 (0.50, 2.30)</td>
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<tr>
<td>diabetes</td>
<td>25 / 119</td>
<td>1.28 (0.84, 1.95)</td>
</tr>
<tr>
<td>no diabetes</td>
<td>175 / 878</td>
<td>1.26 (1.08, 1.48)</td>
</tr>
<tr>
<td>age&gt;60 yrs</td>
<td>102 / 565</td>
<td>1.21 (0.98, 1.49)</td>
</tr>
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</table>

**Figure 2.** Associations of CHIP with 30% decline in eGFR among subgroups of interest. Forest plot of adjusted hazard ratio for association of CHIP with 30% decline in eGFR (meta-analysis of ARIC, CHS, and MESA studies) among (1) individuals with eGFR < 60 mL/min/1.73 m² at baseline, (2) diabetes at baseline, (3) no diabetes at baseline and age >60 years at baseline. Adjusted for age, age squared, sex, baseline eGFR, diabetes, and log(urinary albumin-creatinine ratio) if available at baseline. Abbreviations: CHIP, clonal hematopoiesis of indeterminate potential; eGFR, estimated glomerular filtration rate.
University Medical Center, Nashville, Tennessee (MBS); Department of Veterans Affairs, Nashville, Tennessee (RCH); Department of Medicine (CV) and Department of Pathology and Molecular Medicine (MUR), Queen’s University, Kingston, Ontario, Canada; Department of Medicine and Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada; St. Joseph’s Healthcare Hamilton, Hamilton, Ontario, Canada (MBL); Population Health Research Institute, Hamilton, Ontario, Canada (MBL); Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, North Carolina (NF); Institute of Genetic Epidemiology, Faculty of Medicine and Medical Center, University of Freiburg, Freiburg, Germany (AK); Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland (AK); Program in Medical and Population Genetics and the Cardiovascular Disease Initiative, Broad Institute of Harvard, Cambridge, Massachusetts (PN); Cardiovascular Research Center, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts (PN).

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Authors’ Contributions: Research idea and study design: BK, AB, CV, PN, CRC; data acquisition: AB, CRC, MS, BP, AK, PN, NF; data analysis/interpretation: BK, CRC, RH, AB, CV, MR, ML; statistical analysis: BK, CRC; supervision or mentorship: MR, ML, CRC. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual’s own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

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Data Sharing: Individual whole-genome sequence data for TOPMed whole genomes, individual-level harmonized phenotypes, harmonized germline variant call sets, the CHIP somatic variant call sets, RNA-seq and peripheral blood methylation data used in this analysis are available through restricted access via the dbGaP.

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References


