# Solid Organ Transplant Recipients Exhibit More *TET2*-Mutant Clonal Hematopoiesis of Indeterminate Potential Not Driven by Increased Transplantation Risk

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## ABSTRACT

**Purpose:** Solid organ transplant recipients comprise a unique population of immunosuppressed patients with increased risk of malignancy, including hematologic neoplasms. Clonal hematopoiesis of indeterminate potential (CHIP) represents a known risk factor for hematologic malignancy and this study describes the prevalence and patterns of CHIP mutations across several types of solid organ transplants.

**Experimental Design:** We use two national biobank cohorts comprised of >650,000 participants with linked genomic and longitudinal phenotypic data to describe the features of CHIP across 2,610 individuals who received kidney, liver, heart, or lung allografts.

**Results:** We find individuals with an allograft before their biobank enrollment had an increased prevalence of *TET2* mutations (OR, 1.90; $P = 4.0e{-}4$), but individuals who received transplants post-enrollment had a CHIP mutation spectrum similar to that of the general population, without enrichment of *TET2*. In addition, we do not observe an association between CHIP and risk of incident transplantation among the overall population (HR, 1.02; $P = 0.91$). And in an exploratory analysis, we do not find evidence for a strong association between CHIP and rates of transplant complications such as rejection or graft failure.

**Conclusions:** These results demonstrate that recipients of solid organ transplants display a unique pattern of clonal hematopoiesis with enrichment of *TET2* driver mutations, the causes of which remain unclear and are deserving of further study.

## Introduction

Clonal hematopoiesis (CH) is the presence of a shared somatic mutation within a fraction of blood cells, and the prevalence of CH is strongly associated with increasing age (1). One subtype of CH, called clonal hematopoiesis of indeterminate potential (CHIP), is defined by the presence of a mutation in a set of myeloid-malignancy-associated genes with a variant allele fraction (VAF) of at least 2% in the absence of cytopenia or hematologic malignancy. CHIP increases the risk of mortality and accelerates the progression of cardiovascular disease (2–7). Moreover, individuals with CHIP are not only at increased risk for hematologic malignancies but may also be at increased risk for certain solid tumors, such as lung cancer (8–11).

Recipients of solid organ transplants comprise a unique immunosuppressed patient population that is at elevated risk for numerous medical conditions, including cardiovascular disease as well as hematologic and solid malignancies (12–15). Knowing that CHIP is also associated with these sequelae and given the documented associations between CHIP and several potential indications for solid organ transplant, such as heart failure, chronic obstructive pulmonary disease, chronic liver disease, and chronic kidney disease, there is *a priori* reason to believe that this population may also experience high prevalence of CHIP (4, 16–19). A limited number of studies have examined CHIP mutations among transplant recipients, although these studies each examined a single allograft type. In the sole study to include a control population, an analysis of a single-center cohort of 85 lung transplant recipients and 33 matched controls found a greater burden of DNA damage response (DDR) CH, but not other types of CH, in the transplant recipients (20). Three additional retrospective studies have identified rates of CHIP in heart transplant recipients (14% to 20%) and lung transplant recipients (16%) that are relatively higher than what is observed in the general population (21–23). However, the prevalence of CHIP in the setting of solid organ transplant more generally has yet to be analyzed, and previous studies have exclusively examined cohorts drawn from a limited number of large academic medical centers.

The extent to which CHIP influences the pathology of transplant complications, including rejection, is still an open question. It is well-established that many CH mutations can lead to dysregulated immune cell function and disproportionate inflammatory responses (2, 4, 24–26), yet it is not known whether similar inflammation-related morbidity would be observed in individuals receiving lifelong immunosuppressive therapy. To that end, the existing literature on CH in solid organ transplant attempts to address whether CH is associated with transplant complications, but the answers from these studies have been mixed. In lung transplant recipients, CH with DDR mutations was found to be associated with post-transplant cytomegalovirus (CMV) viremia (20), whereas CHIP overall has not been found to predict

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## Translational Relevance

Solid organ transplant recipients are at increased risk for developing malignancy. Clonal hematopoiesis of indeterminate potential (CHIP) is a described risk factor for solid and liquid tumors as well as numerous diseases that can be indications for transplant, such as heart failure and chronic liver disease. Because of these apparent commonalities, we hypothesized that CHIP might be more prevalent among individuals with an organ transplant. Using data from two national biobanks, we show that CHIP with mutations in *TET2*, but not mutations in other genes, is more prevalent in allograft recipients. Longitudinal follow-up of the study cohorts, including >20,000 individuals with CHIP, uncovered no indication that CHIP increases the overall likelihood of transplantation. This suggests that in the post-transplant setting there may be selection for *TET2* CHIP, a potential malignancy risk factor not previously appreciated in this population and one that could readily be identified using existing clinical sequencing tests.

overall survival or chronic lung allograft dysfunction (23). Meanwhile, a single-center study of heart transplant recipients ($N = 127$) found a positive association between CH and cardiac allograft vasculopathy (CAV) and mortality (21), whereas a second study of two centers ($N = 479$) found no association between CH and either CAV or mortality (22).

Thus, we set out to study the epidemiology of CHIP in solid organ transplant recipients. To do this, we turned to two national biobank cohorts that link blood-derived genomic data with longitudinal participant phenotypes: the U.S.-based All of Us (AoU) cohort and the U.K. Biobank study (UKB). Here, we present the first study characterizing the association between CHIP and transplant status across multiple different transplant types, using data from more than 2,600 allograft recipients and approximately 650,000 controls within two community-based national biobank databases. As these are general-purpose national population biobanks, some pieces of transplant-specific data (e.g., HLA matching) are unavailable, but the size of the cohorts allows for an exploratory analysis of longitudinal billing-code allograft complication data.

## Materials and Methods

### Study cohorts

The cohorts consisted of participants with whole-genome sequencing (WGS) in the AoU study ($N = \sim$250K) or whole-exome sequencing (WES) in the UKB study ($N = \sim$450K). Sequencing was performed on DNA from peripheral blood collected at the time of biobank enrollment. CHIP was ascertained using stringent sequence- and population-based filtering techniques as previously described (9). Briefly, Mutect2 was used to identify putative CHIP mutations in known driver genes from aligned sequencing files, whereas a custom script was used to identify mutations in *U2AF1*. Variants with total read depth <20 were removed, as were those with fewer than 3 reads of the alternate allele. Calls were then curated to remove artifacts and germline mutations. Finally, CHIP calls were restricted to variants with at least a 2% VAF. Recipients of kidney, liver, heart, and lung allografts were identified via participant self-report on enrollment survey and electronic health record (EHR) codes (full details in Supplementary Methods). The linked EHR data in both cohorts include whatever records are available before participant biobank enrollment and periodically updated prospective data obtained directly from healthcare systems without requiring additional action on the part of the participant. Although these studies provide researchers with some structured data (e.g., ICD codes), they do not provide free-text medical notes.

Our final analysis included 24,513 individuals with CHIP (9,211 in AoU and 15,302 in UKB) and 2,610 individuals with an organ transplant at the time of biobank enrollment (2,166 in AoU and 444 in UKB; **Table 1**). To comply with participant privacy policies in the AoU research study that disallow reporting of subgroups counts of $N < 20$ as well as row-level (individual-level) data, certain numerical data from this cohort have been censored to obscure exact subgroup counts while allowing for the accurate depiction of observed trends; unredacted numerical data were supplied during peer review to assist in the evaluation of the article.

**Table 1.** Cohort summary statistics.

| | *All of Us* | | |
|---|---|---|---|
| | **Transplant: No** | **Transplant: Yes** | ***P*[a]** |
| **N** | 236,313 | 2,166 | — |
| Kidney | — | 1,297 | — |
| Liver | — | 498 | — |
| Heart | — | 447 | — |
| Lung | — | 265 | — |
| Multiple Types | — | 291 | |
| Male Sex (%) | 92,587 (39.3) | 1,194 (55.1) | <0.001 |
| Age (SD) | 51.57 (17.00) | 57.28 (14.00) | <0.001 |
| Smoking History: Yes (%) | 92,587 (40.4) | 829 (39.2) | 0.257 |
| CHIP: Yes (%) | 9,097 (3.8) | 114 (5.3) | 0.001 |
| **N for EHR Linked Analyses** | 172,028 | 1,901 | — |
| Prior Cancer: Yes (%) | 24,604 (14.3) | 623 (32.8) | <0.001 |
| Anti-thymocyte globulin: Yes (%) | <20 (0.0) | 208 (10.9) | <0.001 |
| Basiliximab: Yes (%) | <20 (0.0) | 139 (7.3) | <0.001 |
| Cyclosporine: Yes (%) | 550 (0.3) | 141 (7.4) | <0.001 |
| Tacrolimus: Yes (%) | 316 (0.2) | 1,037 (54.6) | <0.001 |
| Sirolimus: Yes (%) | <20 (0.0) | 128 (6.7) | <0.001 |
| Everolimus: Yes (%) | 45 (0.0) | 62 (3.3) | <0.001 |
| Azathioprine: Yes (%) | 1,008 (0.6) | 157 (8.3) | <0.001 |
| Mycophenolate mofetil: Yes (%) | 748 (0.4) | 834 (43.9) | <0.001 |
| Methotrexate: Yes (%) | 2,724 (1.6) | 25 (1.3) | 0.405 |
| Glucocorticoids: Yes (%) | 68,973 (40.0) | 1,442 (75.9) | <0.001 |
| | *UK Biobank* | | |
| | **Transplant: No** | **Transplant: Yes** | ***P*[a]** |
| **N** | 450,688 | 444 | — |
| Kidney | — | 326 | — |
| Liver | — | 80 | — |
| Heart | — | 39 | — |
| Lung | — | 19 | — |
| Multiple Types | — | 19 | — |
| Male Sex (%) | 205,824 (45.7) | 285 (64.2) | <0.001 |
| Age (SD) | 56.52 (8.10) | 56.75 (7.74) | 0.550 |
| Smoking History: Yes (%) | 268,591 (59.9) | 268 (60.4) | 0.880 |
| CHIP: Yes (%) | 15,285 (3.4) | 17 (3.8) | 0.706 |
| Prior Cancer: Yes (%) | 30,584 (6.8) | 85 (19.1) | <0.001 |

Abbreviations: CHIP, clonal hematopoiesis of indeterminate potential; EHR, electronic health records; SD, standard deviation.
[a]The $\chi^2$ test for categorical variables and one-way ANOVA for continuous variables.

Written informed consent was obtained for all participants in the AoU and UKB studies by the respective supervising bodies. The AoU research protocol was reviewed and approved by the Institutional Review Board of the All of Us Research Program, which follows all regulations and guidance from the NIH Office for Human Research Protections, including the Common Rule. The UKB study protocol was reviewed and approved by the North West Multi-Center Research Ethics Committee (REC references: 11/NW/0382, 16/NW/0274, and 21/NW/0157) and the research was conducted in compliance with the World Medical Association's Declaration of Helsinki.

### Comparison of transplant incidence in the U.S. and U.K.

Yearly data (2004–2021) on total population, and the annual number of kidney, liver, heart, and lung transplantations for the United States (U.S.) and United Kingdom (U.K.) were obtained directly from the publicly available Global Observatory on Donation and Transplantation (GODT) dataset (27), which is a collaborative effort by the World Health Organization and Spanish Transplant Organization, Organización Nacional de Trasplantes, to catalog worldwide transplantation rates. For each country, these data were used to calculate the annual transplant incidence per million population for each organ type individually and for all four transplant types combined (Supplementary Fig. S1).

### Assessing CHIP among transplant recipients

The association between transplant status and CHIP at the time of enrollment was tested using by univariate comparison of proportions and by multivariate logistic regression with covariates for age at study enrollment, sex, smoking history, and the first 10 principal components of genetic ancestry. Given that (i) there are persistent disparities in the rates of solid organ transplantation between the U.S. and the U.K., particularly with respect to liver, heart, and lung transplantation (Supplementary Fig. S1), and (ii) external constraints on which patients received a transplant could affect the magnitude of any observed transplant:CHIP relationship, we then proceeded to use random effects meta-analysis to find the average estimated associations (27, 28).

### Cancer history sensitivity analysis

Because malignancy is associated with higher prevalence of CHIP mutations (11) and transplant is associated with risk of malignancy (13–15), we conducted a sensitivity analysis to evaluate whether the association between transplant and CHIP mutations was attenuated when history of cancer was considered. Data on prior history of cancer were available in UKB via the UK cancer registry and in AoU for a subset of participants with linked EHR data. History of any prior malignancy at time of enrollment (excluding individuals with isolated basal cell carcinoma, a common and relatively benign form of cancer) was determined from these data. The association between transplant and CHIP mutations was retested with the same covariates as above with the addition of the cancer history variable.

### Germline variation sensitivity analysis

Inherited variation in DDR genes and telomere-maintenance genes is known to increase risk for developing CHIP and could potentially exert a confounding influence on our results if they also increase the risk for transplant. In AoU, we extracted binary variables for the presence of one or more alternate alleles for several germline variants. Variant calls had been curated by the AoU project using WGS aligned against the GRCh38/hg38 reference genome. We examined variants known to be associated with CHIP in general (5–1285859-C-A in *TERT*, 22–27918624-G-A in *CHEK2*, and 14–100712378-C-G in *DLK1*), with *TET2* CHIP specifically (17–7668434-T-G in *TP53*), or with *TP53* CHIP specifically (22–41990834-C-T in *SEPT3*), focusing on loci involved with telomere regulation, DDR, or others with known association to transplant indications. Variants were tested for association with transplant status, and only 14–100712378-C-G in *DLK1* exhibited a nominal association ($P = 0.06$). The association between transplant and CHIP mutations was retested with the same covariates as above with the addition of a binary 14–100712378-C-G variable.

### Evaluating the association of transplant medication exposures and CHIP

Retrospective pre-enrollment drug exposure data were available in the AoU for a subset of participants with linked EHR data. Analogous pre-enrollment medication data were not available from the UKB cohort. We obtained records for the following medications that may be used for transplant immunosuppression: basiliximab (OMOP 19038440), anti-thymocyte globulin (OMOP 19136207), cyclosporine (OMOP 19010482), tacrolimus (OMOP 950637), sirolimus (OMOP 19034726), everolimus (OMOP 19011440), methotrexate (OMOP 1305058), azathioprine (OMOP 19014878), mycophenolate mofetil (OMOP 19003999), and glucocorticoids (OMOP 1551099, 1550557, 1506270, and 1518254). The association between drug exposure and CHIP mutations was tested via multivariate regression with covariates for transplant status, age at study enrollment, sex, smoking history, history of cancer, and the first 10 principal components of genetic ancestry.

### Identification of incident transplantation

We also identified incident transplantation events among individuals without a transplant at baseline. We tested for an association between incident transplant and CHIP using both univariate log-rank tests and multivariate Cox proportional hazards models adjusted for age, sex, smoking history, and the first 10 principal components of genetic ancestry. We aggregated hazard ratios (HR) by random effects meta-analysis. Finally, we tested for differences in the CHIP mutational distribution in those individuals who had no allograft at biobank enrollment and our two distinct sets of transplant recipients: those who already had an allograft on enrollment or those without an allograft at baseline but who subsequently received a transplanted organ.

### Allograft complication analyses

In an exploratory analysis, we evaluated the association between CHIP and transplant complications (which are fully defined for each organ type in the Supplementary Methods) in three ways. First, we examined the incident complication rate among individuals with an allograft at the time of biobank enrollment; individuals with a complication before enrollment were excluded (Method #1). Second, we quantified the incident complication rate those among individuals who were CHIP-positive but transplant-negative at enrollment who later went on to receive an allograft (Method #2). For the Method #1 and #2 cohorts, we performed univariate comparison of complication rate by CHIP status after assuring a comparable distribution of allograft organs among $CHIP^+$ and $CHIP^-$ participants. We additionally performed multivariate Cox proportional hazards analysis (Method #1) or multivariate logistic regression (Method #2) adjusted

for age, sex, and transplant type for the AoU data; too few events in the UKB cohort precluded multivariate testing. We excluded individuals with multiple allograft types from these multivariate analyses to increase the interpretability of the results.

To make use of the full cohort of individuals with transplant on enrollment, we turned to a third approach to examine complications, which aligned with the results from each of the previous methods. Reasoning that CHIP clones often persist across time and likely arose years before biobank enrollment for most participants, we quantified the EHR lifetime transplant complication rate for all participants with a graft at enrollment (Method #3). Similar to previous studies, but limited in our access to transplant-specific variables such as HLA matching scores, we used a multivariate model adjusting for age, sex, and allograft type to calculate odds ratios for EHR lifetime complications, which we aggregated with random effects meta-analysis. More specific complication data available in AoU but not UKB were also tested in this cohort by univariate comparison of proportions.

### VAF sensitivity analyses

Because larger CHIP clones commonly exhibit a stronger association with clinical phenotypes than small-VAF clones (2, 11), to supplement our analyses we also repeated several of our key tests looking at large-VAF CHIP clones (VAF ≥ 10%).

### Statistical analysis

Cohort attributes stratified by transplant status were assessed via the $\chi^2$ test for categorical variables and one-way ANOVA for continuous variables (**Table 1**). In all other cases, statistical significance of unadjusted raw proportions was determined using the Fisher's exact test. For instances where the Fisher's exact test was used to compare four or more categories, simulated $P$ values were calculated with $N =$ 2,000 replicates. The Stouffer's method for combining $P$ values was used to calculate overall probability estimates where informative. A multivariate logistic regression approach, using the maximum sample size for each analysis, was used wherever possible to provide the greatest possible statistical power. Covariates for basic demographics (age and sex) were included in all models, whereas models in which CHIP was the outcome of interest were additionally adjusted for smoking history and genetic ancestry, which are strongly associated with CHIP (9, 11, 17). Because AoU and UKB are observational cohorts, participant randomization was not performed. For the same reason, experimenter blinding was not performed.

Analysis of the AoU cohort was conducted in the All of Us Researcher Workbench using a Jupyter notebook running RStudio (v4.2.2; RRID:SCR_000432). Analysis of the UKB cohort was also conducted in RStudio (v4.2.2).

### Data and code availability

No new sequencing data were generated for this article. The CHIP calls for the All of Us cohort are hosted in the "Clonal Hematopoiesis in All of Us Genomes" workspace; the All of Us Support Team (support@researchallofus.org) can add any users with controlled-tier access to this workspace upon request. The UKB CHIP calls are available to UKB-approved researchers and are associated with Application ID 43397 and the following returned dataset IDs that are in the process of being made available to the research community: 3542, 3543, 3544, 3560, and 3577. Questions about access to the UKB resource may be directed to: access@ukbiobank.ac.uk. The scripts used for data analysis in this article are available upon request to michael.savona@vumc.org.

## Results

### *TET2* CHIP is increased among recipients of solid organ transplants

We identified 2,610 transplant recipients (**Table 1**; Supplementary Fig. S2A and S2B) along with 24,513 individuals with CHIP (**Table 1**). As in the general population, the prevalence of CHIP in transplant recipients was associated with increasing age (**Fig. 1A**; Supplementary Fig. S3A). We found the prevalence of CHIP to vary widely according to the type of allograft. In AoU, the prevalence of CHIP in single-organ transplant recipients ranged from 4.1% in kidney recipients to 7.9% in liver recipients, compared with an overall prevalence of 3.8% in non-transplanted individuals (**Fig. 1B**). In UKB, the overall prevalence of CHIP in transplant was lower, at just 17/444 (3.8%) with a range from 0/14 (0%) in lung recipients to 3/31 (9.7%) in heart recipients, with a base prevalence of 3.4% among the non-transplant population (Supplementary Fig. S3B). We found no evidence of an association between CHIP VAF and transplant status (**Fig. 1C**). Regardless of transplant status, *DNMT3A*, *TET2*, and *ASXL1* were the most commonly mutated genes in both cohorts (**Fig. 1D**; Supplementary Fig. S3C and S3D). No allograft recipients in the UKB and just 6% of those in AoU exhibited mutations in two or more genes (**Fig. 1E**; Supplementary Fig. S3C).

We did not find a significant association between overall CHIP and transplant in adjusted random-effects meta-analysis of both cohorts (OR, 1.17; $P = 0.081$; **Fig. 2A**; Supplementary Table S1). When we conducted sensitivity analyses of large clones with a VAF ≥ 10% (Supplementary Fig. S4) we also did not find any significant association (OR, 1.10; $P = 0.53$; Supplementary Fig. S4A and Supplementary Table S2). However, we did see differences in the distribution of CHIP gene mutations in transplant recipients that caused us to examine their individual associations more closely. In the AoU cohort, we observed that the number of *DNMT3A* mutations as a proportion of all CHIP mutations was significantly lower among transplant recipients, whereas the proportion of *TET2* mutations was increased (**Fig. 1D**). Adjusted meta-analysis of both cohorts confirmed that transplant recipients had significantly more mutations in *TET2* (OR, 1.90; $P = 4.0e{-}4$), with non-significant differences in *DNMT3A* (OR, 0.83; $P = 0.21$), and *ASXL1* (OR, 1.45; $P = 0.18$; **Fig. 2B–D**; Supplementary Tables S3–S5). We did not observe any mutations in DDR genes *TP53* and *PPM1D* among transplant recipients in the UKB, although there was a clear trend toward greater prevalence of these mutations in allograft recipients in the AoU cohort (OR, 1.72; $P = 0.078$; **Fig. 2E**; Supplementary Table S6). The association between transplant and *TET2* CHIP remained significant, and the effect sizes for other CHIP remained similar, when we performed a sensitivity analysis that included prior history of cancer as a variable (Supplementary Tables S7–S11). We also assessed whether germline variants known to be associated with CHIP, some of which affect genes involved in telomere regulation or DDR (11), were associated with transplant in the AoU cohort. Although we found a CHIP risk variant in *DLK1* to have a modest association with transplant ($P = 0.06$; Supplementary Table S12), inclusion of this variant did not appreciably affect the association between CHIP mutations and transplant (Supplementary Tables S13–S15).

We next examined the prevalence of *TET2* mutations by allograft type to understand whether certain types of organ transplants were driving this trend. The increased prevalence of *TET2* CHIP was significant among those receiving a kidney (OR, 2.01; $P = 3.5e{-}3$) or a liver (OR, 2.11; $P = 0.037$) but not in heart allograft recipients (OR 3.22; $P = 0.30$) when these groups were considered in isolation (**Fig. 3A–C**; Supplementary Tables S16–S18). There were no *TET2*

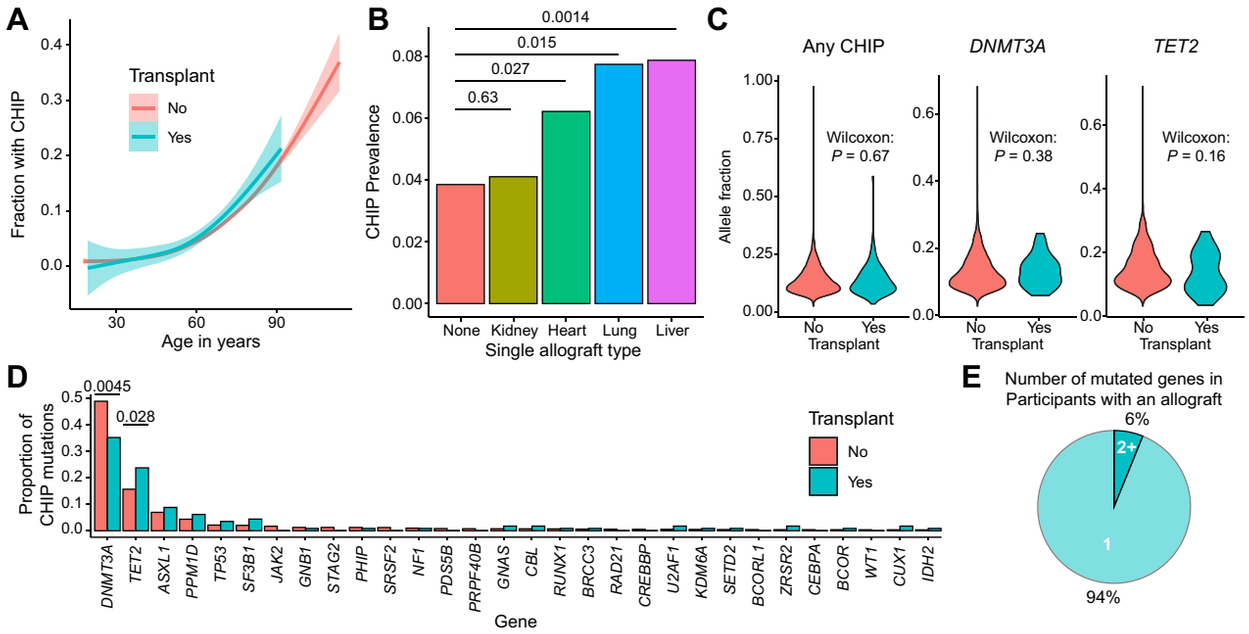


**Figure 1.**

Characterization of clonal hematopoiesis of indeterminate potential in transplant recipients within the All of Us cohort. **A,** Prevalence of clonal hematopoiesis of indeterminate potential (CHIP) among individuals who are recipients of a kidney, liver, heart, or lung allograft (blue) and those without an allograft (red). **B,** Fraction of individuals with CHIP, stratified by type of organ transplant. Individuals with multiple transplant types are not included in this comparison. *P* values are from the Fisher's exact test. **C,** Variant allele fraction for individuals with any type of CHIP, *DNMT3A*-mutated CHIP, or *TET2*-mutated CHIP, stratified by transplant recipient status. *P* values are from the Wilcoxon test. **D,** The relative per-gene fraction of the total number of mutations for CHIP carriers who are transplant recipients (blue) or not (red) for the top 30 most commonly mutated genes. **E,** The percentage of CHIP-positive allograft-positive individuals who have one (light blue) or more than one (dark blue) mutated gene. *P* values are from the Fisher's exact test.

mutations identified among lung recipients in UKB ($N = 14$), precluding meaningful meta-analysis. When we analyzed lung recipients in AoU, we observed an increased prevalence of *TET2* mutations (OR, 2.62; $P = 0.035$; **Fig. 3D**; Supplementary Table S19). From this, we concluded that *TET2* CHIP, but not necessarily other CHIP variants, is more prevalent in recipients of solid organ allografts than in non-transplanted individuals and, furthermore, that this difference is not driven by a single type of organ transplantation.

Our next question was whether there were any associations between exposure to specific transplant-related medications and CHIP mutations. So, we examined AoU pre-enrollment prescription data for drugs used in either induction or maintenance immunosuppression in transplant, and observed several drugs associated with specific CHIP genes. Prior exposure to anti-thymocyte globulin was associated with a greater prevalence of *TET2* CHIP (OR, 3.92; $P = 0.015$), whereas DDR CHIP was higher in the setting of previous exposure to azathioprine (OR, 3.20; $P = 3.5e{-}4$) or mycophenolate mofetil (OR, 3.07; $P = 2.0e{-}3$; Supplementary Fig. S5A and S5B and Supplementary Tables S20–S24). Thus, it appears that certain immunosuppressive transplant medications may have specific associations with different types of CHIP, although these findings should be tested in additional cohorts.

## No evidence for an association between CHIP and likelihood of transplantation among the general population

Following this, we asked whether CHIP status influences the likelihood of receiving a transplant. Although AoU has less follow-up than UKB (median 2.9 vs. 12.4 years), the higher rate of transplantation meant that a similar number of incident transplantation events were observed in both cohorts despite the differences in follow-up time. Among participants without a graft at baseline, we found no statistically significant difference in risk for transplantation according to CHIP status, either by univariate log-rank test (**Fig. 4A** and **B**) or meta-analysis of adjusted multivariate Cox proportional hazards model (meta-HR, 1.02; $P = 0.91$; **Fig. 4C**; Supplementary Table S25). When we examined transplant incidence among those with small CHIP clones (VAF < 10%) and large CHIP clones (VAF ≥ 10%), we again did not find any significant association (Supplementary Fig. S4B). When looking at the distribution of CHIP genes in this incident transplant group, we were struck by the fact that, unlike what we observed in individuals with an allograft at study enrollment, the distribution of CHIP genes was remarkably similar to that observed in the non-transplant population, without apparent enrichment of *TET2* (combined $P = 1.0$; **Fig. 4D**). Supporting this, we observed that the relative abundance of *TET2*:*DNMT3A* mutations among individuals who received a transplant fewer than 2 years before joining AoU was virtually identical to the ratio seen in the general population, but that the cumulative relative abundance of *TET2* quickly rose when we considered individuals further removed from transplant, reaching a plateau by 5 years out from transplantation (Supplementary Fig. S6A–S6D). From this, we found no evidence to suggest that, despite its known associations with vascular disease and organ dysfunction, CHIP leads to a higher rate of transplantation among the general population. We also observed that the spectrum of CHIP mutations in newly transplanted individuals is consistent with the distribution of CHIP mutations among the general population.

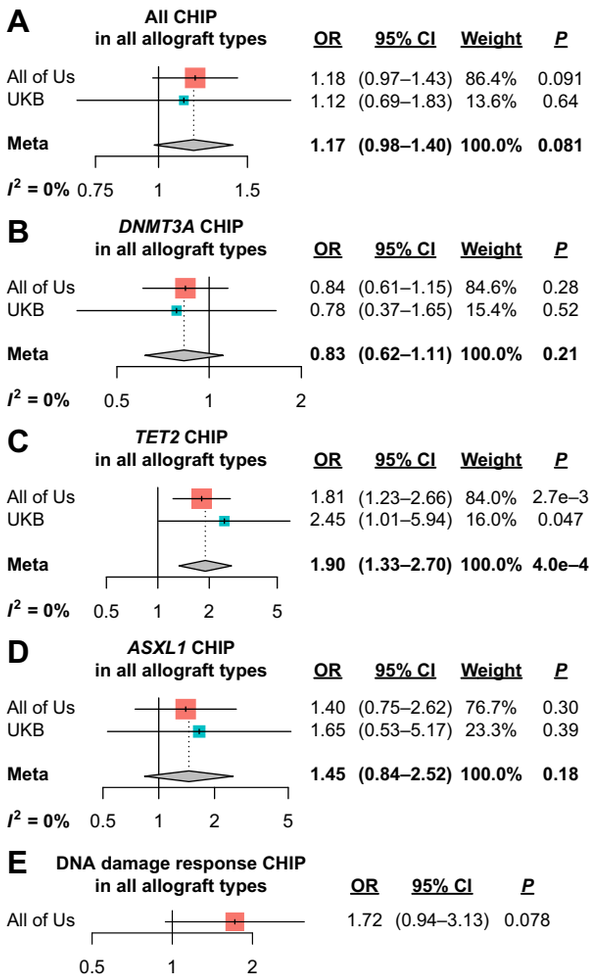


**Figure 2.**

Solid organ transplantation is associated with *TET2* clonal hematopoiesis of indeterminate potential. **A–D,** Adjusted logistic regression and random effects meta-analysis results from All of Us and UK Biobank (UKB) cohorts are depicted as forest plots of odds ratios (OR) and 95% confidence intervals (95% CI). ORs for mutation status were determined by logistic regression adjusted for transplant status (depicted), age, sex, smoking history, and the first 10 principal components of genetic ancestry. Shown are the ORs for the presence of (**A**) any clonal hematopoiesis of indeterminate potential (CHIP) variant, (**B**) *DNMT3A* mutations, (**C**) *TET2* mutations, or (**D**) *ASXL1* mutations among all transplant recipients. **E,** OR and 95% CI for DNA damage response (DDR) variants in the All of Us cohort.

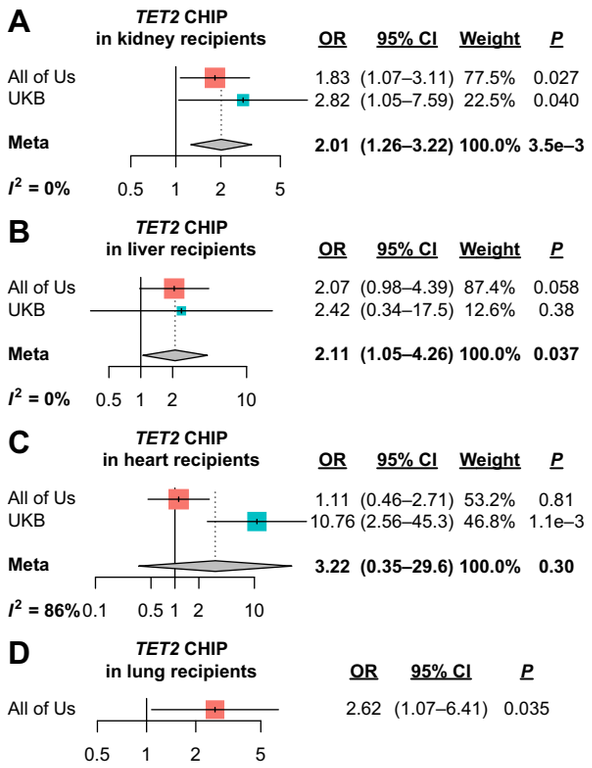


**Figure 3.**

The magnitude of enrichment of *TET2* clonal hematopoiesis of indeterminate potential is consistent across multiple allograft types. **A–C,** Adjusted logistic regression and random effects meta-analysis results from All of Us and UK Biobank (UKB) cohorts are depicted as forest plots of odds ratios (OR) and 95% confidence intervals (95% CI). ORs for mutation status were determined by logistic regression adjusted for transplant status (depicted), age, sex, smoking history, and the first 10 principal components of genetic ancestry. Shown are the ORs for the presence of *TET2* clonal hematopoiesis of indeterminate potential (CHIP) among (**A**) recipients of kidney allografts, (**B**) recipients of liver allografts, and (**C**) recipients of heart allografts. **D,** OR and 95% CI for *TET2* CHIP in the All of Us cohort among recipients of lung allografts.

## CHIP does not have a strong association with overall allograft complications

Finally, given that previous reports have suggested possible causal associations between CHIP and certain transplant complications, we sought to assess this relationship within our cohorts. Although AoU and UKB capture data on transplant complications (Supplementary Methods and Supplementary Fig. S7A–S7D and Supplementary Fig. S8), they lack data on key predictors of risk for graft complications, such as HLA match scores or indication for transplant. As such, we offer a caveat on the following analysis as exploratory in nature and necessarily only a partial description of the relationship of CHIP to allograft-associated disorders. We began by assessing the incidence of transplant complications in individuals who had an allograft at the time of study enrollment but who had no prior allograft complications after assuring a similar distribution of allograft organs in CHIP$^+$ and CHIP$^-$ participants (Supplementary Fig. S9A and S9B). We found no significant difference in the proportion of these participants who developed a graft complication according to CHIP status in univariate comparisons (combined $P = 1.0$; **Fig. 5A**) or a multivariate Cox proportional hazards model (HR, 0.62; $P = 0.35$; Supplementary Table S26). Next, we examined the incidence of complications among individuals who received their first allograft after their biobank study enrollment. Again, despite a similar distribution of organ types (Supplementary Fig. S9C), we found no significant difference in complication incidence in univariate assessment (**Fig. 5B**) nor in a multivariate model (OR, 0.63; $P = 0.47$; Supplementary Table S27). The AoU and UKB datasets contain participant phenotype data across the lifetime of their linked EHRs, both before and following biobank enrollment. Because CHIP clones are often stable for many years (29, 30), we chose to look at the totality of complications across the EHR, both retrospectively and prospectively, to use a larger portion of our cohort than in the previous approaches. The

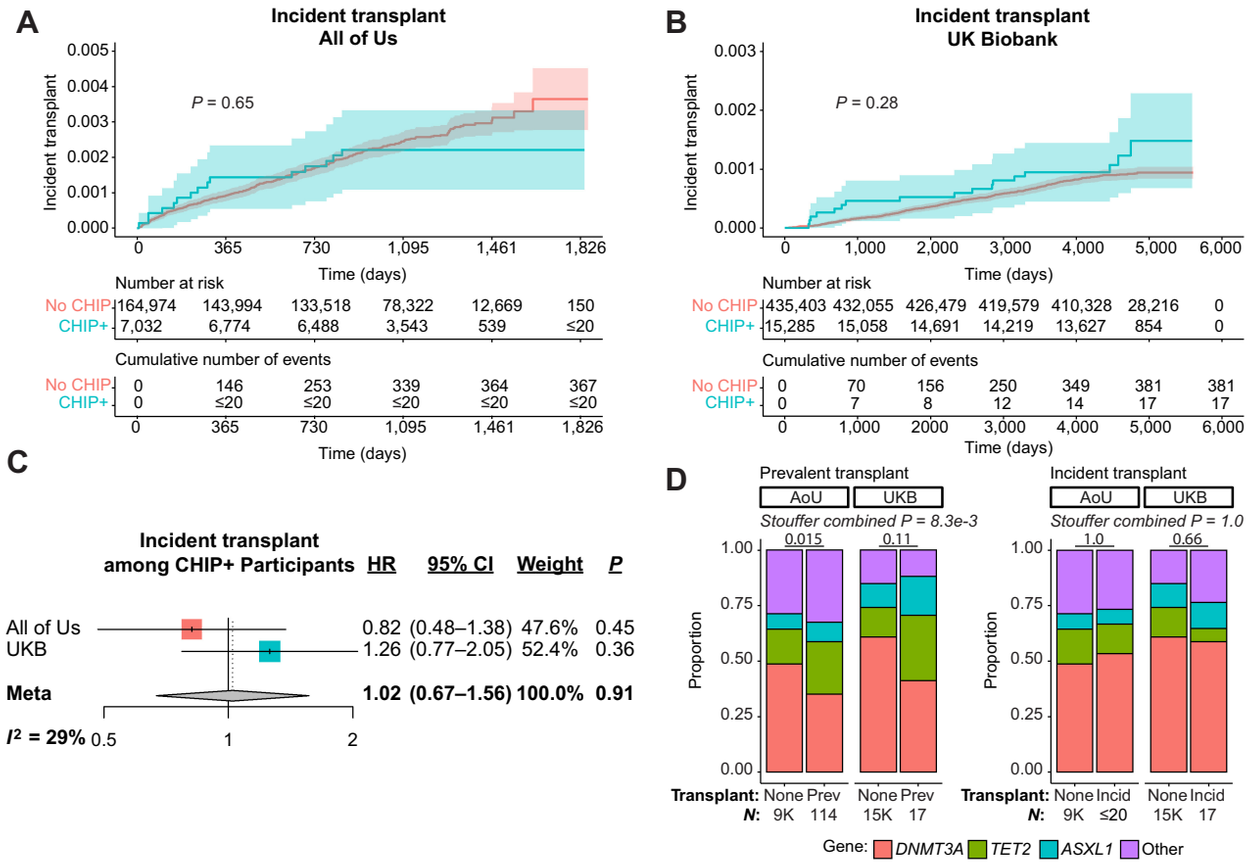


**Figure 4.**

No evidence for a strong association between clonal hematopoiesis of indeterminate potential and overall risk of incident transplant. **A** and **B,** Transplant incidence curves for the All of Us (AoU; **A**) and UK Biobank (UKB; **B**), stratified by clonal hematopoiesis of indeterminate potential (CHIP) status. *P* values represent the log-rank test. **C,** Adjusted Cox proportional hazards models and random effects meta-analysis hazard ratios (HR) and 95% confidence intervals (95% CI) for incident transplantation in the AoU and UKB cohorts. HRs for incident transplant were determined by regression adjusted for CHIP (depicted), age, sex, smoking history, and first 10 principal components of genetic ancestry. **D,** Bar plots of the proportion of *DNMT3A*, *TET2*, *ASXL1*, or other gene mutations among CHIP-positive individuals without a transplant at their biobank enrollment (None), with a transplant at biobank enrollment (Prev), and those who had an incident transplant (Incid). For **D**, *P* values represent the Fisher's exact test, with combined *P* value from the Stouffer's method shown where appropriate.

larger sample size afforded by this approach allowed us to evaluate not only aggregate complications but also several more granular phenotypes available only in the AoU dataset. However, similar to the previous analyses, we found participants with CHIP to have no significant differences in terms of aggregate complications, graft rejection, or any of the organ-specific phenotypes evaluated (Supplementary Fig. S10A–S10G and Supplementary Tables S28 and S29). With this larger sample, we also assessed aggregate complication prevalence by mutated gene. Although complications were nominally more prevalent in individuals with *ASXL1* and DDR CHIP and nominally less common for those with *DNMT3A* and *TET2* CHIP, there were no statistically significant differences (Supplementary Fig. S10C). Finally, we evaluated the prevalence of post-transplant lymphoproliferative disease (PTLD) according to CHIP status but saw no significant difference; there were too few PTLD cases to make inferences on a per-gene basis (Supplementary Fig. S10G). In sum, we did not find evidence for any strong associations between CHIP and transplant complications in our analysis.

## Discussion

Here, we present the largest study to date exploring the relationship of CHIP to solid organ transplantation in more than 2,600 allograft recipients alongside approximately 650,000 non-transplanted controls. In using data from two different community-based national biobanks, we were able to assess these relationships across multiple types of allografts and rigorously compare our findings with non-transplant controls. We found that transplant recipients do not have greatly increased prevalence of CHIP overall, but that individuals living with an allograft are more likely to have *TET2* CHIP. We uncovered no evidence to support the notion that CHIP, including *TET2* CHIP, is a strong independent predictor of risk for incident transplantation among the general population. Finally, our study did not show any evidence that CHIP is associated with increased transplant complications such as allograft rejection, although there are important caveats that should be considered when interpreting these results.

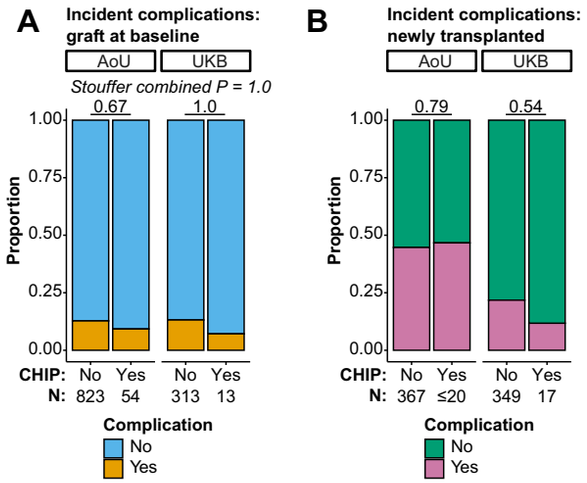


**Figure 5.**

No evidence for a strong association between clonal hematopoiesis of indeterminate potential and incident allograft complications. **A** and **B,** Bar plots stratified by clonal hematopoiesis of indeterminate potential (CHIP) status showing proportion of participants who experienced an incident complication (Incident Comp; gold or pink) and those that did not (blue or green) for individuals with a prior transplant but without prior complications (**A**) and individuals who received their first transplant after study enrollment (**B**). The All of Us (AoU) data depicts kidney, liver, heart, and lung transplant complications, whereas the UK Biobank (UKB) data does not include data on lung transplant complications because it is not reported as a unique entity in that study. *P* values represent the Fisher's exact test, with combined *P* value from the Stouffer's method shown where appropriate.

There are several plausible explanations for why *TET2* CHIP might be more prevalent among transplant recipients. Perhaps the most obvious potential explanation is that these mutations may predispose to conditions requiring transplant. *TET2* has strong evidence linking it to several medical conditions that can potentially lead to workup for transplantation, including myocardial infarction (2, 6), heart failure (4, 7), chronic obstructive pulmonary disease (17), pulmonary arterial hypertension (31), chronic liver disease (19), and renal fibrosis and chronic kidney disease (2, 18, 32). However, our finding that *TET2* CHIP is enriched among those who received an allograft before enrollment but not among those who received a transplant after enrollment argues against this scenario, under which *TET2* mutations should also be more common among those newly requiring transplant. A second potential explanation is that *TET2* mutations could be more common due to survival bias. Several recent preliminary reports from one research group have found that CHIP is associated with reduced risk in patients with heart failure who received a transplant and also that *TET2*-mutated hematopoietic cells are protective against heart allograft failure in a mouse model (33, 34). Lymphocytes play a key role in allograft complications and mechanistic studies have shown that loss of *TET2* leads to impaired plasma cell differentiation and T-cell effector differentiation and cytokine production (35–38); the effects of a clonal loss of *TET2* on the broader lymphoid compartment remain unstudied. Although a putative biological mechanism would be necessary to consider the hypothesis that survival advantage accounts for the increased rate of *TET2* mutations in the post-allograft setting, it could potentially account for why *TET2* might not be enriched among new transplants but more common in established transplants. We also note that among transplant recipients in our primary cohort, those with *TET2* CHIP had the lowest prevalence of complications, although this was not a statistically significant finding. Another hypothesis is that certain CHIP clones, such as *TET2*-mutant clones, are normally effectively suppressed by immunosurveillance but might have the opportunity to expand under the intensive immunosuppressive regimens required by transplantation. This explanation could similarly explain a discrepancy between *TET2* prevalence in established versus new allograft recipients. Our data showing a strong association between anti-thymocyte globulin exposure and *TET2* CHIP are in alignment with this hypothesis, although this finding should be validated in an independent cohort. Prospective studies evaluating CHIP in the pre-, peri-, and post-transplantation settings will be necessary to fully untangle the reasons behind the associations that have been described by us and others.

We found it curious that heart transplant was the only allograft type in AoU that was not positively associated with *TET2*, which is more puzzling in light of their relatively strong association in the UKB. Because *TET2* CHIP is known to substantially increase the risk for and severity of cardiovascular disease (2, 4, 6, 7), which is one of the top drivers of mortality in the U.S. and U.K., there may be competing phenomena that influence its prevalence among heart allograft recipients. The presence of a *TET2* mutation might make it more likely that an individual would develop cardiovascular disease necessitating transplant but might also simultaneously increase the risk of mortality among individuals before heart transplantation. And neither our study nor those that have preceded it have had the statistical power to definitively assess the effect of *TET2*, in isolation from other CHIP genes, on cardiac graft dysfunction and post-transplant mortality (21, 22). Thus, the case of *TET2* in heart transplant may feature dynamics that set it apart from other transplant types, although this will need to be resolved by further human and mechanistic data.

Our geographically distributed community-based study population complements the existing literature on CHIP in solid organ transplantation, which has drawn exclusively from a small number of academic medical centers, and we have presented several findings that are in alignment with this literature. In particular, one prior cohort of lung transplant recipients observed *TET2* as the most frequently mutated CHIP gene (23). And, although it did not reach statistical significance in our study, we did find a high prevalence of DDR CHIP in the AoU cohort, which is similar to the findings that DDR CHIP is more common in lung allograft recipients (20) and that *PPM1D* was the second most-commonly mutated gene in a multicenter cohort of heart transplant recipients (22). We did not observe any large differences in VAF for mutated genes observed in our transplant and non-transplant populations, which is also in line with previous work (20).

However, there are a few points on which our results differ from prior work, although we believe that differences in study populations and sequencing platforms may explain a large portion of ostensibly discrepant findings. For one, our study finds a far lower prevalence of CHIP among transplant recipients than previous studies, which have reported prevalences ranging from 13% to 40% (20–23). With the exception of one study using WES (23), these studies all conducted targeted sequencing of CHIP genes that provided much greater sequencing depth than that provided by the WGS (AoU) or WES (UKB) used here. Deeper sequencing is better able to identify low-VAF clones (39), which could possibly result in different biases in the observed distribution of CHIP gene mutations. Timing of DNA isolation relative to transplantation may also be a factor, as substantial portions of the previously studied cohorts underwent DNA isolation either before or within months of transplantation.

Our results on transplant complications deserve special mention in the context of previous work. That we found no evidence to support an

increased likelihood of rejection or incident complications among CHIP-positive allograft recipients largely aligns with the four prior studies, only one of which found significantly increased complications from CHIP overall (20–23). One study found that DDR CHIP was associated with post-transplant CMV viremia (20), and our results showed that DDR CHIP had a trend toward a higher prevalence of complications. A study of liver recipients with graft-versus-host disease (GVHD) did find high rates of *DNMT3A* mutations in recipient bone marrow aspirates, with mutations identified in 5/7 GVHD patients (with at least one clone being of donor origin) versus 1/6 non-GVHD liver-transplant controls (40). This study suggests that *DNMT3A* may influence the likelihood of GVHD, and although we did not find allografts with *DNMT3A* to have a higher prevalence of complications, we could not specifically evaluate GVHD, and this is worthy of deeper study and biologic correlation. Our finding of a lack of association between CHIP and transplant complications does not necessarily rule out specific CHIP:complication associations that have been previously described for three main reasons. First, we lacked the ability to control for transplant-specific factors that influence outcomes. Second, if complication rates do differ according to which CHIP gene is mutated (e.g., lower for *TET2*), the observed distribution of CHIP genes in our cohort compared with others may partly explain a lower complication prevalence. The plausibility of this is supported by the significant phenotypic heterogeneity observed between different CHIP genes, which is highly dependent on disease context; CHIP gene heterogeneity is so well-recognized that gene-specific factors are used in the Clonal Hematopoiesis Risk Score prognostic model that predicts development of myeloid neoplasms from CHIP (2, 41–43). Third, the population that already had an allograft and CHIP upon enrollment might suffer from ascertainment bias: If some CHIP mutations do increase morbidity or mortality post-transplant, individuals with these mutations might not have been able to be recruited or been well enough to participate when the AoU and UKB studies were enrolling and thus would not be observed in our study.

We acknowledge several limitations to our study and the use of these large biobanks in the examination of solid organ transplantation. Foremost, the AoU and UKB cohorts have several important differences. In particular, the U.S. has a much higher rate of transplantation, especially for liver, heart, and lung allografts (Supplementary Fig. S1) and the proportion of individuals with an allograft was much higher in AoU than in the UKB, particularly for these three organ types. In addition, there are modest differences in the overall prevalence of CHIP (3.8% in AoU vs. 3.4% in UKB). This disparity in CHIP prevalence likely reflects the unique demographics of these studies as well as differences in sequencing platforms and methods. Challenges to comparing CHIP across two studies using different sequencing types (WGS in AoU and WES in UKB) include different sensitivity to low-VAF clones due to sequencing depth (median depth for both studies is ∼40X, but the median depth at any given genomic locus may differ by platform), platform-specific bias in terms of how likely it is that a given mutation will be faithfully captured by its sequencing methodology (which could influence *DNMT3A*:*TET2* ratios, which differ slightly in AoU and UKB), and platform-specific sequencing artifacts (9, 39). We do our best to account for the two former challenges by using random-effect meta-analysis, whereas we require our CHIP variants to recapitulate known associations with age and germline variation in *TERT* to filter out sequencing artifacts (9). The UKB has greater demographic homogeneity and lower prevalence of both transplant and CHIP, which affects the ability to detect differences and make generalizations. As alluded to above, our study could also be affected by ascertainment bias in the composition of the participants in AoU and the UKB cohorts. In addition, the phenotypic data for these cohorts are limited to relatively broad billing-code-based phenotypes, which translates to low granularity about types of complications we do capture and also means that we were unable to control for key transplant-specific variables affecting risk for complications. The drug prescription data in AoU are relatively sparse and likely undercount the participants exposed to a given medication. Finally, owing to the relatively low prevalence of both transplant and CHIP, our study is underpowered to detect small differences in effect sizes, particularly among gene- or organ-specific subgroups.

Clonal hematopoiesis is a known disruptor of immune cell function, and our data showing individuals living with solid organ transplants have a higher prevalence of mutations in *TET2* but not other CHIP genes strongly suggest that there are as-yet-undefined immune interactions between mutated hematopoietic cells and the treatments required by solid-organ transplantation or the transplanted organs themselves. With this in mind, consideration should be given to the question of whether there are differences in clonal selection pressures for *TET2* under long-term immunosuppression, which may have bearing on the mechanisms of malignant transformation in transplant recipients. Moreover, future work should further investigate the potential for CHIP, and *TET2* mutations in particular, to act as an aggravating or ameliorating factor with respect to the specific disorders that are indications for transplantation and to specific allograft complications. These will be challenging questions to answer, perhaps necessitating the use of large, prospective cohorts of transplant patients, but nonetheless deserving of inquiry in light of the striking biological signal of *TET2* CHIP enrichment across multiple types of solid organ transplants.

## Authors' Disclosures

A.J. Silver reports grants from NIH during the conduct of the study. A.G. Bick reports personal fees from TenSixteen Bio during the conduct of the study. C.W. Pinson reports grants from NIH to institution during the conduct of the study. M. R. Savona reports grants from Biff Ruttenberg Foundation during the conduct of the study; personal fees from BMS, CTI, Forma, Geron, GSK, Karyopharm, Novartis, Rigel, Ryvu, and Treadwell; and grants from Astex, Incyte, Takeda, and TG Therapeutics outside the submitted work; in addition, M.R. Savona reports patents for PCT/US2014/053148 issued to Boehringer and PCT/US22/31403 pending. No disclosures were reported by the other authors.

## Authors' Contributions

**A.J. Silver:** Conceptualization, data curation, formal analysis, investigation, visualization, methodology, writing–original draft, writing–review and editing. **C. Vlasschaert:** Data curation, formal analysis, investigation, writing–review and editing. **T. Mack:** Data curation, investigation. **B. Sharber:** Investigation. **Y. Xu:** Formal analysis, investigation, writing–review and editing. **A.G. Bick:** Formal analysis, investigation, writing–review and editing. **C.W. Pinson:** Formal analysis, investigation, writing–review and editing. **M.R. Savona:** Conceptualization, formal analysis, supervision, investigation, writing–review and editing.

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## Note

Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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