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Long-term Outcomes of Peripheral Blood Stem Cell Unrelated Donors Mobilized with Filgrastim

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Abstract:
Allogeneic hematopoietic cell transplantation is a life-saving procedure used to treat of a variety of devastating diseases. It requires hematopoietic stem cells collected via filgrastim mobilized peripheral blood stem cells or bone marrow harvest from volunteer unrelated donors. There is a paucity of safety data regarding donors' long-term adverse events. This prospective, observational study combined peripheral blood stem cell donors enrolled on the NMDP Investigational New Drug trial and bone marrow donors between July 1, 1999, and September 30, 2015. The primary objective was to describe the long-term incidence of myeloid malignancies. Secondary objectives included describing the long-term incidence of lymphoid malignancies, non-hematologic malignancies, autoimmune disorders, and thrombotic events. 21643 donors (14530 peripheral blood stem cells and 7123 bone marrow) were included. The incidence rate of myeloid disorders per 100000 person years in donors of peripheral blood stem cells was 2.53 (95% CI: 0.82-7.84) and in donors of bone marrow it was 4.13 (95% CI: 1.33-12.8). The incidence rate ratio of peripheral blood stem cells /bone marrow donors was 0.61 (95% CI: 0.12-3.03; p=0.55). The incidence of other malignancies, autoimmunity, and thrombosis did not differ between donor types. This comprehensive study of long-term effects of filgrastim in unrelated donors of peripheral blood stem cells provides strong evidence that donors who receive filgrastim are not at increased risk of these events compared to bone marrow donors. It also provides reassurance to current donors undergoing stem cell mobilization as well as individuals considering joining stem cell registries such as NMDP.

Conflict of interest: COI declared - see note

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Author contributions and disclosures: H.E.S designed the research plan, analyzed the data, and wrote the manuscript; M.K and S.B-S. analyzed the data; H.K. was the project manager in the clinical trial., D.M. gathered data; J.S., D.S., and C.D.B.O. edited the final version of the manuscript; L.J.B. reviewed medical records and critically reviewed and edited the final version of this manuscript; B.E.S and M.A.P critically reviewed and edited the final version of this manuscript; and J.P.M. and S.M.D designed the research plan, reviewed medical records, analyzed the data, critically reviewed and edited the final version of this manuscript.

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Agreement to Share Publication-Related Data and Data Sharing Statement: Individual data will not be shared. Aggregated data can be obtained upon reasonable request from the corresponding author, Heather E. Stefanski (hstefans@nmdp.org).

Clinical trial registration information (if any):

Long-term Outcomes of Peripheral Blood Stem Cell Unrelated Donors Mobilized with Filgrastim

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Individual data will not be shared. Aggregated data can be obtained upon reasonable request from the corresponding author, Heather E. Stefanski (hstefans@nmdp.org).

Key Points:

- This was a prospective long term follow-up study including 14530 PBSC and 7123 BM volunteer unrelated donors from NMDP.
- PBSC and BM donors had no differences in incidence rates for myeloid, lymphoid, other cancers, autoimmune diseases, or thrombotic events.

ABSTRACT

Allogeneic hematopoietic cell transplantation is a life-saving procedure used to treat of a variety of devastating diseases. It requires hematopoietic stem cells collected via filgrastim mobilized peripheral blood stem cells or bone marrow harvest from volunteer unrelated donors. There is a paucity of safety data regarding donors' long-term adverse events.

This prospective, observational study combined peripheral blood stem cell donors enrolled on the NMDP Investigational New Drug trial and bone marrow donors between July 1, 1999, and September 30, 2015. The primary objective was to describe the long-term incidence of myeloid malignancies. Secondary objectives included describing the long-term incidence of lymphoid malignancies, non-hematologic malignancies, autoimmune disorders, and thrombotic events. 21643 donors (14530 peripheral blood stem cells and 7123 bone marrow) were included. The incidence rate of myeloid disorders per 100000 person years in donors of peripheral blood stem cells was 2.53 (95% CI: 0.82-7.84) and in donors of bone marrow it was 4.13 (95% CI: 1.33-12.8). The incidence rate ratio of peripheral blood stem cells /bone marrow donors was 0.61 (95% CI: 0.12-3.03; p=0.55). The incidence of other malignancies, autoimmunity, and thrombosis did not differ between donor types. This comprehensive study of long-term effects of filgrastim in unrelated donors of peripheral blood stem cells provides strong evidence that donors who receive filgrastim are not at increased risk of these events compared to bone marrow donors. It also provides reassurance to current donors undergoing stem cell mobilization as well as individuals considering joining stem cell registries such as NMDP.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (alloHCT) is a life-saving procedure for treatment of devastating diseases. The NMDP was established in 1987 to facilitate alloHCT from anonymous, volunteer adult unrelated donors (URDs) to patients in need. Hematopoietic stem cells are typically collected from URDs in two ways: via bone marrow (BM) harvest or by recombinant human granulocyte colony stimulating factor (filgrastim) mobilized peripheral blood stem cell (PBSC) collection. BM has been used as a source of hematopoietic stem cells (HSC) from the 1960s[1], however, since recognition that HSC could be mobilized from the BM by filgrastim treatment and collected via apheresis in the 1990s, PBSCs have been increasingly used[2,3]. Data collected to date have been primarily focused on short-term side effects for both BM and PBSC donors[4-22].

Previous reports suggested filgrastim increases the risk for myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) in patients with severe chronic neutropenia[23], breast cancer[24,25] and lung cancer[25]. There have also been reports in URDs that developed myeloid malignancies after receiving filgrastim[26,27]; however additional studies with longer follow-up provided reassurance that filgrastim does not increase the risk of cancer in URDs [11,28-32].

It is documented that autoimmune diseases, such as iritis, can rarely be exacerbated following filgrastim administration in normal donors[33]. Worsening autoimmune diseases can also be seen in patients with multiple sclerosis (MS)[34,35], systemic lupus erythematosus (SLE)[36-38], rheumatoid arthritis (RA)[39] and other immune-mediated vasculidities[40-42] when being treated for neutropenia with filgrastim.

Thrombosis has been a concern as a side effect of filgrastim. Administration of filgrastim leads to a potentially pro-thrombotic state via stimulation of tissue factor and increased endothelial

markers[43]. Additionally, there have been reports of healthy donors having acute arterial thrombosis related to filgrastim[44].

Since 1997, the NMDP has maintained an Investigational New Drug (IND) application accepted by the Food and Drug Administration (FDA) for manufacture of PBSC products from URDs. To address whether filgrastim administration in URDs has significant long-term consequences, we evaluated the incidence of malignant, autoimmune and thrombotic disorders after HSC donation in PBSC donors. The results of this study, the largest and most comprehensive, are presented in this manuscript.

Design and Methods

NMDP initiated an IND to collect AEs for donors that underwent PBSC donation in 1997. All donors were mobilized with subcutaneous filgrastim (Neupogen®, Amgen, Thousand Oaks, CA, United States [U.S.]) at an approximate dose of 10 μg/kg/d for 5 days. The study population presented in this paper was comprised of two cohorts of URDs from the U.S. and was activated on October 1, 2010, with all follow-ups being completed by September 30, 2020. There was an early group, registered either prospectively on NMDP PBSC IND trial or, if a BM donor, on NMDP Registry BM follow up trial, between July 1, 1999, and September 30, 2010, and a later donor group who underwent a collection from October 1, 2010, to September 30, 2015. The trials were approved by NMDP Institutional Review Board.

The primary objective of this study was to describe the long-term incidence of malignant myeloid disorders (AML, MDS, chronic myelogenous leukemia [CML], or chronic myeloproliferative disorders) in PBSC and BM donors and to compare incidences between the donor cohorts, with BM donors serving as the control. The secondary objectives were to describe

111 malignant lymphoid disorders (acute lymphoblastic leukemia [ALL], chronic lymphocytic
112 leukemia [CLL], Hodgkin lymphoma, or non-Hodgkin lymphoma), non-hematologic malignant
113 disorders (as defined by the Surveillance, Epidemiology, and End Results [SEER] Program
114 database[45]), autoimmune diseases, and thrombotic events (venous and arterial), in PBSC and BM
115 donors.

116 Donors completed biennial surveys to report new diagnoses of Malignancy, Autoimmune, or
117 Thrombotic (MAT) events over approximately 10 years until study conclusion. All donor follow-
118 up assessments were administered by trained staff members of the Center for International Blood
119 and Marrow Transplant Research (CIBMTR) Survey Research Group (SRG) and Donor Center
120 staff. Donors were asked if they had developed any cancers, autoimmune disorders, or had a
121 blood clot anywhere other than where they've had an IV placed since their donation or previous
122 follow-up, and if yes, when diagnosis occurred.

123 When donors reported a MAT event, the SRG requested a medical records release form and
124 contacted donors' clinics to obtain the relevant medical records. NMDP medical staff reviewed,
125 and then documented whether the reported MAT event was correct and occurred post-collection,
126 correct but occurred pre-collection, incorrect or not a MAT event, duplicative of a previously
127 reported event, or unverified with existing records. If a donor did not return a medical records
128 release form, or SRG was unable to obtain records from their clinic, the reported MAT event was
129 coded as unverified.

130

131 **Subjects**

132 Inclusion criteria included: URDs who donated either BM or PBSC between July 1, 1999, and
133 September 30, 2015; URDs who received at least one injection of filgrastim or more but did not

donate PBSC between July 1, 1999, and September 30, 2015; donation was managed by a participating U.S. donor center; and URDs provided informed consent for participation in this study. Exclusion criteria included: URD who donated filgrastim-mobilized BM; donation was managed by a non-U.S. donor center; or donor was unable to verbally communicate in any of the following languages: English, Spanish, Mandarin Chinese, Cantonese Chinese, Vietnamese, Korean, or Portuguese. This study was registered as EUPAS19126 and as NCT01362179.

Statistical Methods

Counts and percentages were used to describe frequency of donor characteristics. Donors in the BM group included those who later underwent filgrastim mobilization, and outcomes from BM donation were censored at the time of mobilization. Donors in the PBSC group who had previously donated BM were followed for outcomes as part of the PBSC group. A descriptive analysis estimated the overall and age-specific incidence rate of MAT events. Rate ratios for MAT events were estimated for donors of PBSC vs. BM. To determine if there were differences in myeloid, lymphoid, and other cancer events in donors who donated PBSC or BM compared to the general population, we used the SEER Program database[45], which provides incidence rates on cancer statistics among the U.S. population, as a post-hoc analysis. Age-adjusted rates were calculated using the 2000 U.S. Standard Population. P-values and 95% confidence intervals for all rate ratios were calculated using Poisson regression methods. A P-value of < 0.05 was considered significant. Statistical analyses were done using SAS version 9.4 (Cary, NC, USA).

Results

A total of 32634 donors were contacted to participate in this study (Figure 1) and 21833 (66.9%) donors were enrolled. Of the subjects enrolled, 39 donors withdrew and141 subjects with missing data were removed, leaving 21653 donors in the final analyses. The total donor years were 118720 and 72643 for donors of PBSC and BM, respectively.

The demographics of the donors are described in Table 1. There were 14530 donors in the PBSC cohort, of whom 3.6% had previously donated BM. Most PBSC donors were male (59%) and white (76%). The median age (range) at the first filgrastim injection was 33 (18 to 62) years and the median time to follow up was 7 years (0.6-20.2) (Table 1). There were 7123 donors in the BM donor cohort, of whom 6.3% were later exposed to filgrastim. Most BM donors were male (57%) and white (71%). The median age (range) at the first BM collection was 35 (19 to 61) years and the median time of follow up post-collection was 9 years (0-29.2).

Myeloid Malignancies

The incidence rate of myeloid disorders in PBSC donors was 2.53 (95% CI: 0.82-7.84) and in BM donors was 4.13 (95% CI: 1.33-12.8) per 100000 person years (Table 2). The incidence rate ratio of PBSC/BM donors was 0.61 (95% CI: 0.12-3.03; p=0.55) (Table 2). The incidence rates by age range are shown in Tables 3A-C, but as shown, there are very few events in both groups (3 each).

Lymphoid Malignancies

The incidence rate of lymphoid malignancies in PBSC donors was 14.33 (95% CI: 8.91-23.05) and in BM donors was 13.78 (95% CI: 7.41-25.61) per 100000 person years (Table 2). The

incidence rate ratio was 1.04 (95%CI: 0.48-2.27; p=0.92) (Table 2). The crude incidence rate was highest in donors over 50 years of age in both PBSC (IR: 21.50; 95% CI: 6.93-66.64) (Table 3A) and BM donors (IR: 62.63; 95% CI: 23.51-166.8) (Table 3B) and the incidence rate ratio for donors over 50 years of age was 0.34 (95% CI: 0.08-1.53; p=0.16) (Table 3C).

Non-Hematologic Malignancies

The incidence rate of non-hematologic malignancies, as defined in the SEER database, for PBSC donors was 460.36 (95% CI: 423.0-501.0) and in BM donors was 521.59 (95% CI: 471.1-577.6) per 100000 person years with an incidence rate ratio of 0.88 (95% CI: 0.77-1.00; p=0.05) (Table 2). The crude incidence rates of other malignancies increased as donors aged in both PBSC and BM donors (Tables 3A and 3B). However, in the 18 to 29 age group, there was a statistically significant incidence rate ratio of other malignancies (RR: 0.61; 95% CI: 0.40-0.92; p=0.02) (Table 3C) with the BM group having increased numbers of other types of malignancies, although the numbers were very low. The incidence rate ratio was not statistically significant in the other age groups.

Autoimmune Diseases

The incidence rate of autoimmune diseases (e.g., rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematosus, scleroderma, vasculitidies, multiple sclerosis and immune thrombocytopenia [ITP] etc.) in PBSC donors was 385.19 (95% CI: 351.2-422.4) and in BM donors was 367.62 (95% CI: 325.8-414.9) per 100000 person years with an incidence rate ratio of 1.03 (95% CI: 0.89-1.21; p=0.66) (Table 2). Interestingly, there was a significant difference in

the incidence rate ratio in donors aged 30-39 years. The PBSC donors had an incidence rate of 425.3 (95% CI: 360.5-501.8) (Table 3A) and the BM donors had an incidence rate of 300.71 (95% CI: 238.4-379.3) (Table 3B) and an incidence rate ratio of 1.42 (95% CI: 1.06-1.89; p=0.02) (Table 3C). This phenomenon was not observed in the other age groups.

Thrombotic Events

The incidence rate of thrombotic events in PBSC donors was 132.23 (95% CI: 113.0-154.7) and in BM donors it was 131.63 (95% CI: 107.7-160.9) per 100000 person years and the incidence rate ratio was 1.01 (95% CI: 0.78-1.30; p=0.95). The incidence of thrombotic events was not different between PBSC or BM donors in the different age groups (Tables 3A-C).

SEER data comparison

To address differences between the two cohorts and the general population, the SEER database was used, and age-adjusted rates were calculated using the 2000 U.S. Standard Population[45]. The general population was more likely to have all types of cancer compared to PBSC donors (Table 4A). The incidence rate of myeloid malignancies in PBSC donors was 2.53 (95% CI: 0.82-7.84) and 17.91 (95% CI: 17.85-17.96) in the general population with a rate ratio of 0.14 (95% CI: 0.05,0.44; p<0.001), in lymphoid malignancies the incidence rate in PBSC donors was 14.33 (95% CI: 8.91-23.05) and 33.76 (95% CI: 33.68-33.84) in the general population with a rate ratio of 0.42 (95% CI 0.26-0.68; p<0.001), and in other malignancies the incidence rate in PBSC donors was 460.36 (95% CI: 423.0-501.0) and 568.3 (95% CI: 567.9, 568.6) in the general population with a rate ratio of 0.81 (95% CI: 0.74-0.88; p<0.001) (Table 4A). The incidence rate

of myeloid malignancies in BM donors was 4.13 (95% CI: 1.33-12.8) and 17.91 (95% CI: 17.85-17.96) in the general population with a rate ratio of 0.23 (95% CI: 0.07,0.72; p=0.011), in lymphoid malignancies the incidence rate in BM donors was 13.78 (95% CI: 7.41-25.61) and 33.76 (95% CI: 33.68-33.84) in the general population with a rate ratio of 0.41 (95% CI 0.22-0.76; p=0.005), and in other malignancies the incidence rate in BM donors was 521.59 (95% CI: 471.1-577.6) and 568.3 (95% CI: 567.9, 568.6) in the general population with a rate ratio of 0.92 (95% CI: 0.83-1.02; p=0.100) (Table 4B).

DISCUSSION

This is the largest, most comprehensive study of long-term outcomes in URDs. It provides evidence that filgrastim in the setting of mobilization of PBSC in URDs is not associated with an increase in hematological or non-hematological malignancies, nor is it associated with an increase in autoimmune disorders or thrombotic events.

Concerns were raised about the association of filgrastim and AML due to several reports. Bennett et al. published 2 cases of AML among 200 individuals who had received filgrastim[26]. In these cases, matched sibling donors, who donated PBSC to their siblings with AML, developed AML approximately 4 years after filgrastim exposure. NMDP reviewed their donor outcomes and published on 20 cases of cancer (none of them leukemia or lymphoma) reported among 4015 URDs who had passed their first anniversary of PBSC donation[46]. There have been reports from multiple registries that looked at the incidence of cancer post donation during different time frames in PBSC donors. Nacheva et al. tested 50 PBSC donors for mutations common in hematological malignancies and showed that PBSC samples collected before, on the day of donation, 90 and 180 days after G-CSF administration had no damagingly effects on the genome

integrity and did not differ between samples from individuals that donated BM 3-5 years prior or healthy people[32]. Additional reporting by NMDP showed no increase of cancer, autoimmune diseases or stroke related to filgrastim in 6768 PBSC donors[17]. MD Anderson reported that none of 343 donors from their institution had been diagnosed with acute or chronic leukemia with a median follow up of 39 months[47]. The Japan Society for Hematopoietic Cell Transplantation reported long term follow up 1708 PBSC donors and showed no difference in hematological malignancies compared with a retrospective cohort of BM donors[48]. A prospective Swedish national cohort study analyzed the cancer incidence after donation in 1082 Swedish PBSC donors and did not find differences in the incidence of hematologic malignancies or other malignancies between PBSC donors and BM donors or non-donating siblings[49]. Of note, different formulations of filgrastim have been used in URDs, such as lenograstim or biosimilars, and data has shown no differences in efficacy or side effects [50-53]. Moreover, the World Marrow Donor Association (WMDA) has recommended that bioimilars may be used for mobilization [51]and has a mechanism for ongoing surveillance of donor adverse events[54]. While the PBSC donors in this study received Neupogen, these results could be applicable to donors that received other types of filgrastim. The study presented here is the first study that analyzed long-term effects of filgrastim on URDs over a 10-year period and confirmed no association between PBSC donors and an increased risk of any type of malignancy including myeloid, lymphoid, or other types of cancer compared to BM donors.

Other studies have compared cancer rates in PBSC donors to the general population. Hölig et al. published the results of 3928 PBSC donors at the University of Dresen and showed that malignancies were found in 0.3% of the donors; the incidence of Hodgkin lymphoma differed significantly compared to the general population[11]. There was not an increased risk in Hodgkin

lymphoma in our study, however the number of donors was much greater in this study and is more reassuring than the previous study[11]. Halter et al. recently published a retrospective multicenter EBMT study covering 51024 first allogeneic hematopoietic stem cell donations (27770 BM donors and 23254 PBSC donors) from predominantly related donors and found the incidences of hematologic malignancies were below the age-specific incidence of the normal population[30]. To elucidate if PBSC donors were more likely to develop cancer compared to the general population, we used the SEER database as a comparison. URDs that donate BM and PBSC are, in general, healthier than the general population as they are younger and must also meet eligibility criteria to donate and their overall rates of cancer are lower. An important consideration of PBSC and BM donors is that follow-up is shorter than the life-time follow up of the general population. However, this comparison suggests that filgrastim did not potentiate cancer risk in this population and the findings presented here give additional reassurance that both hematological and non-hematological malignancies are not increased in PBSC donors.

One of the secondary objectives of this study was to determine if filgrastim increased the incidence of autoimmune disorders. Filgrastim has been used in patients with lupus, multiple sclerosis, Felty's syndrome and temporal arteritis to treat neutropenia [35-38,40-42]. In URDs who received filgrastim, we did not see an increase in the incidence of the development of autoimmune diseases. However, when the results were stratified based on age, PBSC donors that were 30-39 years of age had a higher risk of having autoimmune diseases compared to BM donors, although the numbers were of events were very low (140/3871 [3.6%]). This same phenomenon was not observed in the other age ranges. A recent report by Conrad et al. estimates that 1/10 people are affected by autoimmune diseases[55]; the 3.6% observed in the 30-39 PBSC age group is less than the expected rate in the general population, giving support that short term

filgrastim use in a donor does not appear to potentiate autoimmune disorders. The low incidence of autoimmune disorders in BM donors could be because the BM donors at risk could have been screened out prior to donation.

Thrombosis has been a concern as a side effect of filgrastim due to reports of arterial thrombosis and a potentially increasedpro-thrombotic state[43,44]. This study showed that the incidence of thrombotic events in PBSC donors was not increased compared to BM donors. This confirmed evidence from another report showing stroke was not increased in PBSC donors [17] and that short term-filgrastim use does not appear to be associated with thrombosis.

There are several limitations to this study. BM donors who were later exposed to filgrastim were censored at the time of filgrastim exposure, thus limiting the amount of follow-up time at risk (this issue is addressed to some degree by the very large number of BM donor follow up years in this trial). Also, donors that had incorrect contact information were not included on this study. Another limitation is that verification could not be performed on all MAT events during medical record review. To address this specific limitation, we attributed unverified events as an event to overestimate, rather than underestimate, the number of late events. Additional limitations include relatively short follow-up of 7 years for donors enrolled after 2010, self-reporting and the donors that did not enroll could have increased late effects. Due to the overestimation of late events as well as the number of donor years studied, these limitations are not as worrisome.

This is the largest, prospective study addressing the safety of filgrastim in URDs. These results provide evidence that filgrastim is not associated with an increase in the incidence of myeloid or lymphoid malignancy, other types of cancer, autoimmune diseases, or thrombotic events. Most importantly, this provides URDs with reassurance that in this large study of thousands of healthy

donors followed on average for more than ten years, we saw no adverse effects associated with receiving filgrastim.

AUTHOR CONTRIBUTION

H.E.S designed the research plan, analyzed the data, and wrote the manuscript; M.K and S.B-S. analyzed the data; H.K. was the project manager in the clinical trial., D.M. gathered data; J.S., D.S., and C.D.B.O. edited the final version of the manuscript; L.J.B. reviewed medical records and critically reviewed and edited the final version of this manuscript; B.E.S and M.A.P critically reviewed and edited the final version of this manuscript; and J.P.M. and S.M.D designed the research plan, reviewed medical records, analyzed the data, critically reviewed and edited the final version of this manuscript.

CONFLICTS OF INTEREST

D.S., C.D.O.B and J.S are employed by Amgen. All Amgen employees are Employed by Amgen and own Stock. B.E.S Consulting: OrcaBio, Mallinkrodt.; M.A.P. Adaptive*:* Research Funding; Gentibio*:* Membership on an entity's Board of Directors or advisory committees; Miltenyi*:* Research Funding; Vertex*:* Membership on an entity's Board of Directors or advisory committees; BlueBird*:* Membership on an entity's Board of Directors or advisory committees; Novartis*:* Consultancy; CARGO*:* Membership on an entity's Board of Directors or advisory committees. All other authors declare no COI.

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FIGURE LEGEND

358 **Figure 1.** Study enrollment flow chart
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517 **Table 1. Demographic characteristics of donors**

Characteristic	PBSC Donors No. (%)	BM Donors No. (%)	p-value
Number of donors	14530	7123	
Number of filgrastim exposures – No. (%)			
1	13579 (93)	NA	
2	416 (3)	NA	
3	6 (<1)	NA	
Number of BM donations – No. (%)			
1	NA	6496 (91)	
2	NA	169 (2)	
3	NA	12 (<1)	
Number of both BM donations and filgrastim exposures[a] – No. (%)			0.846
1 BM donation -1 filgrastim exposure	498 (3)	416 (6)	
1 BM donation - 2 filgrastim exposures	13 (<1)	12 (<1)	
2 BM donations -1 filgrastim exposure	18 (<1)	18 (<1)	
Sex – No. (%)			0.019
Female	5975 (41)	3048 (43)	
Male	8555 (59)	4075 (57)	
Race – No. (%)			<0.001
White	10980 (76)	5070 (71)	
Hispanic	1252 (9)	798 (11)	
Black	498 (3)	396 (6)	
Asian / Pacific Islander	800 (6)	407 (6)	
Native American	103 (1)	68 (1)	
Multiple races / Other	848 (6)	360 (5)	
Unknown / Decline	49 (<1)	24 (<1)	
Age at first BM collection or first filgrastim injection, years – No. (%)			<0.001
Median (min-max)	33 (18-62)	35 (19-61)	<0.001
18 to 29	5896 (41)	2542 (36)	
30 to 39	3871 (27)	2186 (31)	
40 to 49	3231 (22)	1804 (25)	
50+	1532 (11)	591 (8)	
Year of first BM collection or first filgrastim injection – No. (%)			<0.001
1989	0	1 (<1)	
1990	0	4 (<1)	
1991	0	3 (<1)	

1992	0	7 (<1)	
1993	0	19 (<1)	
1994	0	9 (<1)	
1995	0	10 (<1)	
1996	0	25 (<1)	
1997	0	30 <1)	
1998	0	36 (1)	
1999	15 (<1)	281 (4)	
2000	137 (1)	492 (7)	
2001	195 (1)	435 (6)	
2002	317 (2)	457 (6)	
2003	466 (3)	375 (5)	
2004	453 (3)	307 (4)	
2005	537 (4)	243 (3)	
2006	587 (4)	272 (4)	
2007	652 (4)	276 (4)	
2008	777 (5)	280 (4)	
2009	850 (6)	297 (4)	
2010	1001 (7)	329 (5)	
2011	1450 (10)	510 (7)	
2012	1772 (12)	656 (9)	
2013	2010 (14)	656 (9)	
2014	1817 (13)	625 (9)	
2015	1479 (10)	484 (7)	
2016	15 (<1)	4 (<1)	
ian (min-max) follow-up - years	7.0 (0.6-20.2)	9.0 (0.0-29.2)	<0.001

PBSC = peripheral blood stem cells; BM= bone marrow; No=number; NA = not applicable; min=minimum; max=maximum

[a] X-Y lists the total number of BM donations followed by the total number of exposures to filgrastim. Donors in the BM group who later had exposure to filgrastim were censored at the time of filgrastim exposure.

Table 2. Incidence rates of MAT events

	PBSC donors			BM donors				
Outcomes	**Person-years**	**Number of events**	**Incidence rate[a] (95% CI)**	**Person-years**	**Number of events**	**Incidence rate[a] (95% CI)**	**Rate ratio (95% CI)**	**p-value**
Myeloid	118712	3	2.53 (0.82-7.84)	72641	3	4.13 (1.33-12.8)	0.61 (0.12-3.03)	0.55
Lymphoid	118649	17	14.33 (8.91-23.05)	72572	10	13.78 (7.41-25.61)	1.04 (0.48-2.27)	0.92
Other malignancies	116213	535	460.36 (423.0-501.0)	70553	368	521.59 (471.1-577.6)	0.88 (0.77-1.00)	0.05
Autoimmune	116566	449	385.19 (351.2-422.4)	71269	262	367.62 (325.8-414.9)	1.03 (0.89-1.21)	0.66
Thrombosis	117977	156	132.23 (113.0-154.7)	72172	95	131.63 (107.7-160.9)	1.01 (0.78-1.30)	0.95

MAT = malignancy, autoimmune, or thrombotic events; PBSC = peripheral blood stem cells; BM = bone marrow; CI=confidence interval

[a]Incidence rate per 100000 person-years.

Table 3. Incidence rate of MAT events, stratified by age

a. Crude incidence rate of MAT events in PBSC donors

Age, years	**18 to 29**	**30 to 39**	**40 to 49**	**50+**
Number of donors	5896	3871	3231	1532
Donor-years	41450	33548	29717	13969
Myeloid				
Donor-years	41444	33584	29715	13968
Events	1	0	1	1
Crude rate[a]	2.41	0.00	3.37	7.16
95% CI	(0.341-7.13)	N/A	(0.47-23.89)	(1.01-50.82)
Lymphoid				
Donor-years	41432	33558	29704	13956
Events	4	5	5	3
Crude rate[a]	9.65	14.90	16.83	21.50
95% CI	(3.62-25.72)	(6.20-35.79)	(7.01-40.44)	(6.93-66.64)
Other malignancies				
Donor-years	41249	33099	28644	13221
Events	49	105	225	156
Crude rate[a]	118.79	317.23	785.50	1179.97
95% CI	(89.80-157.2)	(262.1-384.0)	(689.6-894.7)	(1009.5-1379.1)
Autoimmune				
Donor-years	40855	32915	29105	13690
Events	137	140	115	57
Crude rate[a]	335.33	425.34	395.12	416.35
95% CI	(238.7-396.4)	(360.5-501.8)	(329.2-474.2)	(321.3-539.5)
Thrombosis				
Donor-years	41345	33401	29409	13821
Events	25	40	60	31
Crude rate[a]	60.47	119.76	204.02	224.29
95% CI	(40.86-89.48)	(87.86-163.2)	(158.5-262.7)	(157.8-318.8)

MAT = malignancy, autoimmune, or thrombotic events; PBSC = peripheral blood stem cells; CI = confidence interval

[a]Incidence rate per 100000 person-years.

b. Crude incidence rate of MAT events in BM donors by age

Age, years	**18 to 29**	**30 to 39**	**40 to 49**	**50+**
Number of donors	2542	2186	1804	591
Donor-years	21549	23995	20671	6428
Myeloid				
Donor-years	21549	23993	20671	6428
Events	0	2	1	0
Crude rate[a]	0.00	8.34	4.84	0.00
95% CI	N/A	(2.08-33.33)	(0.68-34.34)	N/A
Lymphoid				
Donor-years	21547	23985	20653	6387
Events	1	3	2	4
Crude rate[a]	4.64	12.51	9.68	62.63
95% CI	(0.65-32.95)	(4.03-38.78)	(2.42-38.72)	(23.51-166.8)
Other malignancies				
Donor-years	21305	23513	19786	5949
Events	41	91	156	80
Crude rate[a]	192.44	387.02	788.45	1344.74
95% CI	(141.7-261.3)	(315.3-475.1)	(674.4-921.8)	(1081.7-1671.8)
Autoimmune				
Donor-years	21194	23611	20208	6257
Events	73	71	84	34
Crude rate[a]	344.44	300.71	415.67	543.43
95% CI	(273.9-433.1)	(238.4-379.3)	(335.8-514.6)	(388.6-759.8)
Thrombosis				
Donor-years	21460	23871	20506	6335
Events	20	27	34	14
Crude rate[a]	93.19	113.11	165.80	221.01
95% CI	(60.14-144.4)	(77.58-164.9)	(118.5-232.0)	(131.0372.9)

MAT = malignancy, autoimmune, or thrombotic events; BM= bone marrow; CI = confidence interval

[a]Incidence rate per 100000 person-years.

c. Rate ratio of observed MAT events in PBSC donors and BM donors by age

Age, years	**18 to 29**	**30 to 39**	**40 to 49**	**50+**
Myeloid				
Rate Ratio	NE	NE	0.70	NE
95% CI			0.04, 11.2	
P-value			0.80	
Lymphoid				
Rate Ratio	2.09	1.20	1.75	0.34
95% CI	(0.23-18.7)	(0.29-5.00)	(0.34-9.01)	(0.08-1.53)
P-value	0.51	0.81	0.50	0.16
Other malignancies				
Rate Ratio	0.61	0.81	0.98	0.89
95% CI	(0.40-0.92)	(0.61-1.07)	(0.80-1.21)	(0.68-1.17)
P-value	0.02[a]	0.1344	0.87	0.41
Autoimmune				
Rate Ratio	0.98	1.42	0.93	0.74
95% CI	(0.73-1.30)	(1.06-1.89)	(0.70-1.24)	(0.48-1.13)
P-value	0.86	0.02[a]	0.62	0.16
Thrombosis				
Rate Ratio	0.69	1.04	1.24	1.01
95% CI	(0.38-1.24)	(0.63-1.69)	(0.81-1.88)	(0.54-1.90)
P-value	0.21	0.89	0.32	0.97

MAT = malignancy, autoimmune, or thrombotic events; PBSC = peripheral blood stem cells; BM=bone marrow; NE = not evaluable; CI = confidence interval

[a]Statistically significant result ($p<0.05$).

Table 4. Age-adjusted incidence rates of malignancies in donors compared to the U.S. general population.

a. PBSC donors vs U.S. General Population - SEER

	PBSC donors			US General Population - SEER				
Outcomes	**Person-years**	**Number of events**	**Incidence rate[a] (95% CI)**	**Person-years**	**Number of events**	**Incidence rate[a] (95% CI)**	**Rate ratio (95% CI)**	**p-value**
Myeloid	118712	3	2.53 (0.82-7.84)	2211987365	396134	17.91 (17.85-17.96)	0.14 (0.05-0.44)	<0.001[b]
Lymphoid	118649	17	14.33 (8.91-23.05)	2211987365	746740	33.76 (33.68-33.84)	0.42 (0.26-0.68)	<0.001[b]
Other malignancies	116213	535	460.36 (423.0-501.0)	2211987365	1256982 1	568.3 (567.9-568.6)	0.81 (0.74-0.88)	<0.001[b]

PBSC = peripheral blood stem cells; SEER = Surveillance, Epidemiology, and End Results Program database[4,5]; CI = confidence interval; U.S = United States

[a]Age-adjusted incidence rate per 100,000 person-years.

[b]Result is statistically significant (p<0.05).

b. BM donors vs U.S. General Population - SEER

	BM donors			US General Population - SEER				
Outcomes	**Person-years**	**Number of events**	**Incidence rate[a] (95% CI)**	**Person-years**	**Number of events**	**Incidence rate[a] (95% CI)**	**Rate ratio (95% CI)**	**p-value**
Myeloid	72641	3	4.13 (1.33-12.8)	2211987365	396134	17.91 (17.85-17.96)	0.23 (0.07-0.72)	0.011[b]
Lymphoid	72572	10	13.78 (7.41-25.61)	2211987365	746740	33.76 (33.68-33.84)	0.41 (0.22-0.76)	0.005[b]
Other malignancies	70553	368	521.59 (471.1-577.6)	2211987365	1256982 1	568.3 (567.9-568.6)	0.92 (0.83-1.02)	0.100

560 BM = bone marrow; SEER = Surveillance, Epidemiology, and End Results Program database[4,5]; CI = confidence

561 interval; U.S = United States

562 [a]Age-adjusted incidence rate per 100,000 person-years.

563 [b]Result is statistically significant ($p<0.05$).

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Figure 1. Study enrollment flow chart