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Immune Reconstitution Following Allogeneic Hematopoietic Stem Cell Transplantation

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Abstract

Objective: To evaluate pattern of immune reconstitution (IR) following allogeneic hematopoietic stem cell transplantation (HSCT)
Methodology: This observational study was conducted at Department of Clinical Hematology and Bone Marrow Transplant, Quaid-e-Azam International Hospital Islamabad from January 2023 to December 2024. Sixty-two consecutive patients undergoing allogeneic HSCT for various hematological diseases were evaluated. Following parameters were recorded at 6 and 12 months post-HSCT: Absolute lymphocyte count (ALC), lymphocyte subsets and immunoglobulin levels. Patients with incomplete follow up or graft failure/rejection were excluded from analysis
Results: Absolute lymphocyte count recovery was seen in 77.4% of patients by 6 months which increased to 87.1% at 12 months post-HSCT. CD3+CD8 cells recovery was seen in 91.90% while 54.8%, 33.90% & 22.6% respectively had CD16+CD56+, CD19+ and CD3+CD4 cells recovery by 6 months post-HSCT. Percentage of patients with CD3+CD4 recovery increased to 61.3%, while other subset recovery percentages were: CD3+CD8+ 90.3 %, CD16+CD56+ 43.5 % and CD19+ cells in 51.6 % by 12-months post-HSCT. Immunoglobulin recovery at 6 months was observed in 79%, 85.4%, and 90.3% of patients for IgA, IgG, and IgM respectively and at 12 months 83.9%, 88.7%, and 82.3% of patients had normal levels of IgA, IgG, and IgM respectively. Early CD3+CD4+ recovery was associated with age <18 years, non-malignant diseases, and lower incidence of acute graft-versus-host disease. CD34 dose <4 x 106/Kg had better CD3+CD4+ recovery compared with >4 x 106/Kg dose.
Conclusion: Our study revealed that factors like benign disorders, younger age and absence of aGVHD are associated with early IR, while older age, malignant diseases, major ABO-mismatch and non-sibling donors were associated with delayed IR.
Key Words: Hematopoietic stem cell transplant, Immune reconstitution, Absolute lymphocyte count, Lymphocyte subsets, Graft versus host disease.

Introduction

Hematopoietic stem cell transplantation (HSCT) is an established treatment approach for patients with certain benign and malignant hematological diseases. The main outcome expected from HSCT is the lifetime engraftment of the donor-derived hematopoietic stem cells (HSCs). Conditioning using chemotherapy/immunotherapy ± radiotherapy is given to the recipient to eradicate abnormal marrow and immune system followed by infusion of donor-derived allogeneic HSCs. The patient experiences a brief period of pancytopenia and profound immune deficiency, then a new lymphohematopoietic system sets up in recipients leading to hematopoietic and immune reconstitution (IR). Immune reconstitution is defined as minimum cell count approaching lower limit of the normal range or a threshold of clinical significance e.g. absolute lymphocyte count >300/ul on post-BMT day 60.[2] The process includes the reconstitution of innate and adaptive immunity with recovery of normal immunoglobulin levels. The immune cells start reappearing in the following order: monocytes, neutrophils, and natural killer cells within weeks. In contrast, B and T cells develop from lymphoid progenitor cells and need specific microenvironments for effective differentiation from their primitive forms, usually resulting in a delayed and incomplete recovery.[3]

Various studies have been carried out evaluating immune reconstitution over the past few years. Norlin *et al* evaluated IgG levels at 3, 6, and 12 months.[4] Spadea*et al* used a multivariate model delineating IR and its key influencing factors by day 100 post-transplant.[5] ALCs and lymphocyte subtypes along with clinical outcomes at different time points following bone marrow transplant were studied by Belinovski*et a.l*[6] Immune reconstitution kinetics after bone marrow transplant done with different stem cell sources was studied by Ando *et al.*[7] They also

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studied its impact on HSCT outcomes. Elmariah*et al* reviewed IR following umbilical cord blood and haploidentical transplant.[8]

HSCT program was first introduced in Pakistan in 1995[9], and over three decades, this facility is now available in 13 centers nationwide. The main indications for transplant include beta-thalassemia, aplastic anemia, congenital bone marrow failure syndromes, and acute leukemia. There is only one study published from this country analyzing the pattern of post-transplant immune reconstitution. This study was limited to analysis at 6 months post-transplant.[10]

In this study, we determined the pattern of immune restoration following HSCT and evaluated factors that can affect immune reconstitution post-allogeneic bone marrow transplant at two different time-points.

Methodology

This observational study was done at the Department of Clinical Hematology and Bone Marrow Transplant Center, Quaid-e-Azam International Hospital, Islamabad from January 2023 to December 2024. Our study included 62 consecutive patients of all ages and both genders who underwent allogeneic bone marrow transplants for various malignant and non-malignant diseases. Our exclusion criteria included patients who had undergone autologous bone marrow transplant, had incomplete 1-year follow-up, missing laboratory reports, graft rejection, or graft failure during the follow up period. The study was reviewed and ethically approved by the Institutional Review Board (IRB BMT/QIH-350/2023) Informed consent was obtained from patients or their guardians.

Pre-transplant conditioning, stem cell collection, stem cell infusion, and GVHD prophylaxis were according to standard protocols and guidelines. Patients were kept in specialized rooms fitted with HEPA filters and a laminar airflow system. Conditioning chemotherapy was followed by stem cell infusion at day zero. Prophylaxis for Pneumocystis jerovecii was given with Pentamidine nebulization on day -1 followed by Trimethoprim-sulfamethoxazole from day 28. Oral antiviral and antifungals started from day -2. The granulocyte colony-stimulating factor was given from day 5 to when the absolute neutrophil count exceeded 1500 cells/uL. Immunosuppression commenced with Cyclosporin on day -2 and day +5 in fully HLA-matched and Haplo-matched transplants respectively. Immunosuppression was tapered off by day 180 and 365 post-transplant in the absence of GVHD in malignant and benign disorders respectively.

Pre-transplant assessment data followed by post-transplant follow-up data at 6- and 12-months was recorded on a structured proforma. The proforma included variables such as age, gender, disease, donor age, donor gender, donor relation, sex mismatch between patient and donor, ABO mismatch, type of conditioning protocol, date of transplant, source of stem cells, stem cell dose, engraftment day, cytomegalovirus (CMV) reactivation, acute and chronic graft versus host disease (GVHD). Immune reconstitution variables recorded at 6- and 12 months post-HSCT included immunoglobulin levels (IgA, IgG, IgM), absolute lymphocyte count, CD3+CD4+, CD3+CD8+, CD 19, CD 16+56 cell counts, and CD4 to CD8 ratio.

Peripheral blood samples were taken for immunoglobulin and lymphocyte subset analysis on 6- and 12 months post-HSCT. Lymphocyte subsets analysis was done by multicolor flow cytometry using BD FACSCanto™ II Flow Cytometer and included the absolute quantification of total CD3+ T cells, helper T cells ($CD3^+CD4^+$), cytotoxic T cells ($CD3^+CD8^+$), B cells ($CD19^+$), and natural killer cells ($CD16^+CD56^+$). Immunoglobulin levels were determined by radial immunodiffusion method. Lymphocyte subset recovery was compared with reference ranges as reported by Higgs *et al.*[11]

For data analysis, IBM SPSS Statistics version 23 was used. The normality of the dependent variables was assessed using the Kolmogorov-Smirnov test. The mean and standard deviation (Mean ± SD) were calculated for quantitative variables, while frequencies and percentages were calculated for qualitative variables.

Independent samples t-test was run to compare immune reconstitution variables between two distinct groups of a categorical clinical factor. One-way ANOVA with Bonferroni post-hoc correction was performed to assess differences in immune reconstitution variables across multiple groups based on ABO compatibility. Pearson correlation analysis was used to evaluate the relationship between continuous (scale) dependent and independent variables. The chi-square test of independence was applied to examine associations between categorical

dependent and independent variables. Univariate regression analysis was conducted to assess the relationship between individual independent variables and immune reconstitution outcomes. Multivariate regression analysis was conducted to determine independent predictors of immune reconstitution while adjusting for potential confounders.

Results

A total of 62 patients were analyzed for the study. Table I shows patient's and transplant characteristics and Table II shows immune reconstitution parameters. Two adverse transplant outcomes, one graft failure and one death were recorded during the study period.

Table I: Patient and transplant characteristics. (n=62)[1]	
Characteristics	Value
Age (years)	13.71±11.05
Patient's Gender n (%)	
Male	37 (59.7%)
Female	25 (40.3%)
Donor age (years)	17.14±12.42
Donor Gender n (%)	
Male	35 (56.4%)
Female	27 (43.6%)
Sex Mismatch n (%)	
Female donor to male recipient	13 (79%)
Others	49 (21%)
Diagnoses n (%)	
Beta Thalassemia Major	41 (66.1%)
Acute Lymphoblastic Leukemia	6 (9.7%)
Acute Myeloid Leukemia	7 (11.3%)
Fanconi anemia	2 (3.2%)
Aplastic Anemia	1 (1.6%)
Congenital Dyserythropoietic Anemia	1 (1.6%)
Glanzmann Thrombasthenia	1 (1.6%)
Myeloproliferative Neoplasm	1 (1.6%)
Paroxysmal Nocturnal Hemoglobinuria	1 (1.6%)
Pure Red Cell Aplasia	1 (1.6%)
TNC dose (x10^8/kg)	5.84 ±4.21
CD34 dose (x10^6/kg)	7.21±6.00
Harvest type n (%)	
BMH	58 (93.6%)
PBSC	3 (4.8%)
Both	1 (1.6%)
Transplant type n (%)	
Fully matched	57 (92%)
Haplo-matched	5 (8%)
ABO Blood group mismatch n (%)	
No ABO mismatch	43 (69.4%)
Minor ABO mismatch	11 (17.7%)
Major ABO mismatch	8 (12.9%)
Conditioning type n (%)	
MAC	59 (95.2%)
NMA	3 (4.8%)
CD-34 cell dose (x10^6/kg) n (%)	
≥4	14 (22.6%)
<4	48 (77.4%)
TNC dose (x10^8/kg) n (%)	
≥4	31 (50%)
<4	31 (50%)
aGVHD n (%)	
Yes	19 (30.6%)
No	43 (69.4%)
cGVHD n (%)	
Yes	11 (17.7%)
No	51 (82.3%)
CMV I/R n (%)	
Yes	24 (38.7%)
No	38 (61.3%)

Table II : Immune Reconstitution Paramètres (n=62)	
Parameters	Mean±SD
Neutrophil Engraftment Day	12.23±1.84
IgA levels at 6 months (g/L)	1.37±0.76
IgG levels at 6 months (g/L)	11.76±4.78
IgM levels at 6 months (g/L)	0.96±0.41
Absolute Lymphocyte cell count at 6 months (cells/ul)	2264.7±810
CD3+CD4+ cell count at 6 months (cells/ul)	363±178
CD3+CD8+ cell count at 6 months (cells/ul)	1092.9±520.8
CD19+ cell count at 6 months (cells/ul)	296.6±205.2
CD16+CD56+ at 6 months (cells/ul)	243.1±160.7
CD4:CD8 at 6 months	0.36±0.17
IgA levels at 1 year (g/L)	1.51±8.4
IgG levels at 1 year (g/L)	13.2±5.6
IgM levels at 1 year (g/L)	1.0±0.5
Absolute Lymphocyte cell count at 1 year (cells/ul)	2822.1±1049
CD3+CD4+ cell count at 1 year (cells/ul)	555.3±224
CD3+CD8+ cell count at 1 year (cells/ul)	1231.6±544.4
CD19+ cell count at 1 year (cells/ul)	417.1±215.5
CD16+CD56+ at 1 year (cells/ul)	196.3±113.6
CD4:CD8 ratio at 1 year	0.52±0.3

[1]*Key: aGVHD – Acute graft versus host disease BMH – Bone marrow harvest, cGVHD – Chronic graft versus host disease, CMV I/R: Cytomegalovirus infection and reactivation, MAC – Myeloablative conditioning, NMA – Non myeloablative conditioning, PBSC – Peripheral blood stem cells, TNC – Total nucleated cells*

The absolute lymphocyte count recovery at 6 months was seen in 77.4%, which increased to 86.9% at 12 months-HSCT. Lymphocyte subset and immunoglobulin recovery patterns are summarized in Figure 1 & 2 respectively.

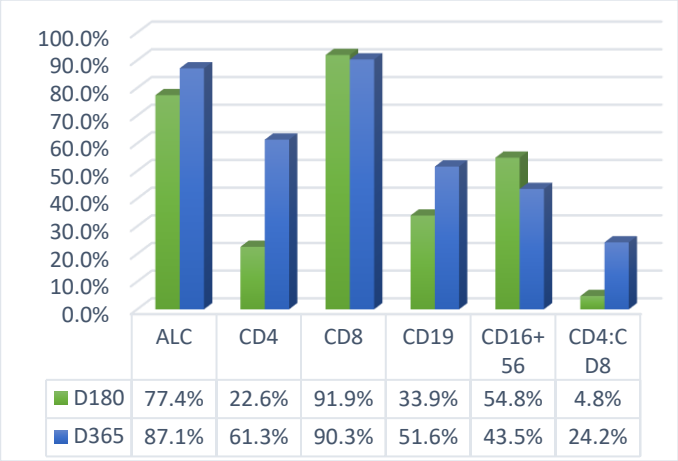

Figure 1: Lymphocyte subset recovery pattern.

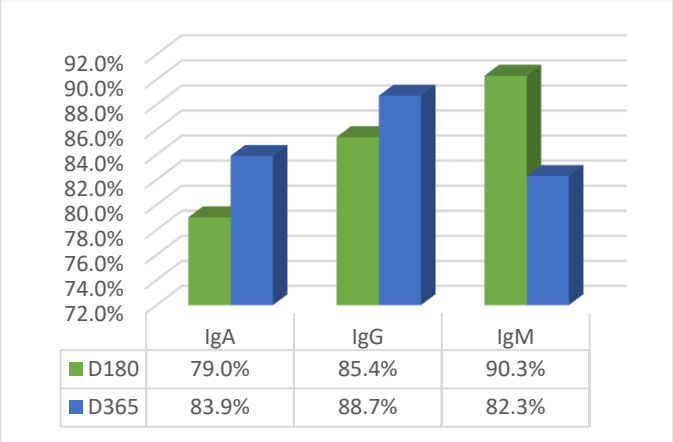

Figure 2. Immunoglobulin levels recovery pattern.

To compare neutrophil engraftment day, immunoglobulin levels and lymphocyte subset recovery among patients, four groups were selected: 1. Benign versus Malignant; 2. Adult versus Pediatric; 3. MAC versus NMA conditioning and 4. Female Donor to Male Recipient versus Others. Mean neutrophil engraftment day was 12.46 in benign group compared to 11.43 days for malignant group, the difference being statistically significant (p=0.04). Mean of CD3+CD4+ count (cells/ul) at 1 year in benign cases was 590.79 versus. 424.31 in malignant cases (p=0.001). Means of IgG levels (g/L) at 1 year were significantly lower in benign compared with malignant group; 12.39 versus 16.36 (p=0.02). In adults, mean value of CD3+CD4+ cell count (cells/ul) at 1 year was 436.50 compared to 584.41 (p=0.04) in pediatric group while IgG levels (g/L) at 1 year had higher mean value in the adult group than pediatric 17.09 opposed to 12.29 (p=0.01). CD19+ cell count (cells/ul) at 6 months was significantly lower in the MAC group having a mean 288.6 versus 454 in NMA (p=0.003). As for the IgA levels (g/L) at 6 months, the MAC group had significantly (p=0.01) higher mean (1.4) than NMA (0.73). Mean IgA levels (g/L) were lower in female donor-to-male recipients (1.4) compared to other donor-to-recipient group 0.97 at 6 months (p=0.033) and 1.6 versus 1.0 (p=0.017) at 1 year respectively. The female donor to male recipient group had higher mean cell counts than other donor-to-recipient group for CD16+CD56+ (cells/ul) at 6 months 324.3 against 221.5 (p=0.04) and for CD3+CD4+ (cells/ul) at 1 year 638.6 versus 532.7 (p=0.02). There was no significant difference observed in means of CD3+CD8+, CD19+ and CD16/56 in benign versus malignant and adult versus pediatric groups. IgG, CD3+CD4+, CD3+CD8+, CD16/56 and IgG, CD3+CD8+, CD19+ were insignificant for the remaining two groups (p value > 0.05).

Significant difference was observed among donor-recipient ABO compatibility groups for IgG levels at 6 months (p=0.009), lymphocyte count at 1 Year (p=0.002), and CD16 and 56 cell count at 1 Year (p=0.005), while the differences for neutrophil engraftment day, IgA, IgM levels, absolute lymphocyte, CD3+CD4+, CD3+CD8+, CD19+, CD16+CD56+ cells count at 6 months and IgA, IgG, IgM levels, CD3+CD4+, CD3+CD8+, CD19+ cells count, CD4:CD8 ratio at 1 year were not significant (p-value > 0.05). To further characterize the donor patient ABO compatibility, post-hoc analysis with Bonferroni correction was done to see the differences among major, minor, and no ABO mismatch groups. Mean IgG levels at 6 months were significantly higher in minor ABO-mismatched transplants compared with major ABO-mismatched transplants (p=0.04). Surprisingly, major ABO-mismatched transplants had a higher absolute lymphocyte and CD16+CD56+ count recovery at 1 year followed by ABO-identical (p=0.003) and minor ABO-mismatched (p=0.003) groups. No significant difference was observable for CD4 and CD3+CD8+ cell recovery between these groups (p>0.05).

Chi-square found significant associations between immune reconstitution variables and various clinical factors. Immunoglobulin A recovery at 6 months was seen in 54% patients with female donor to male recipient versus 86% for non-female donor to male recipient (p=0.012). Similarly, 45% with cGVHD and 86% without cGVHD had IgA recovery (p=0.003). IgG recovery at 6

months was seen in 87% HLA matched sibling transplants, the values were 75% and 50% for HLA matched parents and matched related donors (p=0.035). In case of cGVHD, 90% of patients without cGVHD and 63% with cGVHD had IgG recovery (p=0.023). TNC dose/kg was associated with CD19+ cell recovery, B cells recovery was seen in 19.3% of patients receiving TNC dose ≤ 4 x 10^8/Kg while 48% receiving dose >4 x 10^8/Kg (p=0.016). The same trend was not seen with CD34 cell dose. CD16+CD56+ NK cell count expansion was positively associated with CMV exposure (p = 0.044) with 70% of patients with CMV-positive PCR achieving the recovery versus 44% with negative CMV-PCR. The CD34 cell dose was positively associated with both IgG and + cell recovery at 1 year post HSCT (p = 0.020, p = 0.026 respectively). Ninety three percent of patients receiving CD34 dose >4 x 10^6/Kg and 71% with dose ≤4 had IgG recovery while the values for CD3+CD4+ cell recovery were 68% and 36% respectively. No significant association was observed between disease type, harvest type, transplant type, conditioning type and acute GVHD with immune reconstitution variables (p>0.05). A positive correlation was seen at 6 months between CD3+CD4+ and CD19+ cell count with patients receiving high TNC/MNC dose (p<0.05). A similar trend was observed between IgG levels at 1 year and patient's age (p<0.01). CD19+ cell count at 6 months and 1 year was negatively correlated with increasing donor's age (p<0.05). Similarly, low CD16+CD56+ NK cell recovery was seen in older patients at 6 months (p<0.05). Also, older patients had lower CD3+CD4+ recovery at 1 year (p<0.01).

To predict the outcome variables, binary logistic univariate regression analysis was run between independent and dependent categorical variables, and the significant results. High TNC dose was a significant predictor of CD19+ count at 6 months (p = 0.019), with TNC dose >4 x 10^8/kg having 3.906 odd ratio. Female donor to male recipient had lower IgA recovery at 6 months (p=0.02, OR 5.143) as compared to non-female donor to male recipient. For IgM levels at 1 year, gender was a significant predictor (p=0.044) with males having higher IgM recovery than females (8.88 OR Patients receiving CD 34 dose ≤4 predicted high CD3+CD4+ count and IgG levels at 1 year (p = 0.03 & 0.03; OR 3.96 & 6 respectively). While aGVHD was predicted by CD34 dose >4 (p=0.019, OR 0.2). Benign disease predicted better CD19+ cell recovery (p=0.006, OR 19.84).

On multivariate logistic regression analysis predicting CD19+ levels at 1 year, all predictor variables including age group and diagnosis group were found insignificant (p value >0.05).

Discussion

Our study investigated the pattern of immune reconstitution in post-HSCT patients at two-time points; 6 months and 12 months post-transplant, focusing on the associations between various clinical factors and humoral and cellular immune recovery. We hypothesized that immune recovery patterns might differ based on underlying disease (benign versus malignant), recipient age, donor age, source of stem cells (bone marrow versus PBSC), graft characteristics (TNC and CD34 dose), CMV reactivation and presence of aGvHD and cGVHD. Our results showed adequate immune reconstitution at 6 months post-transplant except for CD3+CD4+ lymphocytes. Absolute lymphocyte count recovery was seen in 77% of the patients, between the subsets CD3+CD8+ achieving the highest rate (91.9%), followed by CD16+CD56+ (54.8%), CD19+ (33.9%) and CD3+CD4+ (22.6%). Belinovski*et al*, Lankester *et al* and Rahim *et al* have also reported similar patterns of immune recovery post-HSCT at 100 and 180 days respectively. However, Belinovski*et al*. reported better recovery of CD3+CD4+ cells than CD19+. The same results were seen in our study at 12 months post-transplant where CD3+CD4+ cells recovery exceeded CD19+ cells reconstitution making B cells the last to recover.[6,10,12] Age came out as a significant predictor of cellular recovery. Our study showed better CD3+CD4+ recovery in pediatric patients compared with adults. This result confirms several literature reports done in the past[6]. A decrease in the thymic function with age is a well-established phenomenon leading to reduced output of naive T cells. The more robust B cell recovery in younger patients is clinically relevant, as it may contribute to better humoral immunity. Unexpectedly, CD34 dose < 4 x 10^6/Kg had better CD3+CD4+ cell recovery compared with > 4 x 10^6/Kg dose. This could have been due to the finding that patients receiving >4 x 10^6/Kg CD34 dose had more aGVHD in our study. The delayed immune recovery may be explained by the presence of a high number of CD3+ cells within the high CD34+ stem cell dose, which increases the risk of aGVHD, and the management of aGVHD further delays

the IR. Acute GVHD is primarily driven by alloreactive donor T cells following activation by host antigen-presenting cells, ultimately targeting various host tissues. This is associated with impaired IR, yet whether aGVHD is the cause or consequence remains uncertain.[13,14]

Benign disease and lower incidence of aGVHD were found to be associated with early CD3+CD4+ recovery. The same associations were seen in a study at one of Brazil's largest pediatric HSCT centers.[6] For immunoglobulin recovery, low IgG levels after SCT were associated with older age (>18 years), major ABO mismatch, donors other than siblings, low CD34 dose, and presence of acute GVHD. The association of low IgG levels with age <30 years and aGVHD were also the findings of a retrospective study done in Sweden[4].CMV seropositive status had a significant association with CD16+CD56+ (NK cell) counts at 6 months. This is expected since CMV infection is a potent stimulus for NK cell expansion and differentiation. NK cells are crucial in controlling CMV infection, and their recovery is an important aspect of immune reconstitution. These findings are consistent with the findings of a study done in UK which showed that CMV reactivation causes long-term expansion and differentiation of CD16+CD56+ cells.[15,16] At 1-year post-transplant, patients with age >18 years and malignant diseases had significantly lower CD19+ B cell counts compared to those with benign conditions. This suggests that the underlying malignancy, or the more intensive therapies often used to treat it (e.g., prior chemotherapy, irradiation), may have a lasting impact on B cell recovery. This finding has important clinical implications, as impaired B cell reconstitution can increase the risk of infections.[17]

We had several limitations of our study that include, it is single-center study design, limited sample size, heterogeneity of our patients and the primary disease, variability in conditioning regimen, limited functional assays, and differences in post-transplant immunosuppression therapy. Consequently, the findings of this study may not be generalizable.

Conclusion

Our study revealed that factors like benign disorders, younger age and absence of aGVHD are associated with early IR, while delayed immune reconstitution was seen in patients with older age, malignant diseases, major ABO mismatch, donor other than siblings and presence of acute GVHD.

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Disclosure: The study abstract at an initial stage with less number of patients was accepted and published at the 66th ASH Annual Meeting 2024 (Publication Number: 7337).

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