



# Biology of Blood and Marrow Transplantation

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## Preemptive Bone Marrow Transplantation for *FANCD1/BRCA2*



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### ABSTRACT

Children with biallelic mutations in *FANCD1/BRCA2* are at uniquely high risks of leukemia and solid tumors. Preemptive bone marrow transplantation (PE-BMT) has been proposed to avoid the development of leukemia, but empirical study of PE-BMT is unlikely because of the rarity of these children and the unknown benefit of PE-BMT. We used survival analysis to estimate the risks of leukemia and the expected survival if leukemia could be eliminated by curative PE-BMT. We used the results in a decision analysis model to explore the plausibility of PE-BMT for children with variable ages at diagnosis and risks of transplantation-related mortality. For example, PE-BMT at 1 year of age with a 10% risk of transplantation-related mortality increased the mean survival by 1.7 years. The greatest benefit was for patients diagnosed between 1 and 3 years of age, after which the benefit of PE-BMT decreased with age at diagnosis, and the risk of death from solid tumors constituted a relatively greater burden of mortality. Our methods may be used to model survival for other hematologic disorders with limited empirical data and a pressing need for clinical guidance.

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### INTRODUCTION

Fanconi anemia (FA) is a primarily autosomal recessive inherited bone marrow failure and cancer predisposition syndrome, caused by germline mutations in more than 16 genes involved in the *FA/BRCA* DNA damage response pathway [1]. Patients with FA have an approximately 800-fold increased risk of developing leukemia and an overall risk of more than 50-fold for any malignancy or solid tumor; the cumulative incidence of severe bone marrow failure is more than 50% by age 45 years [2]. Characteristic birth defects frequently associated with FA include short stature, café au lait spots, microcephaly, thumb and radial anomalies, and renal structural defects [1]. Biallelic mutations in *FANCD1/BRCA2* have been reported in rare patients with FA with very early-onset leukemia and solid tumors. An analysis of 27 published cases with these mutations found that the cumulative incidence of any malignancy was 97% by 6 years of age and the actuarial risks of leukemia and solid tumor were 79% by 10 years of age and 83% by 7 years of age [3].

Bone marrow transplantation (BMT) is currently the only treatment that has the potential to restore normal

hematologic function in patients with any FA genotype who have bone marrow failure, myelodysplastic syndrome (MDS), or leukemia [4]. The best results were found in recent European experience to involve a matched family donor, patients younger than 10 years of age, transplantation without irradiation, and bone marrow failure without MDS or leukemia, similar to earlier results from the Center for International Blood and Marrow Transplant Research [5,6]. In patients with FA, overall 5-year survival of 80% to 90% may be expected for matched sibling donor transplantation versus 60% to 75% for transplants from unrelated donors [5]. Survival is lower in patients with hematologic malignancies, in part because of the more frequent use of mismatched or unrelated donors and more intensive marrow suppression.

Patients with FA due to biallelic mutations in *FANCD1/BRCA2* have an inordinately high and early risk of leukemia, leading to the suggestion that earlier transplantation be considered before the development of severe cytopenias [4]. There are no published data on the results of such transplantations, however. Through 2013, 10 patients with *FANCD1/BRCA2* who underwent transplantation after they had developed leukemia (with 1 exception who had neutropenia, see Table 1) were reported, with only 2 survivors [7–12]. Seven died less than 1 year after transplantation. These patients were not ideal candidates for transplantation, as 8 had acute myeloid leukemia and 1 acute lymphoblastic

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**Table 1**  
Hematopoietic Stem Cell Transplantation in Patients with *FANCD1/BRCA2* Mutations Reported in the Literature, 2000 to 2013

ID	Age at Hematologic Abnormality, yr	Reason for BMT	Age at BMT, yr	Interval Survival after BMT, yr	Donor	Stem Cell Source	Outcome	Age at Last Report, yr	Reference
AP37P	2.0	AML	2.2	1.67	HLA identical sibling	BM	Dead	3.87	[7]
632/1	3.0	AML	3.7	0.33	6/6 URD	BM	Dead	4.0	[8,9]
632/2	1.75	AML	1.9	0.80	6/6 MSD	BM	Dead	2.7	
800/1	0.9	AML	1.8	0.34	6/6 URD	TCD BM	Dead	2.1	
800/2	0.9	Neutropenia	0.8	0.17	6/6 URD	TCD BM	Dead	0.97	
900/1	5.2	ALL	4.9	2.50	5/6 Mother	TCD BM	Alive	7.4	
984/2	4.9	ALL-AML*	6.7	0.58	6/6 URD	UCB	Alive	7.3	
2751	5.5	AML	5.5	0.50	4/6 and 7/10 related	PB	Dead	6.0	[10]
PT 2	1.7	AML	1.7	0.40	MUD 8/8	NA	Dead	2.1	[11]
Case	2.0	AML	2.0	0.83	HLA identical sibling	BM	Dead	2.8	[12]

ID indicates identifier; AML, acute myeloid leukemia; BM, bone marrow; URD, unrelated donor; MSD, matched sibling donor; TCD, T cell depleted; ALL, acute lymphoblastic leukemia; UCB, umbilical cord blood; PB, peripheral blood; PT 2, patient 2; MUD, matched unrelated donor; NA, not available.

\* Patient had T cell ALL at 4.9 yrs of age, went into remission with chemotherapy, and relapsed with AML at 6.3 yrs of age. While being worked up for BMT, a Wilms tumor was found; after nephrectomy, the patient proceeded to transplantation at age 6.7 yrs.

leukemia [5,13,14], only 3 had matched sibling donors, 5 had unrelated donors, and 2 had partially matched related donors. Cord blood was used in 1 case, peripheral blood in 1, and bone marrow in the others.

BMT before the development of symptomatic hematologic problems might increase overall survival in patients with FA, particularly in those with *FANCD1/BRCA2*. Healthy transplant recipients (even with FA) would presumably have better tolerance of the complications associated with a BMT, and a successful transplantation is anticipated to eliminate the future risk of MDS or leukemia. We have chosen to call this type of transplantation “preemptive” (PE-BMT) [15], as it is preventive, rather than early, which implies that the outcome being avoided is inevitable, and the only issue is the timing. In reality, only about one half of the patients with *FANCD1/BRCA2* are predicted to develop leukemia in their lifetime because of the competing risks of solid tumors and death. However, BMT carries nontrivial risks of mortality and morbidity, and exposing an otherwise healthy child to a risky procedure of unknown benefit violates “primum non nocere (first do no harm)” [16]. A clinical trial of PE-BMT in those with *FANCD1/BRCA2* is not feasible because of the rarity of such patients and the uncertainty regarding the risks and potential rewards of transplantation in this population.

To address this question, we used statistical methods and decision analysis to explore the utility of PE-BMT in this context. Decision analysis provides a mathematical structure for weighing the risks and benefits of competing strategies. We estimated the overall survival curve if leukemia could be eliminated from the *FANCD1/BRCA2* population (actuarial risks) and used the results in a decision analysis to examine the possible benefits of PE-BMT compared with current standard care. We relied on the limited number of published cases with *FANCD1/BRCA2* for data on overall survival and development of malignant complications (acute myeloid leukemia, brain tumors, Wilms tumors, and other solid tumors) before BMT [3,10-12,17-19].

## METHODS

### Decision Model

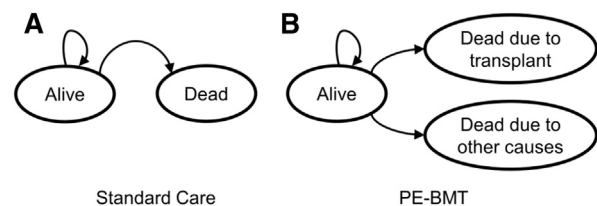
We developed a Markov decision model from the parental perspective to determine how PE-BMT at 1 year of age would affect the mean survival of children with *FANCD1/BRCA2* compared with a strategy of standard care according to the recent literature reports. Markov, or state-transition, models allow for the recursive simulation of events and risks that change over time and have been used by others to simulate outcomes of BMT strategies in the presence of uncertainty [20-22]. In our Markov model, a cohort of hypothetical cases transition between 2 mutually exclusive states—alive and dead—over multiple cycles (Figure 1). All hypothetical

cases begin in the alive state and transition over time to the dead state, out of which they cannot transition. Cases receiving standard care have a probability of transitioning to the dead state that is equal to the age-dependent conditional probability of dying among cases reported in the literature. Children with *FANCD1/BRCA2* receiving PE-BMT are at risk of dying from malignancies other than leukemia or from transplantation-related mortality (TRM). TRM is the excess mortality attributable to BMT, including risks of infection, graft-versus-host disease (GVHD), and regimen-related toxicity, which is distinct from other causes of death in this population, such as solid tumors. We biased our model in favor of PE-BMT and posited that PE-BMT would not affect the incidence of solid tumors or other causes of death and that the risk of leukemia would be eliminated. BMT in other FA complementation groups was associated with an increased incidence of head and neck squamous cell carcinoma compared with FA patients who did not have a BMT [23]. However, cancer risks associated with more recent conditioning regimens may be lower, and the solid tumors (midline brain, and Wilms tumors) observed in *FANCD1/BRCA2* are different from those in other FA groups (head and neck and gynecologic squamous cell carcinomas); the risks may not be increased by BMT or GVHD.

We chose a cycle length of 3 months, evaluated the decision over 160 cycles, or 40 years duration after transplantation, and we assumed that all events occur half-way through each cycle (“half-cycle correction”) [24]. We did not adjust the expected survival to reflect decrements in quality of life because we could not find health-state utilities from the parental perspective applicable to our very young population. Hence, we developed a model to provide objective estimates of survival to be used by parents in the context of a family’s values and circumstances. We also did not discount the value of future life-years. We modeled the decision conditioned on survival to ages ranging from 3 months to 10 years to determine at what ages PE-BMT might remain feasible; this analysis informs the decision for patients diagnosed with FA at various ages. All annual probabilities and rates were transformed to the appropriate 3-month equivalents (see Supplement for details). The decision model was implemented in TreeAge Pro 2014 (TreeAge Software, Inc, Williamstown, MA).

### Data Sources

We included the 36 cases of patients with *FANCD1/BRCA2* published between the years 2000 through 2013 in our analysis [3,10-12,17-19]. We fit several parametric survival curves, including exponential, Weibull,



**Figure 1.** Markov decision model for children with *FANCD1/BRCA2*. Hypothetical cases transition through the model in 3-month intervals. (A) Beginning in the alive state, patients receiving standard care are at risk of dying from any cause similar to what is expected historically (leukemia or solid tumors). (B) Patients receiving PE-BMT are at risk of dying from causes related to transplantation or from causes other than leukemia, such as solid tumors.

Gompertz, log-normal, and log-logistic functions, to estimate survival from any cause of death, and we used Akaike information criterion and visual inspection to assess goodness-of-fit. We estimated the (hypothetical) actuarial survival of children with *FANCD1/BRCA2* if leukemia could be eliminated from this population by censoring cases at the development of leukemia and counting death as an event. We calculated the cumulative incidence function in the presence of competing risks [25] and the complement of the Kaplan-Meier product-limit estimators [26] to determine the crude and actuarial risks, respectively, of leukemia and other causes of death. Whereas the crude risk reflects the proportion of patients who experience an event, the actuarial risk represents the hypothetical proportion of patients who would experience an event if the risks of competing events could be removed. All survival analyses were conducted using Stata/SE 13.1 (StataCorp LP, College Station, TX).

The presumptive advantage of PE-BMT is that providing transplantation to healthy children with FA without leukemia would yield better outcomes than providing transplantation to such children presenting with leukemia, and that by eliminating the risk of leukemia from this population, the children would have greater overall survival. However, because of the particularly early onset of leukemia in these children, an effective policy of preemption would require transplantation during infancy, an age group for which there are no data on TRM for FA. Rather than compare infants with *FANCD1/BRCA2* to adolescents with FA in other complementation groups, we consulted recent publications on BMT in infants with severe combined immunodeficiency or Hurler syndrome who received a BMT within the first year of life (and were without infection at the time of BMT) to estimate a plausible risk of TRM (10%) in otherwise healthy infants (ie, those without a malignancy) [27,28]. For our base case of a 1-year-old patient with *FANCD1/BRCA2*, we assumed that the cumulative probability of TRM was 10% and that this risk would be spread evenly over the first year after transplantation.

#### Sensitivity Analysis

We varied the decision over a range of ages at BMT and of risks of TRM (Table 2). Long-term survival after BMT in infants and young children with nonmalignant disorders, such as severe combined immunodeficiency or Hurler syndrome, was reported to range from 50% to 95%, with most of the mortality occurring within the first year after BMT [27,28]. We thus explored how the decision would change over a wide range of TRM, between 0% and 60% over 1 year after transplantation. We performed 1-way and 2-way sensitivity analyses and present threshold values of TRM at which a given strategy has superior mean survival.

## RESULTS

### Survival Analysis

We determined that log-logistic functions provided the best fit for estimating both overall survival and the hypothetical survival if leukemia could be eliminated from the published *FANCD1/BRCA2* population (see Supplement for parameterizations). The median overall survival estimated by the parametric models was 3.5 years of age and the 10-year overall survival was 8% (Figure 2A). The crude risks of leukemia and death from other causes after treating these as competing risks were 49% (95% confidence interval [CI], 32% to 65%) and 48% (95% CI, 30% to 63%) by 10 years of age, respectively (Figure 2B). The actuarial risk of leukemia (if the risk of death from other causes could be removed) was 79% (95% CI, 53% to 95%) by 10 years of age. If the risk of leukemia could be eliminated in this population, the median survival would be 5 years of age and the 10-year overall survival

would be 19% (Figure 2C) because of the high risk of brain and Wilms tumors in this population. The per-year hazard (rate) of death from any cause (mainly leukemia or solid tumors) was largest at 4 years of age (Figure 2D, dotted line). The hazard of death from causes other than leukemia would peak around 5 years of age if the risk of leukemia could be removed (solid line).

### BASE CASE RESULTS AND SENSITIVITY ANALYSES

For 1-year-old patients receiving standard care, the mean survival was an additional 4.1 years, the median survival was an additional 2.8 years, and overall survival after 5 years and 10 years was 24% and 7%, respectively (Figure 3A, dotted line). Under a base case strategy of PE-BMT at age 1 year and a 10% risk of TRM over 1 year (solid line), the mean survival was an additional 5.8 years, the median survival was an additional 3.8 years, and overall survival 5 and 10 years after transplantation was 39% and 15%, respectively. Thus, PE-BMT at 1 year of age increased the mean survival by 1.7 years and the median survival by 1.0 years; hence, PE-BMT was the dominant strategy under base case assumptions. Similar analyses are shown in Figure 3B and C, suggesting that PE-BMT provides the most survival benefit when performed when the child is younger than 3 years of age.

As noted above, for children diagnosed at 1 year of age, the expected survival with no intervention is an additional 4.1 years (Figure 4A). PE-BMT would increase the mean survival by 2.3 years if there were no TRM (Figure 4B) or 1.7 years with a 10% risk of TRM, and PE-BMT would remain the superior strategy so long as the risk of TRM over 1 year was 38% or lower. If instead PE-BMT carried a 60% risk of TRM, the expected survival would decrease by 1.3 years. Consider next a child presenting at 6 months of age. The mean survival expected in the absence of PE-BMT is an additional 4.5 years (Figure 4A). PE-BMT with a 10% risk of TRM would increase the expected survival by 1.7 years (Figure 4B). If the decision were made for a child of 3 years of age, the expected survival would increase by a similar amount, 1.6 years. More generally, PE-BMT remained a viable option at low risks of TRM but ceased being the superior strategy for children presenting at ages older than 5 years with risks of TRM greater than 30%. However, the small numbers of published cases of older children and adolescents with *FANCD1/BRCA2* limit our confidence in projections made for children presenting for PE-BMT at ages older than 3 years.

### DISCUSSION

PE-BMT may increase the mean survival of children with *FANCD1/BRCA2* if the procedure is safe enough and the timing is early enough. In our modeling scenarios, “safe enough” in this high-risk setting corresponds to 1-year TRM below 30% and “early enough” is providing transplantation for children younger than 5 years of age. The potential benefit of PE-BMT was very sensitive to the risk of TRM but less sensitive to the age at PE-BMT. Our results depend on the validity of our parametric models for the competing risks of death from leukemia and other causes, which include solid tumors, especially brain and Wilms tumors. However, our risk estimates reflect the totality of cases reported through 2013, and our modeled survival curves appear to adequately recapitulate the observed experience.

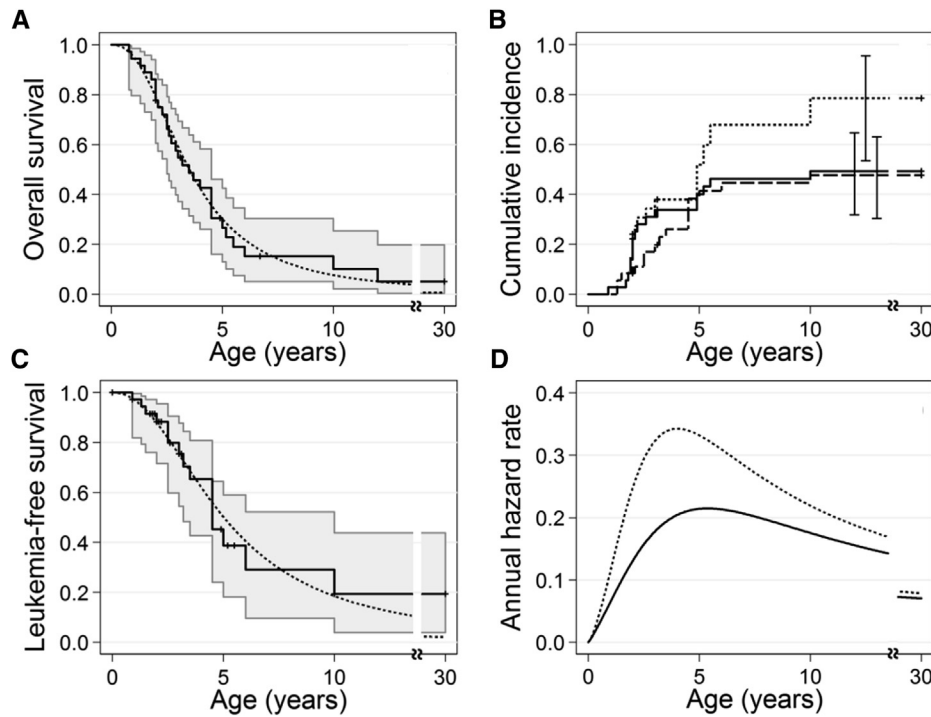
Although the permissible risk of TRM for PE-BMT is higher than what has been reported in BMT among children

**Table 2**  
Markov Model Parameters and Range Tested in Sensitivity Analysis

Model Parameter	Base Case Value(s)	Range Used in Sensitivity Analysis	Source
Overall survival	Age dependent	*	Figure 2A
TRM over 1 yr	10%	0%-60%	Pai et al. [27]
Survival after PE-BMT	Age-dependent	*	Figure 2C
Age at decision	1 yr	.25-10 yr	N/A

N/A indicates not available.

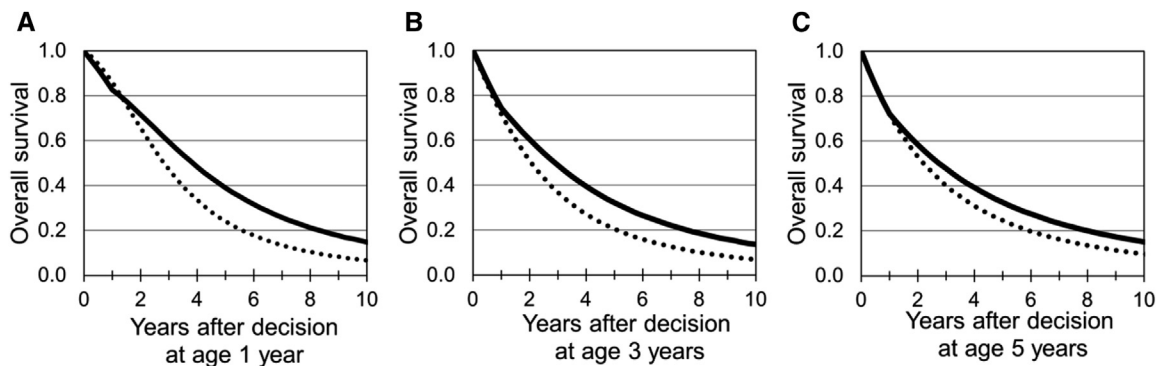
\* Probabilities were not varied in sensitivity analysis.



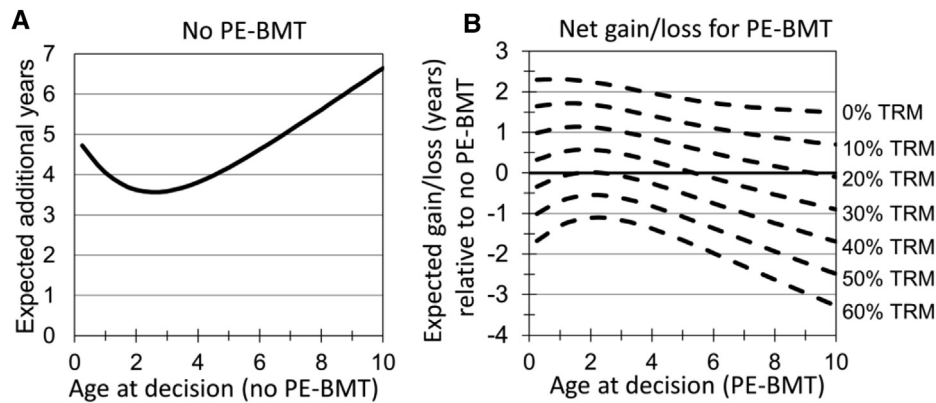
**Figure 2.** Survival in patients with *FANCD1/BRCA2*. (A) Overall survival. Both nonparametric Kaplan-Meier (solid line) and log-logistic parametric (dotted line) estimators indicate poor survival; less than 10% are expected to survive into their teens. Shaded area indicates 95% confidence intervals. The last survivor was lost to follow-up at age 30. (B) Crude and actuarial risks of leukemia. The actuarial risk of developing leukemia (dotted line) is 79% by age 10. Treating leukemia and death from other causes as competing risks, the crude risks of leukemia (solid line) and death from other causes (dashed line) are 49% and 48% by age 10, respectively. The vertical lines indicate the 95% confidence intervals at those fixed ages. (C) Survival if the risk of leukemia could be eliminated. We censored at the development of leukemia. Both nonparametric Kaplan-Meier (solid line) and parametric log-logistic (dotted line) functions estimated that in the absence of leukemia, 20% would survive until age 10. (D) Annual hazard rates. We plotted the per-year hazard rates for overall survival (dotted line) and survival if leukemia could be eliminated by PE-BMT (solid line). The hazard rate for overall survival peaks between 4 and 5 years of age while the hazard rate for survival if leukemia could be eliminated peaks at 5 years of age.

with other FA complementation groups [5,13,29] and in infants who undergo transplantation for other conditions [27,28], the expected survival after PE-BMT is still notably short because of the greater competing risks. Even if there were no risk of TRM from PE-BMT, the median survival of this population would be 5 years of age because of the mortality imposed by the solid tumors (Figure 2C). Improved treatment regimens for the solid tumors associated with *FANCD1/BRCA2* are likely to play as big a role in increasing life expectancy as will improvements in survival after BMT.

We did not explicitly model the influence of donor and stem cell source. Among FA patients with other complementation groups who underwent transplantation for any reason between the years 2000 and 2009, nonrelapse mortality after 1 year was 14% for those with matched sibling donors versus 24% for those with matched unrelated donors (nonrelapse mortality is a proxy for TRM) [5]. PE-BMT would, thus, seem a viable option for many with matched sibling donors but for relatively few with matched unrelated donors. Importantly, an individualized risk of TRM for any given patient-donor combination depends on a number of risk



**Figure 3.** Simulated survival curves for cohorts of children presenting for PE-BMT. (A) PE-BMT after presentation at 1 year of age. Simulated survival curve for children receiving PE-BMT at age 1 year (solid lines) compared with what could be expected if no preemptive action is taken (dotted lines). (B) PE-BMT after presentation at 3 years of age. (C) PE-BMT after presentation at 5 years of age. Estimates rely heavily on extrapolation.



**Figure 4.** Expected survival of children presenting at ages up to 10 years. (A) Expected survival of children with no PE-BMT. The expected (mean) survival of children (y-axis) after presenting at age in years (x-axis). If no preemptive action is taken, a child presenting at 1 year of age is expected to survive an additional 4 years. (B) The net gain/loss in expected survival from PE-BMT. The additional expected life-years gained or lost (y-axis) by receiving PE-BMT at an age at presentation ranging from birth to 10 years (x-axis) and risk of TRM ranging from 0% to 60% over 1 year (dotted lines). PE-BMT at 1 year of age and a 10% risk of TRM would increase the expected survival by 1.7 years. Estimates for ages greater than 3 years rely heavily on extrapolation.

factors associated with survival, including stem cell source, donor-recipient gender or cytomegalovirus status mismatch, and conditioning regimen—factors that are not formally included in our model. These factors should be qualitatively assessed as increasing or decreasing the risk for the individual patient at hand versus the population average risk.

Whether parents would elect for their child to undergo PE-BMT is unknown if the survival benefit offered by PE-BMT is only marginal; if there were no risk of TRM, an optimally timed preemptive transplantation would increase the mean survival by less than 2.5 years. There is also a potential ethical concern about performing a risky procedure on an apparently healthy child. For example, in a study of parental decision making for children with sickle cell disease, 15% of parents stated they would refuse a curative bone marrow transplantation even if there were no excess risk of mortality, and only 36% of parents were willing to accept a 15% or greater risk of short-term mortality [30]. Although children with sickle cell disease do not face the same types of risks as children with *FANCD1/BRCA2*, the aversion to BMT for sickle cell disease in the absence of symptoms is illustrative of parental aversion to any procedural risk.

The quality of life for patients with *FANCD1/BRCA2* and for their families should also factor into shared decision making. This is complicated, as the parents are proxies for their young children, and it is difficult to evaluate using traditional quality of life instruments in this context. Certainly, BMT in pediatric populations is associated with decreased quality of life that has both physical and psychosocial bases. Development of GVHD and infection are associated with a worse quality of life [31]. In addition, children who receive BMT are kept in protective isolation, both inside and outside the hospital in the months after BMT, which may affect their development at a critical time. Neurocognitive delays were found to be most significant in young patients (ages 0 to 3 years), particularly in those who had received total body irradiation [32]. It is difficult to estimate how hospitalization per se impacts the development of children. Even for those who do not undergo BMT, management of solid tumors in this population may also interfere with development and lead to significant other late effects [33].

Despite obvious limitations of decision analysis methodology, our results provide an objective quantification of risks versus benefits that can help parents and physicians decide

whether or not to pursue PE-BMT for children with *FANCD1/BRCA2*. Furthermore, the methods discussed here can be utilized in the context of other disorders for which hematologic malignancy is a major concern.

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#### SUPPLEMENTARY DATA

Supplementary data related to this article can be found at [10.1016/j.bbmt.2015.07.006](https://doi.org/10.1016/j.bbmt.2015.07.006).

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