Oral Health-Related Quality of Life in Pediatric Hematopoietic Cell Transplant Survivors

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Abstract

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Background: Radiation, chemotherapy, and graft versus host disease (GVHD) associated with HCT can result in oral and dental late effects that persist throughout survivorship. Few studies have documented how these changes affect survivors of pediatric HCT.

Aim: Determine the incidence of oral health concerns and their effects on oral health-related quality of life (OHRQoL) among a population aged 2-30 years that underwent HCT as children.

Methods: A 21-item survey was sent to 351 patients and their families in one of 3 versions, depending on patient age. Eligible respondents had received an HCT at Seattle Cancer Care Alliance at age <21.0 years, were at least 1 year post-transplant, and had received their HCT within the last 10 years.

Results: One hundred and forty-nine (42%) patients returned the survey. Mean patient age at the time of transplant was 9.0 years, mean age at the time of survey was 13.9 years. Health concerns in the last month were reported by 66% of responders. The majority (79.9%) received an allogeneic transplant; 91.9% underwent myeloablative conditioning; 52.4% received TBI as part of their conditioning. The presence of one or more oral health concerns was associated with increased years since transplant (OR= 1.18, 95% CI 1.01-1.37, multivariate analysis). Patients who were older at the time of survey were more

likely to report two or more symptoms (OR=1.06, 95% CI 1.01-1.12). For those transplanted <6 years old, patients who received ≥ 12 Gy TBI reported more dental development concerns than those that had no TBI (OR=2.57, 95% CI 0.61,10.83). Most patients who had a diagnosis of oral cGVHD were aware of this, but 10% were not. The majority of respondents (74.5%) reported seeing a dentist at least twice in the last 12 months.

Conclusions: Most responding pediatric HCT survivors reported few bothersome oral and dental late effects. Patients may rate their concerns with little severity as they compare them to what they experienced with previous disease treatments. Results indicate adolescents may be more acutely aware of changes in their mouths than younger patients. Future studies should compare OHRQoL reports with clinical findings. The integration of consistent supportive oral care services into HCT care at Seattle Cancer Care Alliance may be positively influencing patients' oral health including their understanding of the value of consistent follow-up dental care.

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DEDICATION

To Dave, for keeping the kitchen in order, the laundry clean, and lunches packed throughout my residency and for intuitively offering red wine, puffy Cheetos, and hugs at the most necessary times. I love you.

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I.BACKGROUND

In the past several decades, survival rates for childhood cancers have risen dramatically. As recently as the mid-1970s, survival at five years after diagnosis was estimated to be 58%. The National Institutes of Health now estimates the five-year survival rate to be nearly 85% and we expect that most children will outlive their cancer diagnosis [1]. As these individuals live longer, however, the long-term consequences of their life-saving treatments become more evident.

It is well understood that anti-cancer regimens of chemotherapy and radiotherapy are toxic not only to cancer cells, but also to patients' healthy cells. Survivors of childhood cancer are at least eight times as likely as their siblings to develop severe or life-threatening chronic health conditions [2]. Children who survive cancer therapy battle toxic effects to nearly every organ system. Identifying these effects and determining how to mitigate them has become a major field of study within pediatric oncology, but studies examining oral and dental late effects are few [3]. Most existing knowledge of oral health effects is extrapolated from studies of adults treated in the 1960s-1990s. It is unclear whether such data hold any validity for children in today's environment of evolving cancer treatments [3].

Hematopoietic Cell Transplantation

A special population among childhood cancer survivors are those that receive hematopoietic cell transplantation (HCT). Barriga and colleagues have summarized four indications for HCT which are to: 1) rescue a patient with cancer from the need for ongoing high dose chemotherapy +/- radiation therapy, 2) correct a severe congenital or acquired blood disorder by replacing the patient's hematopoietic system with the donor's system, 3) increase the control of a malignant disease by leveraging the graft versus host reaction, and 4) reset the immune system to abolish autoimmunity [4]. Examples of diseases that may benefit from HCT include malignancies such as leukemias and lymphomas, and non-malignant diseases such as sickle cell disease, thalassemias, bone marrow failure syndromes, and inherited metabolic disorders.

Hematopoietic stem cells fit for transplant can be found in bone marrow (often taken as punctures from the iliac crests), peripheral stem cells (proliferated by granulocyte colony stimulating factor within the marrow and then mobilized to the bloodstream), and placental blood cells (collected from the umbilical cord

at the time of newborn delivery). The transplant may be autologous (donor cells being harvested from the same individual that will receive them back), allogeneic (donor cells being harvested from a separate individual), or syngeneic (harvested from an identical twin). In order for the patient to receive the donor cells, their body must be prepared through a conditioning regimen. In conditioning, chemotherapy is given alone or coupled with total body radiotherapy to ablate the host's innate response to reject the hematopoietic cells and to allow instead for engraftment to proceed. The conditioning process also attacks the cancer itself [4].

According to 2016 data, approximately 2,500 pediatric HCTs are completed in the United States annually. The majority of transplanted cells come from an allogeneic donor [5]. Expansion of global databases to obtain the most appropriate HCT donors (and thus the most desired effects on the host and his or her disease) have made HCT a viable option for many more individuals than would have been possible in the past [4]. As with pediatric cancers overall, survivorship after HCT continues to increase [6].

Oral Effects of HCT

Chemotherapy and radiation therapy can cause oral mucositis, xerostomia, and dysgeusia that resolve substantially in the months after cell transplantation. In addition to these transient oral effects, children's developing teeth, bones, and soft tissues are susceptible to long-term and even permanent damage [7] .

Dental Development Effects

Dental growth and maturation begins during fetal development and continues through the eruption and root maturation of the permanent teeth [8, 9] . A common class of chemotherapy drugs called alkylating agents have been identified as especially toxic for the dental formation and development process, affecting the primitive mesenchymal cells and the preodontoblasts of the pulp [3]. Radiation therapy also has the capacity to affect dental development as well, by damaging the developing tooth bud. Resulting dental abnormalities from chemotherapy or radiation therapy may include thin and tapered roots, prematurely closed root apices, cone-shaped or globular crowns, hypomineralized teeth, microdontia, enlarged pulp chambers, delays in permanent tooth eruption, and/or missing teeth [3, 7, 10-14]. Children who receive chemotherapy with radiation are more prone to dental developmental effects than those who receive

chemotherapy alone [3, 10, 12, 13]. The effects are also dose-dependent; individuals who receive greater radiation exposure or greater cumulative exposure to alkylating agents report more dental health issues [13, 14]. Children treated before five or six years old are considered to be at highest risk for dental abnormalities since their dental stem cells are especially active in these first few years of life [13, 14]. Children transplanted younger than one year of age can be affected in both the permanent and primary dentition [10].

In some children receiving chemotherapy or radiation, the tooth number, size, and shape is grossly unaffected, but enamel defects can create brown or yellow spots on the teeth. A 1997 study of survivors and their siblings revealed significantly more enamel defects in childhood cancer survivors who had received chemotherapy, radiation therapy, and/or bone marrow transplant compared to their healthy siblings. This included a significantly higher prevalence of esthetic defects in the anterior teeth, which, it was noted, may have psychological consequences [15].

Bony Development Effects

Conditioning therapies affect developing bones through direct toxicity to bone and possibly by reducing growth hormone secretion, though neuroendocrine-related HCT effects on bone growth remain a debated topic [16]. Children who receive HCT grow to heights approximately one standard deviation shorter than their peers, on average [16]. Since the condyles are a major growth center for the mandible, chemotherapy and radiation can lead to a shorter lower face height. Decreased alveolar bone height and development of malocclusion (poor alignment of the jaws and/or teeth) has also been seen [11]. Some authors suggest that the decrease in lower face height is influenced less by growth stunting at the condyle and more so by the shorter alveolar bone height that occurs secondary to decreased dental development [11]. As with the dentition, chemotherapy with total body irradiation (TBI) has been observed to be more detrimental to mandibular growth than chemotherapy alone [12]. The effects on craniofacial development can be greater in children who start treatment earlier, especially at six years of age or younger [7]. Managing malocclusion with orthodontic treatment can be especially challenging in this population because they also often have teeth with atypically-shaped crowns and blunted roots.

Salivary Effects

Among the soft tissues, salivary glands have the most noticeable long-term effects from conditioning. Conditioning regimens that include TBI can lead to permanent reduction in saliva secretion and those with chemotherapy alone have been associated with a decrease in normal stimulated whole saliva secretion at up to 12 years post-treatment [7, 14, 17].

Chronic Graft Versus Host Disease

In addition to the aforementioned complications, recipients of an allogeneic, rather than autologous, HCT are uniquely at risk of developing chronic graft versus host disease (cGVHD). Graft versus host disease (GVHD) develops when the lymphocytes of the new, transplanted immune system (the graft) recognize the recipient's body (the host) as foreign. In response, the immune cells of graft origin attack the host tissues. Chronic graft versus host disease, a form of GVHD that can arise after day 100 post-transplant, primarily involves the skin, eyes, gut, joints, and/or oral cavity. The mouth is often the first area involved, and may remain the only area involved [3, 18]. In its most benign state, oral mucosal cGVHD manifests as white lacy lines which appear similar to the striae of lichen planus. In pediatric patients, orofacial cGVHD may progress to cause painful ulcerations and mucosal sensitivity, affect taste sensation, cause severe xerostomia, and produce sclerosis of the oral tissues that leads to restricted mouth opening [19].

Estimates vary widely (9-45%) as to what proportion of pediatric allogeneic HCT recipients develop cGVHD [3, 20]. If not managed, cGVHD will eventually cause failure of vital organs and kill the host (transplant recipient). Treatment for cGVHD can be a lengthy process; a large multi-site study revealed that only 37% of pediatric patients have discontinued therapy within five years of their cGVHD diagnosis [21]. Chronic GVHD is the most common cause of morbidity and mortality in children that receive HCT [22].

Dental Caries

As noted above, both salivary dysfunction and enamel defects have been associated with HCT [15, 17, 19]. In addition to a cariogenic diet, poor oral hygiene, low oral pH, and elevated cariogenic bacterial load, a lack of saliva or the presence of enamel defects predisposes patients to caries development. The

evidence for increased risk of dental caries after HCT is conflicting. In their review of dental late effects in survivors of childhood cancer, Gawade and colleagues noted two studies that revealed an increased DMFT (decayed, missing, filled teeth scored) in survivors of HCT vs. controls [13]. While an additional two studies showed no increase in caries after HCT compared to controls, the authors concluded that HCT patients were receiving intensive caries prevention protocols (fluoride varnish applications, chlorhexidine rinses, and parental training in dental care) that outweighed their risks [13] .

Orofacial Malignancies

Hematopoietic cell transplant also elevates survivors' risk of developing second malignancies. Chemotherapy, radiation, and cGVHD each increase the risk of developing a post-transplant cancer that is unrelated to the pre-transplant diagnosis. Armenian and colleagues found that survivors of childhood cancer treated with HCT had a substantially elevated relative risk of developing a second malignancy compared to childhood cancer survivors who received conventional (non-transplant) therapy (RR=8.6), and sibling controls (RR=14.5) [23]. Fred Hutchinson Cancer Research Center data similarly showed that at a median 7.1 year follow-up time, survivors of HCT were more likely to develop skin and oral cancers than cancer survivors who did not receive HCT [24]. Oral squamous cell carcinomas and salivary gland tumors are some of the most common malignancies to develop [10]. Oral mucosal cGVHD that is not adequately managed has the capacity to transform into malignant lesions [10].

Oral Health-Related Quality of Life

With deliberate clinical and radiographic follow-up, it is possible to document a variety of oral effects of transplant. While the range of potential oral changes associated with pediatric HCT has been established, there has been little study as to how oral late effects impact patients' survival. A study of pediatric survivors of HCT in Sweden suggests that what dentists and doctors emphasize may not be valued by patients in the same way. Upon comparing physician-rated late effects in children to the children's own quality of life (QoL) scores, researchers found that children's own reports of symptoms *were* related to their QoL scores, but there was no correlation between the physician scores and the children's QoL scores [25]. If a major goal

of post- transplant supportive care during acute recovery and long-term survivorship is to increase QoL, it is important for providers to have a clear understanding of what patients consider most impactful on QoL.

Oral health-related quality of life (OHRQoL) is a formally-defined term [26]. It is considered to be one aspect of health-related quality of life, where health is defined by the World Health Organization definition as, "a state of complete physical, mental and social well-being." Such a framework helps practitioners assign the appropriate weight to specific complications. For example, yellow enamel defects noted on incisors that are otherwise healthy teeth may not be an acute concern from a dentist's perspective (i.e., there is little to no risk of infection, tooth loss, etc.), but having teeth that are perceived as unaesthetic compared to teeth of his or her peers could be a significant psychological stressor for a patient.

The number of reports utilizing QoL measures has increased substantially over the last decade [27], but there are still few measures to evaluate OHRQoL in children [28]. The specific oral difficulties faced by pediatric HCT survivors remain poorly characterized [14]. Kaste et al's study describing patient-reported oral health data from childhood cancer survivors and their siblings did not ask respondents whether their oral health problems created adverse effects on their quality of life [14]. All respondents were adults at the time of the survey, so their study did not elicit effects experienced by patients during their childhood years.

Hypotheses

Hypothesis 1: Patients who received a transplant at a younger age will report more oral health concerns.

Null Hypothesis 1: Patients who received a transplant at a younger age will not report more oral health concerns.

Hypothesis 2: Patients will express more oral health concerns and rate their distress higher with greater time post-transplant.

Null Hypothesis 2: Patients will not express more oral health concerns or rate the distress from those concerns higher with greater time post-transplant.

Aims

1. Assess the frequency of oral and dental late effects and their impacts on OHRQoL in child and young adult survivors of pediatric HCT
2. Assess patients' and families' level of confidence of when to see a dentist and their frequency of dental visits
3. Develop care guidelines for dentists and physicians to identify and appropriately counsel those most at risk of long-term oral and dental complications that may decrease OHRQoL

II.PARTICIPANTS AND PROCEDURE

Survey Design

A 21-item survey (Appendix A, B, C) was developed through input of dental and medical clinicians and a health services researcher. We aimed to include elements represented in existing pediatric oral health quality of life surveys, but also incorporate themes identified in published focus group findings [22, 28-32]. Questions related to oral health symptoms were scored using a yes/no option. If a participant indicated a positive response, they were asked to rank how much a particular symptom bothered them using a five-step Likert-type scale. To decrease recall bias, participants were asked only to report symptoms experienced over the past month. Respondents were also asked about their recent use of dental care resources, current medical and dental insurance status, and perceived barriers to oral health care.

Participants

Eligible participants were those who received an HCT in the Seattle Cancer Care Alliance system in the prior ten years (Nov. 29, 2008-Nov. 29, 2017), were less than 21.0 years old at the time of transplant, were at least one year post-transplant, consented to the institution's research protocol, were not incarcerated, and were at least two years old at the time of survey distribution. The survey and instructions were available in English only, but no restrictions were made on distribution as English literacy for potential respondents in the household was unknown.

Procedure

Three types of surveys were constructed as follows, with intended respondent to be determined by the age of the patient at the time of survey distribution. All surveys asked about the same symptoms, but the wording was adjusted to be age group-appropriate.

- Child survey (ages 2-7 years)
    - All questions to be completed by parent/guardian, acting as proxy for child in reporting oral health concerns
- Youth Survey (ages 8-17 years)

    - Oral health concerns section to be completed by the patient
    - Patient ethnicity, race, insurance status, history of dental use and barriers to dental use section to be completed by parent/guardian
- Adult Survey (ages 18+ years)
    - All questions to be completed by adult patient

We contacted patients/parents via email, postal mailing and/or phone call reminders over a period of six weeks (Fig. 1). Personalized email survey invitations were distributed to adult patients, or the parent or guardian of minor patients, through the REDCap (Research Electronic Data Capture) tool hosted at the University of Washington [33]. The introductory email outlined the study purpose and contained a unique hyperlink to access the survey questions (Appendix D, E, F). Paper mailings included similar informational letters (Appendix G, H, I, J). All envelopes were hand-addressed, letters were personalized and hand-signed by the research team, and surveys were printed on colored paper, as these details have been shown to increase questionnaire response rates [34]. Raised cartoon animal stickers were also included in the survey envelopes to create an uneven contour of the envelope and increase open rates (Fig. 2). Participants were able to opt out of the study at the beginning of the online survey or by returning an opt-out postcard in the pre-stamped survey envelope (Fig. 3). Once an opt-out was received, the participant was removed from further contact lists. Each paper survey and opt-out card was marked with the patient's unique patient number from their medical chart so that responses could be matched to particular patient records without using any other identifiers. A phone number and email address to contact the research team with questions or concerns was included with each written communication. We contacted families via phone reminders when we had not received a response to mail or email surveys. A new survey was distributed to participants at that time if they requested one.

The study protocol was approved by the Fred Hutchinson Cancer Research Center IRB committee (IR File #8676). Study data were collected and managed using REDCap.

Statistical Analysis

Demographic and medical history data are routinely collected for patients who receive an HCT at Seattle Cancer Care Alliance and were available through the institutional research database. The medical history data include primary disease diagnosis which was separated into the categories of leukemia/lymphoma, solid tumor, and non-malignant (Appendix K), age at time of transplant, years since transplant and transplant conditioning regimen which was designated as either myeloablative or non-myeloablative (Appendix L), and number of lifetime HCTs received.

Positive responses to the questions about pain in teeth and gums bleeding with brushing were considered to be indicators of caries and gingivitis, respectively. We considered these two variables to be multi-factorial and examined them as a group since their development depends heavily on patient behavior. Dental development concerns were examined in the group transplanted at age five and younger to evaluate those who would have been most susceptible to dental development abnormalities. Xerostomia was examined individually since the mechanism of injury to the salivary glands is not dependent on age or patient behavior, but can have significant effects on oral health and comfort.

Indices of oral health were created to compare the burden of oral health concerns among responders. A value of 0 was assigned to any question answered as 'no (I have not experienced this in the past month).' Yes answers were valued according to how much the patient reported an oral health concern bothering him or her over the past month: 'Not at all' =1, 'A little bit' =2, 'Somewhat'=3, 'Quite a bit'=4, 'Very much' =5. An index value was calculated by adding up each of the response values. Indices were created to investigate an inclusive Oral Health Index (all oral health concern question responses), Non-Development Index (all oral health concern question responses except for abnormally-shaped/sized teeth and missing teeth), GVHD Index (oral health concerns related to GVHD including xerostomia, ulcers, mucosal sensitivity and taste changes), and Dental Development Index (abnormally-shaped/sized teeth and missing teeth only).

Descriptive statistics were calculated. Demographic and medical history data were compared between survey responders and non-responders using Chi-Square or Fisher's exact tests for categorical variables, Wilcoxon ranks sum test or Kruskal Wallis test for medians, and T-tests or ANOVA for continuous

factors. Univariate and mutivariable logistic regression models were used to examine the relationships between oral health symptoms and demographic and medical history data. Analyses were performed using SAS (Version 9.4; SAS Institute Inc, Cary, NC).

III.RESULTS

Of the initial list of 385 eligible participants, one was deceased and another received a transplant outside of the defined study window, leaving 383 potential respondents. Thirty-two of these did not have current contact information available. From the remaining 351 individuals, 149 (42.5%) returned the survey (80 completed an electronic survey and 69 completed a paper survey). Five respondents opted out of the study.

Demographics

The largest survey group by respondents was the youth survey group (41.6%) followed by the adult group (31.5%) and the child group (26.8%). Child surveys were completed by parents/guardians, most commonly by mothers (75.0%). Though surveys directed youth and adult patients to fill out their own oral health concern ratings, parents completed this portion for six of the adult surveys and twenty-five of the youth surveys. Hereafter, we use the term responders or respondents to refer specifically to the patients involved in the study since the collected data reflected their experiences, even though parents and guardians acted as proxies in many circumstances.

Responders were less likely to be Hispanic than non-responders, but there were no other significant differences in demographics or medical history between the responders and non-responders (Table 1). Respondents tended to be white (83%), and male (57%). Their mean age at time of transplant was 9.0 years old. Mean patient age at the time of survey was 13.9 years old. The most common reason for transplant was leukemia/lymphoma (40.3%), followed by non-malignant disease (37.6%), and solid tumors (22.1%). The mean interval of time between transplant and survey was 4.9 years. The majority of respondents (79.9%) had received an allogeneic transplant. Approximately half of the responders received chemotherapy conditioning without TBI (47.7%). Most (91.9%) underwent a myeloablative conditioning regimen. Seventeen responders had received two or more transplants, with all but two undergoing a myeloablative conditioning regimen for their first transplant.

Oral Health Concerns

Sixty-six percent of the respondents reported one or more oral health concerns (Table 2). The oral health concerns reported most frequently were bleeding gums with brushing (38.3%) and teeth looking smaller or a different shape than others (19.6%); few found their reported symptoms to be bothersome. The presence of one or more oral health concerns did not differ by primary disease type, transplant type, or age at transplant, but was associated with increased years since transplant (Table 3). There was a trend of increased likelihood of reporting an oral health concern with increasing TBI, but this was not significant. Those who reported two or more symptoms were slightly more likely to be older at the time of survey or to have had more time pass since transplant than were those who reported one or fewer oral concerns (Table 4).

Multi-Factorial Dental Issues

Report of tooth pain and/or bleeding gums with brushing was slightly higher in those who received ≥ 12 Gy TBI, were older at the time of transplant, were older at the time of survey, or were a greater number of years post-transplant at the time of the survey (Table 5). This association remained significant for age at transplant and years since transplant in the multivariate analysis.

Xerostomia

Xerostomia was reported by 14.8% of respondents and was not found to differ by conditioning regimen, primary disease, or transplant type (Table 6). Xerostomia was strongly associated with older age at transplant ($p<0.001$) and older age at the time of survey ($p<0.001$).

Dental Development Concerns

Among the 61 patients who received a transplant at less than six years of age, 31.6% reported one or more missing or abnormally-shaped/sized teeth. Although this was increased among those who received ≥ 12 Gy TBI compared to those who had not received TBI (OR=2.57, 95% CI 0.61-10.83), it was not statistically significant (Table 7).

Chronic Graft Versus Host Disease

Among the 119 patients that received an allogeneic transplant, 11 (7.4%) reported having oral cGVHD at the time of the survey or in the past (Table 8). These patients were more likely to have a diagnosis of cGVHD (involving any system) ($p=0.039$) as well as oral cGVHD ($p<0.001$) in their medical record. Most patients with xerostomia also had a medical diagnosis of cGVHD ($p<0.001$), but did not have a diagnosis of oral cGVHD. Change in the flavor of food was associated with a diagnosis of cGVHD ($p=0.018$), but not oral cGVHD. Neither mucosal sensitivity nor the presence of oral ulcers was associated with any type of cGVHD diagnosis.

Oral Health-Related Distress

Since very few respondents reported that their symptoms were 'quite a bit' or 'very' bothersome, the oral health indices were similar to the symptom groupings previously defined and thus further analysis of the indices were not done (Table 9).

Dental Utilization

Feeling of Preparedness for Oral Health Changes

Eighty-seven respondents (58.4%) reported receiving information regarding their post-transplant oral health, 19.5% reported not receiving information and 22.1% did not know if they received information. Patients' level of confidence in being 'somewhat' or 'very' prepared for oral health issues after transplant was 96.0%, 95% CI = (91.4%, 98.5%). Two responders reported that they were 'not at all' prepared.

Dental Insurance

Slightly fewer participants reported having dental insurance (86.6%) compared to having medical insurance (96.6%). Of those with dental insurance, three-fourths (74.8%) reported having a private dental insurance plan with the remainder using a government-provided plan.

Dental Visits

The majority of respondents (75.0%, 95% CI=[91.4%, 98.5%]) reported seeing a dentist at least twice in the last year. Six respondents reported not seeing the dentist in the last twelve months; four of them were in the adult age group. Reasons for not receiving care included “can’t find a dentist that takes my insurance” (2), “I don’t have time to go to the dentist” (2), “the dentist is too expensive” (1), “ I am anxious or fearful at the dentist” (1), and “recently moved” (1).

Those with private dental insurance were more likely to report visiting the dentist two or more times in the last year compared to those with no insurance, but the difference was not significant (Table 10). There was a trend towards higher rating of oral health importance being associated with greater likelihood to have two or more dental visits per year in both the univariate and multivariate analyses. In addition, males were more likely to report having seen a dentist ≥2 times (OR=3.66, 95% CI=1.46-9.21, multivariate analysis).

Oral Health Ratings

On a scale of 0-100, participants ranked oral health as a high priority both in terms of overall health (median 75.0, range 10.0-100, Fig. 4) and compared to other issues specific to transplant (median 64.0, range 0.0-100, Fig. 5).

IV.DISCUSSION

Oral Health Concerns

The goal of this study was to better understand the oral health issues and problems that arise in long-term survivors of pediatric HCT and determine which factors might influence them and what effect they have on patients.

Our survey revealed a relatively low burden of oral health concerns, with most respondents reporting one or fewer oral problems, which when reported, tended to be no more than 'a little bit' bothersome. It is not surprising that patients would report fewer oral health concerns than the prevalence that has been reported in the literature. Choosing to ask about patients' own observations provides insight into what they believe affects their quality of life, but limits our findings to changes that patients were able to visualize or perceive in their own mouths. Even compared to other studies that asked respondents to report their own oral health changes, our frequency of concerns appears low. A possible explanation may be a difference in toxicity exposures. In the Kaste et al. study, which surveyed patients who were diagnosed between 1970 and 1986, 143 (1.7%) of their respondents received over 20 Gy to the area of the teeth while the maximum dose for our survey group was 13.6 Gy of TBI and just over one third of respondents received above 12 Gy of TBI [14]. As recent cancer research has increasingly identified the benefits of a graft-versus-leukemia benefit on long-term disease free survival rather than totally depending upon the conditioning regimens to eliminate malignant disease, the goals of conditioning are changing, leading to lesser toxicities for many patients [4], and presumably fewer late effects.

Interestingly, except for dental development concerns, oral health concerns were reported more often by those who were transplanted at an older age. The observation was contrary to our hypothesis, as we had assumed that patients would be most affected by their transplant if their tissues were exposed to conditioning at a younger age. One possible explanation for this finding is that older survivors express more negative changes simply because they have greater sensitivity to them. Forinder and colleagues found a negative association between QoL and age after HCT in a pediatric population, showing a lower self-esteem with aging [25]. Previous studies have found that adolescents are more emotionally affected by their diagnoses than younger patients [35]. Some have suggested that malignancy produces greater

physical and psychological effects for teenagers compared to their younger peers owed to their maturity in awareness of the gravity of their disease and the ways that it restricts their daily life [35].

To approach the issue in a different way, the youngest patients may be less likely to voice changes or concerns. In the experience of pediatric dental providers among our authors, young patients often complain little about changes in their mouths; even large caries or abscessed teeth may go undetected until children present to the dentist. This observation belies either a stoicism among very young children or a lack of effective communication between child and caregiver. Though previous research suggests that having parents as proxy is unlikely to skew the data [36], symptom results for those under age eight depended on the child having either previously voiced a concern to their parent or their parent having noticed the issue. It is also probable that patients who are transplanted at a young age experience hyposalivation and oral discomfort so early in life that they do not recognize it as an abnormality, and thus do not report it.

Xerostomia

Histologic differences may also account for why those transplanted at a younger age had fewer reports of oral health concerns, especially xerostomia. Non-calcifying oral tissues, i.e., not bone or teeth, in young children may be more resilient to the insults of conditioning therapies than in patients who are older. Parents and pediatric providers can attest to the incredible capacity of young children to heal after trauma and other injuries. Their mucosa and salivary tissues are perhaps more resilient than their older peers' in the long term. While a single study measuring salivary gland function in children at one year post-bone marrow transplant found no association between age at transplant and level of salivary gland hypofunction [19], we are unaware of research evaluating the effect of age at transplant on salivary function into successive years of survival. This relationship in pediatric and adolescent cancer populations merits additional study [17].

Multi-Factorial Dental Issues

Patients who were transplanted at an older age largely made up the group that were older at the time of the survey. An older reporting age may also be influencing our outcomes. Two of our question items, "Bleeding gums with brushing" and "Pain in teeth" were felt by the research team to relate to gingivitis and

caries, respectively. Though there is literature to suggest that HCT predisposes survivors to these oral conditions, oral hygiene practices play a significant role in their incidence. More caries and gingivitis would not be surprising to see in the 8- to 17-year-old group as they gain independence in their diet choices and hygiene practices.

Dental Development Concerns

The lack of significant association of reported teeth of a different size or shape or missing teeth with any of the medical history or treatment variables for those transplanted under six years of age suggests that the interval of time between transplant and survey for this cohort was not long enough for noticeable effects to arise. Since the crown of the tooth completes formation approximately three to five years prior to its eruption in the mouth, a minimum of four to six years following transplant would be required for tooth formation to be affected considerably enough to be detected as a difference in shape, size, or agenesis. To more accurately appreciate the effects of transplant on tooth development, it would be beneficial to restrict the analysis to patients who also were at least four years post-transplant.

Chronic Graft Versus Host Disease

Patient-reported oral cGVHD was consistent with medical chart diagnoses of oral cGVHD and cGVHD of any system, suggesting that patients tend to be well-informed of their health status. Ten percent of those patients who reported never having been diagnosed with oral cGVHD did have an oral cGVHD diagnosis listed in their chart. Even though this is a fairly small portion of the responders, it means there are survivors in our study who do not appreciate their risk of progressive oral symptoms or of developing cGVHD involvement of other body systems that could become a threat to life. Since most allogeneic recipients reporting xerostomia and taste changes had been diagnosed with cGVHD (non-specific) but not with oral cGVHD, this could indicate an underdiagnosis of oral cGVHD. Patients who report such symptoms should be referred to their long-term follow-up physicians or oral health providers for further diagnosis, evaluation and management.

Oral Health-Related Distress

Due to a lack of considerably bothersome reported oral health concerns, the variable-grouped oral health indices did not show meaningful differences between treatment groups. The reasons noted above for why few oral health concerns were reported could also explain why few especially distressing concerns were reported. A concept known as “response shift” may also be playing a role in our research. It is especially pertinent to the observation that even when an oral problem was reported, it was rarely reported to be very bothersome [37]. Response shift refers to the phenomenon of survivors framing their current QoL in the context of prior hardships. As many participants presumably endured intense mucositis and taste changes during the initial post-transplant period, they may rate any current oral problems as having a relative low impact on their lives.

Dental Utilization

Patients are dependent on their medical and dental providers to inform them of post-transplant care recommendations. The Children’s Oncology Group statement on oral health outlines the importance of preventive care and regular exams by a dentist to screen for issues such as infections and second malignancies. Consistent with similar guidelines from the American Academy of Pediatric Dentists [7], they recommend these visits at least every six months [38].

Despite the fact that less than 60% of respondents remembered receiving information regarding their post-transplant oral health, nearly all respondents felt at least somewhat prepared for their oral health issues after transplant, indicating that either a large portion received education, but did not remember receiving it, or encountered few challenging post-transplant oral effects.

Accordingly, 96% of survivors in our study reported seeing a dentist at least once in the prior 12 months, well exceeding numbers gathered from 14,054 cancer survivor and sibling participants in the Childhood Cancer Survivor Study (60.4%) [39] , from a 2008-2012 Medical Expenditure Panel Survey study of survivors of adolescent and young adult cancers (41%) [40], and U.S. national averages for the general population of any age group [41]. Nearly 75% of respondents in our study attested to seeing a dentist two or more times a year. While we did not ask respondents about the details of the types of treatment received during their dental visits, the fact that they are connecting with a dental provider on a regular basis is

encouraging. If they are seeing a dentist regularly, they are less likely to have unmet dental needs, and this could explain our low frequency of reported oral health concerns as well.

Numerous papers recount the reasons that patients have difficulty meeting the recommended survivorship follow-ups [39, 40, 42-44]. The task with the findings of this study is to determine why our patients are so very successful at meeting these recommendations. The simplest explanation is that patients are not actually seeing a dentist semi-annually, despite reporting that they are. Since we did not actually track patients' dental visits, we cannot rule out this possibility, but with the assurance that survey responses would not affect patients' medical or dental care or be communicated back to their providers, there was little incentive to be untruthful.

A high rate of dental insurance in the responder group could partially explain our findings. Many studies assert that a lack of dental insurance is correlated with less frequent dental visits [39, 40, 45]. Similar trends have long been seen in childhood and young adult cancer survivors' use of medical care [43, 44, 46]. Since 2010, the Affordable Care Act has mandated that pediatric dental coverage be provided for any pediatric enrollee in Medicaid and in any health plan offering to individuals and small businesses. Medicaid expansion programs have also helped to ensure that more adults in many states (including Washington State) have access to dental benefits [47]. These changes in healthcare provision may be partially responsible for the high percentage of respondents who reported having dental insurance and could indirectly relate to the high numbers seeing a dentist.

The racial makeup of our study population undoubtedly also contributes to high dental utilization numbers as well. Identifying as a racial minority has been repeatedly linked to a lesser likelihood of seeing a dentist [39, 48] but our population was largely white.

As would be expected from individuals who prioritize regular dental care, respondents expressed great value for their oral health relative to their overall health and other transplant-related issues. This high perception of oral health may be a product of persuasive and repeated education. Though patients may not receive (or remember receiving) oral post-transplant education, they are likely exposed to it regularly even after transplant. Two thirds of our respondents reside in Washington State and many return on a regular basis to the Seattle Children's Hospital dental service for follow-up visits. Additionally, care teams at the Seattle Cancer Care Alliance routinely emphasize the importance of oral health and the institution

houses one of the country's only cancer center oral medicine clinics. This dental-directed department interfaces with HCT patients at multiple points throughout the transplant process, beginning with pre-transplant exams and oral disease stabilization and providing management support through the acute and chronic stages of oral complications and then routinely following up with patients for post-transplant oral health assessments and care.

Strengths and Limitations of Study Design

Our research is inclusive of a wide range of ages and inquired about oral late effects and their influence on quality of life in pediatric and young adult survivors. By creating three survey versions, we were able to collect data to represent HCT patients aged one to nearly thirty years old. Our data is also unique because we asked about patients' own perceptions of their oral effects rather than documenting examination results from healthcare providers. This approach allows greater insight into how HCT therapies actually affect long-term QoL as experienced by the patient. Our results could be strengthened if they were paired with objective changes from clinical and radiographic dental exams, to examine the relationship between clinical and radiographic findings and patient-reported OHRQoL.

Because there were no existing tools to measure OHRQoL in survivors of pediatric HCT, we developed our own questionnaire. Due to limited resources, we were unable to validate the survey, so its ultimate sensitivity and accuracy remains unknown and it is unclear whether significant differences of OHRQoL indices between groups represent a clinically meaningful difference. The survey was also available in English only, which could account for why we saw a lower percentage of respondents who identified as Hispanic compared to non-respondents. Patient reports of oral health concerns were restricted to ones that fell within our pre-selected categories. We used a short recall period (symptoms experienced within the last month) in order to reduce recall bias, but it is possible that this excluded many of the symptoms that are important to survivors. It is also possible that some respondents did not understand the questions and underreported their oral health concerns, despite our attempt to tailor the survey language and style to be easily understood by the various age groups. Issues that patients brought up repeatedly in the open-ended question section included enamel defects and tooth discoloration, shortened tooth roots, and tooth sensitivity to cold. Future studies may elect to add these categories. Performing a preliminary

pilot study with possible respondents could help to ensure that we are addressing the most important issues for patients and framing questions in a way that is readily understood. Providing the survey in multiple languages could help to improve respondent numbers and ensure better representation of the transplant population.

Though we received nearly 150 survey responses, the variation between patients meant that it was necessary to categorize treatments and diseases into broad groups, limiting the detail of analysis. Our study included only the immediate pre-transplant conditioning regimens for each patient and did not account for prior chemotherapy or radiation that they may have received in initial efforts to control their disease. This approach meant that two patients with the same conditioning regimen were treated equally, even though one may have received several rounds of chemotherapy and radiation prior to pursuing transplant while another had received none. By including the seventeen responders who received more than one transplant, we introduced the complexity of patients who may have been showing effects of a transplant outside the study window and could have decreased the significance of trends related to age at transplant and time since transplant. However, their participation in the survey makes our study more representative of the pediatric transplant population as a whole. A more complete understanding of patients' exposure could be included in future analyses by tabulating therapies received prior to the most recent transplant.

Finally, this research is subject to nonresponse bias and survivor bias. Though similar to the responders in their demographics and treatment, those patients who chose not to respond to the survey may experience significantly more (or fewer) oral health concerns. It is logical that those who place more value on their oral health would be more likely to respond to an oral health survey. Surveying only survivors introduces the possibility that those with the worst oral complications did not survive to the time of our study, resulting in an underreporting of oral health concerns.

V.CONCLUSIONS

The prevalence of pediatric cancer survivors is expected to approach 500,000 by next year [26]. In their review of life-long risks and health-related QoL outcomes for survivors of childhood and adolescent cancers, Robison and Hudson estimate that “approximately one of every 750 individuals is a survivor of childhood cancer in the United States” [49]. While not all of these are survivors of HCT, many are and will be in the future. The extended complications for survivors of childhood cancer are expected to have a much greater impact on the lives of survivors, and the rest of society, than their relatively short courses of disease management and treatment [49]. Medical and dental providers need to be prepared to address these late effects and help prevent them, when possible.

The fact that our study group reported relatively few oral health concerns, reported their oral health to be moderately to highly important to them, and reported high numbers of regular dental attendance, is heartening. This suggests an overall minimally negative effect on QoL due to oral changes for pediatric survivors of HCT at our institution. We feel this is a testament to the integration of dental and medical care that exists at Seattle Cancer Care Alliance. These results encourage proliferation of such a model throughout the country.

Pediatric HCT survivors are a unique and important group. Future studies should be aimed at continuing to limit oral effects of HCT by reducing toxicity to bone and dental structures as well as salivary glands. Providers should be aware of the possibility of oral and dental developmental late effects in pediatric survivors of HCT, especially in those transplanted before six years of age. Conversations about oral effects and oral cGVHD detection and management should be a regular part of dental and medical visits and asking about symptoms may help to detect previously undiagnosed cGVHD. Providers should also recognize that older pediatric and young adult patients may be more acutely affected by their oral changes and would be wise to employ a listening approach to ensure they fully understand patients’ concerns.

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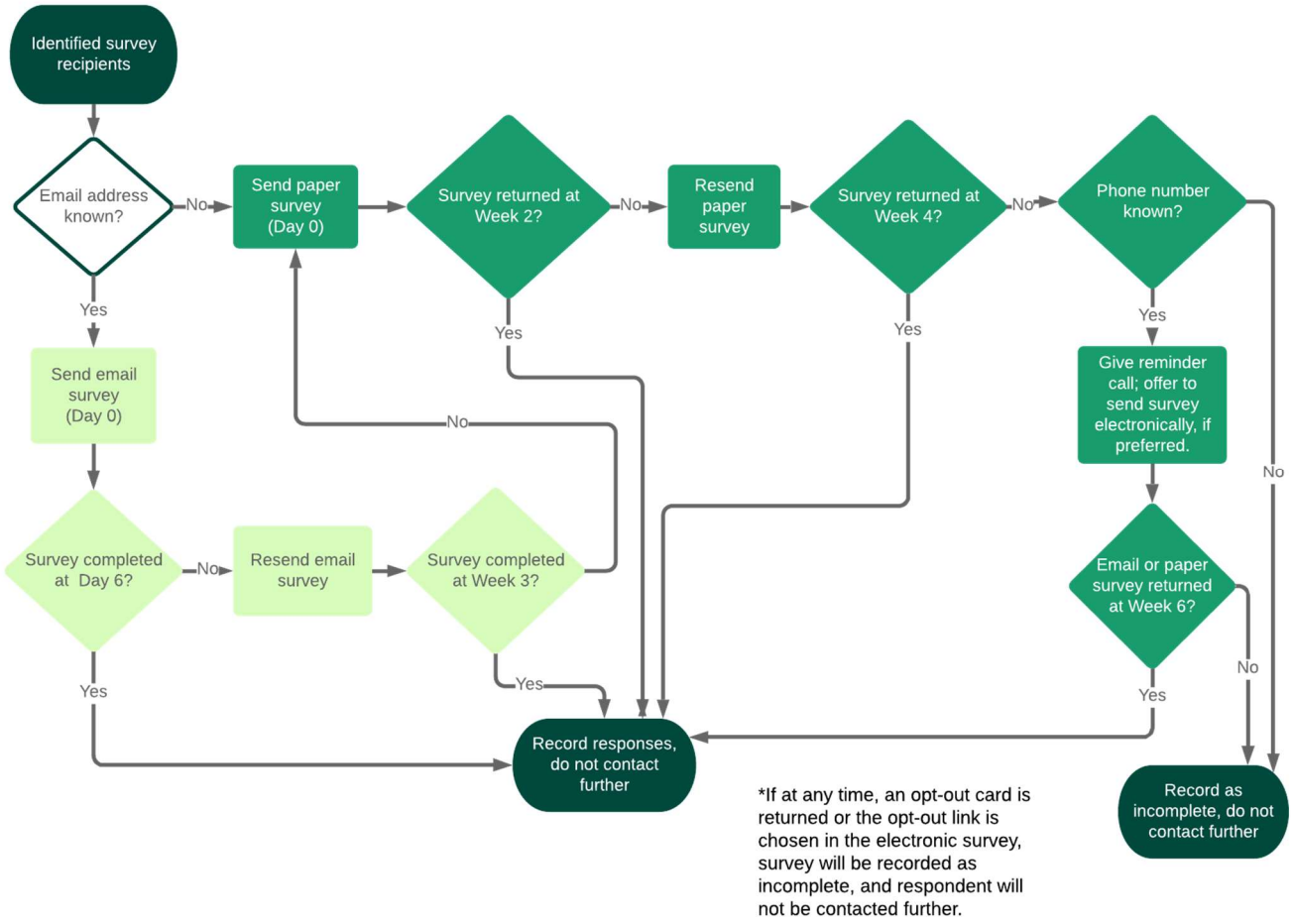

Figure 1. Survey distribution flow diagram.

Figure 2. Puffy stickers included in paper survey mailings.

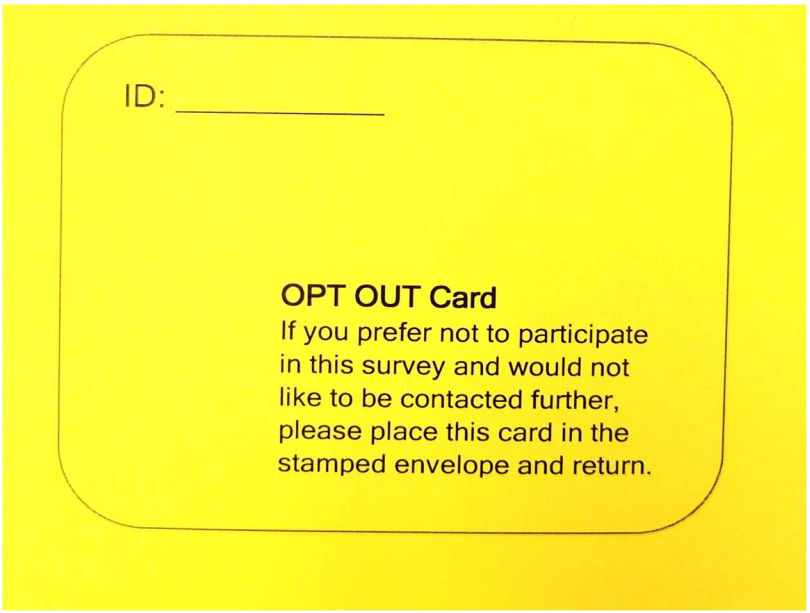

Figure 3. Example of opt-out card included in paper survey mailings.

Table 1. Demographic and transplant factors by response

Variables	Total (N=383)	Non-responders (N=234)	Responders (N=149)	P-value[a]
Age at survey, years: Mean (StD[b])	14.5 (7.1)	14.9 (7.2)	13.9 (6.9)	0.19
Sex				0.90
Male	220 (57.4%)	135 (57.7%)	85 (57.0%)	
Female	163 (42.6%)	99 (42.3%)	64 (43.0%)	
Race				0.46
White/Caucasian	286 (79.0%)	163 (76.5%)	123 (82.6%)	
Asian	36 (9.9%)	22 (10.3%)	14 (9.4%)	
Native American/Alaska Native	7 (1.9%)	6 (2.8%)	1 (0.7%)	
African American/Black	15 (4.1%)	9 (4.2%)	6 (4.0%)	
Other (Multiple, Native Hawaiian)	18 (5.0%)	13 (6.1%)	5 (3.4%)	
Missing	(N=21)	(N=21)	(N=0)	
Hispanic				**0.015**
No	301 (82.7%)	175 (78.8%)	126 (88.7%)	
Yes	63 (17.3%)	47 (21.2%)	16 (11.3%)	
Missing	(N=19)	(N=12)	(N=7)	
Disease type				0.44
Non-malignant	138 (36.0%)	82 (35.0%)	56 (37.6%)	
Solid tumor	76 (19.8%)	43 (18.4%)	33 (22.1%)	
Leukemia/lymphoma	169 (44.1%)	109 (46.6%)	60 (40.3%)	
Transplant type				0.33
Autologous	68 (17.8%)	38 (16.2%)	30 (20.1%)	
Allogenic	315 (82.2%)	196 (83.8%)	119 (79.9%)	
Myeloablative conditioning				0.65
No	34 (8.9%)	22 (9.4%)	12 (8.1%)	
Yes	349 (91.1%)	212 (90.6%)	137 (91.9%)	
TBI (Gy)				0.21
None	167 (43.6%)	96 (41.0%)	71 (47.7%)	
<12	81 (21.1%)	56 (23.9%)	25 (16.8%)	
≥12	135 (35.2%)	82 (35.0%)	53 (35.6%)	
# of transplants				0.68
1	336 (87.7%)	204 (87.2%)	132 (88.6%)	
2	47 (12.3%)	30 (12.8%)	17 (11.4%)	
Age at transplant, years: Mean (StD)	9.5 (6.3)	9.8 (6.3)	9.0 (6.3)	0.23
Years since transplant: Mean (StD)	5.0 (2.6)	5.1 (2.7)	4.9 (2.5)	0.54

[a]P-values are from Chi-square test/Fisher's exact test for categorical variables, and the T-test for comparing means of continuous variables.
[b]Standard deviation

Table 2. Frequency of oral health concerns [N=149]

Variables	N (%[a])
Tooth pain	
No	128 (85.9%)
Yes	21 (14.1%)
Distress from tooth pain	
Not at all	1 (4.8%)
A little bit	14 (66.7%)
Somewhat	3 (14.3%)
Quite a bit	3 (14.3%)
Bleeding gums from brushing	
No	92 (61.7%)
Yes	57 (38.3%)
Distress from bleeding gums	
Not at all	10 (17.5%)
A little bit	38 (66.7%)
Somewhat	7 (12.3%)
Quite a bit	2 (3.5%)
Teeth look smaller/different shape	
No	119 (80.4%)
Yes	29 (19.6%)
Missing	(N=1)
Distress from change in tooth shape	
Not at all	15 (51.7%)
A little bit	10 (34.5%)
Somewhat	4 (13.8%)
Any missing teeth	
No	118 (79.2%)
Yes	12 (8.1%)
Don’t know	19 (12.8%)
Distress from missing teeth	
Not at all	7 (58.3%)
A little bit	3 (25.0%)
Somewhat	2 (16.7%)
Mucosal sensitivity	
No	135 (91.2%)
Yes	13 (8.8%)
Missing	(N=1)

Distress from mucosal sensitivity	
Not at all	1 (7.7%)
A little bit	5 (38.5%)
Somewhat	7 (53.8%)
Ulcers	
No	130 (87.2%)
Yes	19 (12.8%)
Distress from ulcers	
A little bit	11 (57.9%)
Somewhat	5 (26.3%)
Quite a bit	2 (10.5%)
Very much	1 (5.3%)
Dry mouth	
No	127 (85.2%)
Yes	22 (14.8%)
Distress from dry mouth	
Not at all	3 (13.6%)
A little bit	9 (40.9%)
Somewhat	8 (36.4%)
Quite a bit	1 (4.5%)
Very much	1 (4.5%)
Abnormal taste	
No	139 (93.9%)
Yes	9 (6.1%)
Missing	(N=1)
Distress from abnormal taste	
Not at all	3 (37.5%)
A little bit	4 (50.0%)
Very much	1 (12.5%)
Missing	(N=1)

[a]Percentages for Distress from symptom variables are based on those reporting the symptom

Table 3. Presence of one or more reported oral health concerns by transplant factors [N=98 with and N=51 without any oral health concerns reported]

	Univariate			Multivariable		
Variable	**OR (95% CI)**	**P-value[a]**	**Global p-value[a]**	**OR (95% CI)**	**P-value[a]**	**Global p-value[a]**
Myeloablative conditioning	0.62 (0.16, 2.39)	0.49		0.31 (0.05, 1.93)	0.2098	
TBI			0.11			0.07
None	(ref)			(ref)		
<12 Gy	0.63 (0.25, 1.57)	0.32		**0.27 (0.07, 0.99)**	**0.048**	
≥12 Gy	1.78 (0.81, 3.92)	0.15		1.14 (0.28, 4.67)	0.86	
Disease	(ref)		0.48	(ref)		0.94
Non-malignant	0.70 (0.29, 1.69)	0.42		1.34 (0.19, 9.54)	0.77	
Solid tumor	1.20 (0.55, 2.62)	0.65		1.16 (0.30, 4.44)	0.83	
Leukemia/ lymphoma						
Allogenic transplant	1.94 (0.86, 4.38)	0.11		2.11 (0.30, 14.97)	0.46	
Age at transplant (years)	1.03 (0.98, 1.09)	0.23		1.03 (0.96, 1.09)	0.44	
Years since transplant	**1.16 (1.01, 1.34)**	**0.036**		**1.18 (1.01, 1.37)**	**0.036**	
Age at survey (years)	1.05 (1.00, 1.11)	0.06				
Multiple transplants	0.41 (0.15, 1.15)	0.09		0.52 (0.16, 1.65)	0.27	
Male	1.14 (0.58, 2.26)	0.70		1.21 (0.56, 2.61)	0.62	
Race (white)	0.52 (0.19, 1.39)	0.19		0.54 (0.18, 1.56)	0.25	

[a]p-values based on logistic regression, global p-value is for differences in outcome across all levels of factor

Table 4. Number of reported oral health concerns (≥2 vs <2) by transplant factors [N=46 with ≥2 and N=103 with <2 oral health concerns]

	Univariate			Multivariable		
Variable	**OR (95% CI)**	**P-value[a]**	**Global p-value[a]**	**OR (95% CI)**	**P-value[a]**	**Global p-value[a]**
Myeloablative conditioning	1.37 (0.35, 5.32)	0.65		2.09 (0.31, 14.16)	0.45	
TBI			0.40			0.95
None	(ref)			(ref)		
<12 Gy	1.06 (0.38, 2.95)	0.90		0.81 (0.21, 3.12)	0.76	
≥12 Gy	1.66 (0.77, 3.56)	0.19		0.93 (0.25, 3.50)	0.91	
Disease			0.42			0.81
Non-malignant	(ref)			(ref)		
Solid tumor	0.80 (0.30, 2.14)	0.66		1.85 (0.28, 12.10)	0.52	
Leukemia/ lymphoma	1.45 (0.66, 3.16)	0.35		1.10 (0.30, 4.01)	0.88	
Allogenic transplant	2.03 (0.77, 5.35)	0.15		3.98 (0.58, 27.20)	0.16	
Age at transplant (years)	1.04 (0.98, 1.10)	0.16		1.05 (0.99, 1.12)	0.13	
Years since transplant	**1.18 (1.03, 1.36)**	**0.019**		**1.21 (1.04, 1.41)**	**0.012**	
Age at survey (years)	**1.06 (1.01, 1.12)**	**0.031**				
Multiple transplants	0.92 (0.31, 2.80)	0.89		1.23 (0.34, 4.48)	0.75	
Male	0.97 (0.48, 1.96)	0.93		1.29 (0.60, 2.77)	0.52	
Race (white)	1.26 (0.49, 3.25)	0.63		1.60 (0.56, 4.56)	0.38	

[a]p-values based on logistic regression, global p-value is for differences in outcome across all levels of factor

Table 5. Multi-factorial oral health concerns (tooth pain and/or bleeding gums with brushing) by transplant factors [N=65 with and N=84 without any multi-factorial health concerns]

	Univariate			Multivariable		
Variable	**OR (95% CI)**	**P-value[a]**	**Global p-value[a]**	**OR (95% CI)**	**P-value[a]**	**Global p-value[a]**
Myeloablative conditioning	1.09 (0.33, 3.61)	0.89		1.44 (0.26, 7.89)	0.67	
TBI			0.13			0.77
None	(ref)			(ref)		
<12 Gy	1.15 (0.45, 2.94)	0.76		0.93 (0.26, 3.32)	0.91	
≥12 Gy	**2.09 (1.01, 4.32)**	**0.046**		1.51 (0.40, 5.72)	0.54	
Disease			0.61			0.68
Non-malignant	(ref)			(ref)		
Solid tumor	1.14 (0.48, 2.73)	0.77		1.89 (0.30, 11.89)	0.50	
Leukemia/ lymphoma	1.45 (0.69, 3.02)	0.33		0.80 (0.22, 2.91)	0.73	
Allogenic transplant	1.20 (0.53, 2.72)	0.65		1.89 (0.30, 12.08)	0.50	
Age at transplant (years)	**1.08 (1.03, 1.14)**	**0.004**		**1.09 (1.02, 1.16)**	**0.008**	
Years since transplant	**1.14 (1.00, 1.30)**	**0.042**		**1.16 (1.01, 1.34)**	**0.042**	
Age at survey (years)	**1.09 (1.04, 1.15)**	**0.001**				
Multiple transplants	0.36 (0.11, 1.16)	0.09		0.40 (0.11, 1.51)	0.18	
Male	1.24 (0.64, 2.39)	0.52		1.70 (0.81, 3.55)	0.16	
Race (white)	0.88 (0.38, 2.07)	0.77		1.04 (0.40, 2.67)	0.94	

[a]p-values based on logistic regression, global p-value is for differences in outcome across all levels of factor

Table 6. Xerostomia by transplant factors [N=22 with and N=127 without dry mouth]

	Univariate			Multivariable[a]	
Variable	**OR (95% CI)**	**P-value[b]**	**Global p-value[b]**	**OR (95% CI)**	**P-value[b]**
Myeloablative conditioning	0.30 (0.08, 1.11)	0.07		0.58 (0.13, 2.57)	0.47
TBI			0.28		
None	(ref)				
<12 Gy	2.29 (0.65, 8.00)	0.20			
≥12 Gy	2.13 (0.75, 6.02)	0.16			
Disease type			0.34		
Non-malignant	(ref)				
Solid tumor	1.15 (0.30, 4.41)	0.84			
Leukemia/lymphoma	2.08 (0.72, 6.00)	0.17			
Allogenic transplant	2.83 (0.62,12.84)	0.18		3.26 (0.63, 16.75)	0.16
Age at transplant (years)	**1.17 (1.08, 1.28)**	**<0.001**		**1.18 (1.07, 1.29)**	**<0.001**
Years since transplant	1.16 (0.97, 1.39)	0.11		1.18 (0.97, 1.44)	0.11
Age at survey (years)	**1.17 (1.08, 1.27)**	**<0.001**			
Multiple transplants	1.27 (0.33, 4.86)	0.72			
Tooth pain	2.04 (0.66, 6.29)	0.21			
Male	0.58 (0.23, 1.44)	0.24			
Race (white)	0.67 (0.22, 2.03)	0.48			

[a]restricted to four most strongly related in univariate analysis
[b]p-values based on logistic regression, global p-value is for differences in outcome across all levels of factor

Table 7. Dental development concerns (one or more missing or abnormally-shaped/sized teeth) among those transplanted <6 years of age by transplant factors [N=22 with and N=39 without any dental development concerns]

	Univariate			Multivariable[a]	
Variable	**OR (95% CI)**	**P-value[b]**	**Global p-value[b]**	**OR (95% CI)**	**P-value[b]**
Myeloablative conditioning	1.75 (0.17, 17.91)	0.64			
TBI ≥12 Gy	2.57 (0.61, 10.83)	0.20		1.89 (0.41, 8.72)	0.42
Disease type					
Non-malignant	(ref)		0.79		
Solid tumor	0.64 (0.18, 2.34)	0.51			
Leukemia/lymphoma	0.93 (0.26, 3.28)	0.91			
Allogenic transplant	1.51 (0.45, 5.05)	0.50			
Age at transplant (years)	1.17 (0.83, 1.66)	0.38		1.15 (0.79, 1.67)	0.46
Years since transplant	1.13 (0.91, 1.41)	0.25		1.10 (0.88, 1.38)	0.38
Age at survey (years)	1.14 (0.95, 1.36)	0.16			
Multiple transplants	0.39 (0.07, 2.01)	0.26		0.45 (0.08, 2.54)	0.36
Male	1.49 (0.50, 4.48)	0.48			
Race (white)	0.72 (0.15, 3.58)	0.69			

[a]restricted to four most strongly related in univariate analysis
[b]p-values based on logistic regression, global p-value is for differences in outcome across all levels of factor

Table 8. Oral chronic graft versus host disease (cGVHD) and associated symptoms by medical history cGVHD and oral cGVHD diagnoses [N=119 patients who received an allogeneic transplant]

	Medical history					
	cGVHD			Oral cGVHD		
Survey-reported	No N (%[a])	Yes N (%)	p-value[a]	No N (%)	Yes N (%)	p-value[a]
Oral cGVHD			**0.039**			**<0.001**
No	66 (70.2%)	28 (29.8%)		82 (90.1%)	9 (9.9%)	
Yes	4 (36.4%)	7 (63.6%)		2 (20.0%)	8 (80.0%)	
Mucosal sensitivity			0.73			0.20
No	67 (66.3%)	34 (33.7%)		81 (83.5%)	16 (16.5%)	
Yes	6 (60.0%)	4 (40.0%)		6 (66.7%)	3 (33.3%)	
Xerostomia			**<0.001**			**0.05**
No	68 (73.9%)	24 (26.1%)		74 (85.1%)	13 (14.9%)	
Yes	6 (30.0%)	14 (70.0%)		13 (65.0%)	7 (35.0%)	
Taste changes			**0.018**			0.17
No	72 (69.2%)	32 (30.8%)		82 (82.8%)	17 (17.2%)	
Yes	2 (25.0%)	6 (75.0%)		5 (62.5%)	3 (37.5%)	
Ulcers			0.21			1.0
No	65 (68.4%)	30 (31.6%)		75 (81.5%)	17 (18.5%)	
Yes	9 (52.9%)	8 (47.1%)		12 (80.0%)	3 (20.0%)	

[a]row percent

[b]p-value based on Chi-Square test/Fisher's exact test

Table 9. Distribution of summated oral health indices [N=149]

Index	Mean	Standard Deviation	Median	Inter-quartile range	Range
Oral Health[a]	2.6	3	2	0-4	0-18
Non-Developmental[b]	2.1	2.9	1	0-3	0-18
GVHD[c]	1	1.9	0	0-2	0-11
Developmental[d]	0.4	0.9	0	0.5	0-4

[a] includes responses from all eight oral health concern questions (tooth pain, bleeding gums with brushing, abnormally-shaped/sized teeth, missing teeth, mucosal sensitivity, ulcers, dry mouth, taste changes)
[b] includes all oral health concern questions above except abnormally-shaped/sized teeth and missing teeth
[c] includes oral health concern questions related to GVHD (mucosal sensitivity, ulcers, dry mouth, taste changes)
[d] includes responses from dental development (abnormally-shaped/sized teeth and missing teeth) only

Table 10. Dental visits (≥2 vs <2) by transplant and oral health factors [N=111 with ≥2 dental visits and N=37 with <2 visits in the past year for the univariate analysis and N=101 with ≥2 dental visits and N=30 with <2 visits for the multivariable analysis]

	Univariate			Multivariable[a]		
Variable	**OR (95% CI)**	**P-value[b]**	**Global p-value[b]**	**OR (95% CI)**	**P-value[b]**	**Global p-value[b]**
Dental insurance type			0.07			**0.043**
None	(ref)			(ref)		
Public	0.76 (0.18, 3.10)	0.70		1.40 (0.30, 6.53)	0.67	
Private	2.19 (0.60, 8.01)	0.23		**4.17 (0.98, 17.71)**	**0.053**	
Info received regarding post-tx oral health	0.69 (0.32, 1.48)	0.34		0.44 (0.17, 1.18)	0.10	
Oral health rating	0.56 (0.15, 2.07)	0.39				
Any symptom rated >=quite a bit bother	1.36 (0.28, 6.71)	0.71				
Ever had oral cGVHD	0.86 (0.22, 3.45)	0.83				
# oral issues in past month	1.08 (0.80, 1.46)	0.63				
Age at survey (years)	0.99 (0.93, 1.04)	0.59				
Years since transplant	1.05 (0.90, 1.21)	0.55				
Oral health importance	1.02 (1.00, 1.03)	0.09		**1.02 (1.00, 1.05)**	**0.05**	
Oral health transplant issues importance	1.01 (0.99, 1.02)	0.40				
Male	**2.41 (1.13, 5.15)**	**0.023**		**3.66 (1.46, 9.21)**	**0.006**	
Race (white)	1.78 (0.71, 4.42)	0.22		2.22 (0.73, 6.79)	0.16	

[a]restricted to four most strongly related in the univariate analysis

[b]p-values based on logistic regression, global p-value is for differences in outcome across all levels of factor

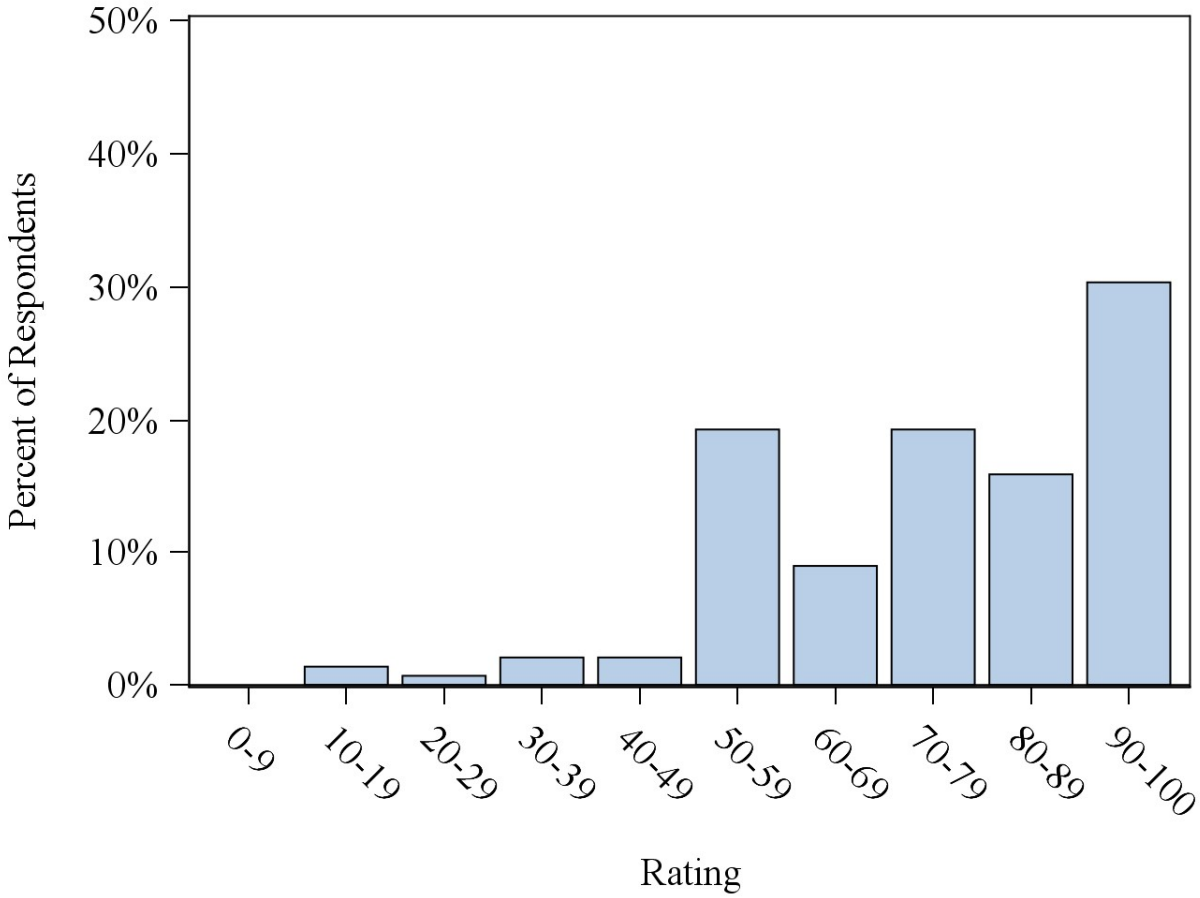

Figure 4. Distribution of patient-rated importance of oral/dental health relative to overall health.

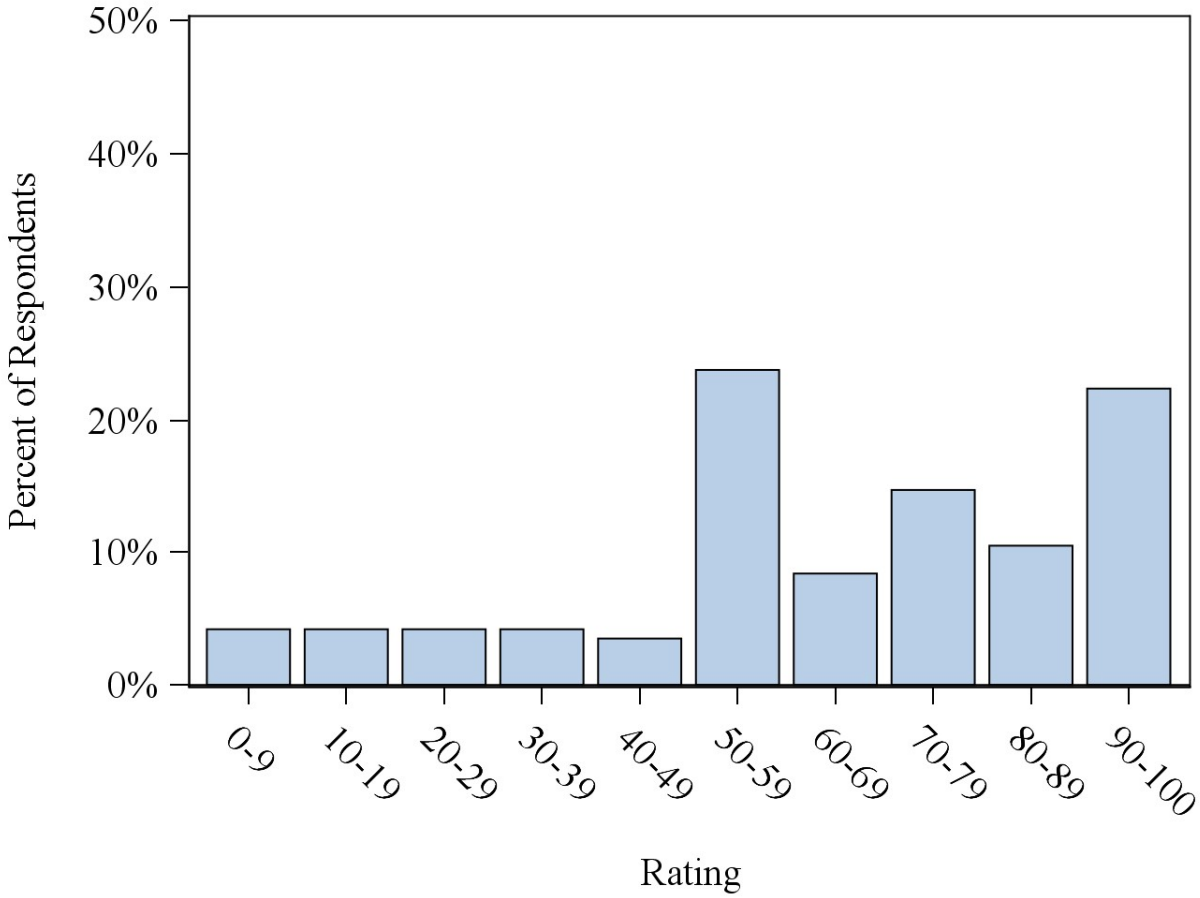

Figure 5. Distribution of patient-rated importance of oral/dental health relative to other transplant issues.

Appendix A.

Parent Survey: ages 2-7

Post-Transplant Oral and Dental Health Survey

Thank you for taking the time to answer the following questions and participate in our study. This survey has to do with how you think having a bone marrow/stem cell transplant affects your child's oral health.

It will take 5-10 minutes to fill out the survey.

We hope that you will feel comfortable sharing about your child's experiences. All of your answers will remain confidential. There are no "right" or "wrong" answers. Please feel free to write down any additional comments. However, if you wish to skip over questions, you may do so.

If you would like to talk to someone about this survey, please contact Dr. Brittany Dean at bensch@uw.edu or 971-260-0169.

POST-TRANSPLANT ORAL AND DENTAL HEALTH SURVEY

A. This Section Asks Questions About The Health of Your Child's Mouth and Teeth.

A.1 In general, would you say that the <u>health of your child's mouth and teeth</u> is:

Excellent	Very Good	Good	Fair	Poor
O_1	O_2	O_3	O_4	O_5

A.2 <u>In the past month</u>, has your child had pain in his or her teeth?

- O_0 No.
- O_1 Yes.

A.2b If yes, how much has the pain in your child's teeth bothered him/her <u>in the past month</u>?

- O_0 Not at all
- O_1 A little bit
- O_2 Somewhat
- O_3 Quite a bit
- O_4 Very much

A.3 <u>In the past month</u>, has toothbrushing or flossing caused your child's gums to bleed?

- O_0 No.
- O_1 Yes.

A.3b If yes, how much has the bleeding with toothbrushing or flossing bothered your child <u>in the past month</u>?

- O_0 Not at all
- O_1 A little bit
- O_2 Somewhat
- O_3 Quite a bit
- O_4 Very much

A.4 Do any of your child's teeth look smaller or a different shape from normal-looking teeth?

- O_0 No.
- O_1 Yes.

A.4b If yes, how much has the size or shape of his or her teeth bothered your child <u>in the past month</u>?

- O_0 Not at all
- O_1 A little bit
- O_2 Somewhat
- O_3 Quite a bit
- O_4 Very much

A.5 Is you child missing any teeth because the teeth never developed?

- O_0 No.
- O_1 Yes.
- O_9 I don't know.

A.5b If yes, how much have the missing teeth bothered your child <u>in the past month</u>?

- O_0 Not at all
- O_1 A little bit
- O_2 Somewhat
- O_3 Quite a bit
- O_4 Very much

A.6 Has your child EVER been diagnosed with chronic graft versus host disease (cGVHD) in their mouth?

- O_0 No, my child has never had mouth cGVHD.
- O_1 Yes, my child had mouth cGVHD but it has completely gone away (resolved).
- O_2 Yes, my child has mouth cGVHD currently.
- O_9 I don't know.

A.6b If your child has mouth cGVHD now, does he or she have (check all that apply):

- O_1 White changes (lines, bumps, or patches) on inside of cheeks and lips, tongue, or roof of the mouth
- O_2 Red areas on inside of cheeks and lips, tongue, or roof of the mouth
- O_3 Ulcers or sores on inside of cheeks and lips, tongue, or roof of the mouth

A.7 <u>In the past month</u>, has the skin (mucosa) inside your child's mouth been more sensitive than normal to things like: toothpaste, spices, acidic foods, carbonated beverages, etc.?

- O_0 No.
- O_1 Yes.

A.7b If yes, how much has the mouth sensitivity bothered your child <u>in the past month</u>?

- O_0 Not at all
- O_1 A little bit
- O_2 Somewhat
- O_3 Quite a bit
- O_4 Very much

A.8 <u>In the past month</u>, has your child had mouth sores or ulcers?

- O_0 No.
- O_1 Yes.

A.8b If yes, how much have the mouth sores or ulcers bothered your child <u>in the past month</u>?

- O_0 Not at all
- O_1 A little bit
- O_2 Somewhat
- O_3 Quite a bit
- O_4 Very much

A.9 In the past month, has your child seemed to have, or complained about having, a dry mouth?

- ○0 No.
- ○1 Yes.

A.9b If yes, how much has the dry mouth bothered your child in the past month?

- ○0 Not at all
- ○1 A little bit
- ○2 Somewhat
- ○3 Quite a bit
- ○4 Very much

A.10 In the past month, has your child complained of food tasting like it does *not* have normal flavor?

- ○0 No.
- ○1 Yes.

A.10b If yes, how much has the taste change bothered your child in the past month?

- ○0 Not at all
- ○1 A little bit
- ○2 Somewhat
- ○3 Quite a bit
- ○4 Very much

A.11 Considering all aspects of your child's health, how important is your child's oral/dental health *to you*?

0	1	2	3	4	5	6	7	8	9	10
Not at all important										The most important

A.12 Considering all issues related to your child's transplant, how important are your child's oral/dental transplant issues *to you*?

0	1	2	3	4	5	6	7	8	9	10
Not at all important										The most important

B. This Section Asks Questions About Your Child's Dental Care.

B.1 Has your child had an opportunity to see a dentist in the past 12 months?

- O_0 No
- O_1 Yes

B.1b If yes, how many times?

- O_1 One time
- O_2 Two times
- O_3 Three or more times

B.1c If no, what made it hard to see a dentist? (check all that apply)

- O_1 I cannot find a dentist that takes my child's insurance.
- O_2 It is too expensive.
- O_3 I do not think it is important for my child at this time.
- O_4 The dentist that my child saw previously is not adequately trained to see him/her now.
- O_5 I was told that my child should not go to the dentist.
- O_6 I do not have time to take my child to the dentist.
- O_7 My child is anxious or fearful at the dentist.
- O_8 Other (please explain): _____

B.2 Did you receive information on what to expect regarding your child's post- transplant oral health (dental health)?

- O_0 No
- O_1 Yes
- O_9 I don't know.

B.2b How prepared did you feel for your child's dental needs after transplant?

- O_0 Not at all prepared.
- O_1 Somewhat prepared.
- O_2 Very prepared.

B3. How confident are you about knowing when your child should see a dentist?

- O_0 Not at all confident.
- O_1 Somewhat confident.
- O_2 Very confident.

B.4 Does your child have *dental* insurance?

- O_0 No
- O_1 Yes
- O_9 I don't know.

B.4b If yes, what type of *dental* insurance coverage does your child have?

- O_1 Government dental insurance (such as Medicaid).
- O_2 Private dental insurance.
- O_9 I don't know.

B.5 Does your child have *medical* insurance?

- O_0 No
- O_1 Yes
- O_9 I don't know.

B.5b If yes, what type of *medical* insurance does your child have?

- ○1 Government medical insurance (such as Medicaid).
- ○2 Private medical insurance.
- ○9 I don't know.

Comments

C.1 Are there any other issues about your child's oral or dental health that you think we should know?

- ○0 No
- ○1 Yes

C1.b If yes, do you think these issues are related to your child's transplant?

- ○0 No.
- ○1 Yes.
- ○9 I don't know.

Please explain:

D. This Section Asks Questions About Your Child and Your Family.

D.1 What best describes your child's ethnic background?

- O_1 Hispanic or Latino (Mexican, Puerto Rican, Cuban, Central or South American descent)
- O_2 Not Hispanic or Latino

D.2 What best describes your child's racial background? (Select as many as apply to your child.)

- O_1 Native American or Alaska Native (including North, Central, or South American)
- O_2 African American/Black
- O_3 Asian (Cambodian, Chinese, Indian, Japanese, Korean, Malaysian, Pakistani, Filipino, Thai, Vietnamese)
- O_4 East Indian
- O_5 Native Hawaiian
- O_6 Pacific Islander
- O_7 White/Caucasian
- O_8 Other, **non-white**, please describe: _____

D.3 What is your specific relationship to your child?

- O_1 mother (biologic or adoptive)
- O_2 father (biologic or adoptive)
- O_3 foster parent
- O_4 grandparent
- O_5 other, please explain: _____

We appreciate the time you spent completing this survey.

Appendix B.

Youth Survey: ages 8-17

Post-Transplant Oral and Dental Health Survey

Thank you for taking the time to answer the following questions about how having a bone marrow/stem cell transplant affects your mouth and how you feel.

It will take 5-10 minutes to fill out the survey. Please fill out pages 1-4 by yourself and ask your parent or guardian to fill out pages 5-7.

We hope that you will feel comfortable sharing your thoughts with us. Only we will see your answers and we will not share them with others. There are no "right" or "wrong" answers. Please feel free to write down any additional ideas or thoughts you have as you answer the questions. If you wish to skip over any questions, you may do so.

If you would like to talk to someone about this survey, please contact Dr. Brittany Dean at bensch@uw.edu or 971-260-0169.

POST-TRANSPLANT ORAL AND DENTAL HEALTH SURVEY:

YOUTH AGES 8-17 PORTION

A. This Section Asks Questions About The Health of Your Mouth and Teeth.

A.1 In general, would you say the health of your mouth and teeth is:

Excellent	Very Good	Good	Fair	Poor
O_1	O_2	O_3	O_4	O_5

A.2 <u>In the past month</u>, have you had pain in your teeth?

- O_0 No.
- O_1 Yes.

A.2b If yes, how much has the pain in your teeth bothered you <u>in the past month</u>?

- O_0 Not at all
- O_1 A little bit
- O_2 Somewhat
- O_3 Quite a bit
- O_4 Very much

A.3 <u>In the past month</u>, has toothbrushing or flossing caused your gums to bleed?

- O_0 No.
- O_1 Yes.

A.3b If yes, how much has the bleeding with toothbrushing or flossing bothered you <u>in the past month</u>?

- O_0 Not at all
- O_1 A little bit
- O_2 Somewhat
- O_3 Quite a bit
- O_4 Very much

A.4 Do any of your teeth look smaller or a different shape?

- O_0 No.
- O_1 Yes.

A.4b If yes, how much has the size or shape of your teeth bothered you <u>in the past month</u>?

- O_0 Not at all
- O_1 A little bit
- O_2 Somewhat
- O_3 Quite a bit
- O_4 Very much

A.5 Are you missing any teeth because the teeth never developed?

- O_0 No.
- O_1 Yes.
- O_9 I don't know.

A.5b If yes, how much have the missing teeth bothered you <u>in the past month</u>?

- O_0 Not at all
- O_1 A little bit
- O_2 Somewhat
- O_3 Quite a bit
- O_4 Very much

A.6 Have you EVER been diagnosed with chronic graft versus host disease (cGVHD) in your mouth?

- O_0 No, I have never been diagnosed with mouth cGVHD.
- O_1 Yes, I have been diagnosed with mouth cGVHD but it has completely gone away (resolved).
- O_2 Yes, I have been diagnosed with mouth cGVHD and I have it currently.
- O_9 I don't know.

A.6b If you have mouth cGVHD <u>currently</u>, do you have (check all that apply):

- O_1 White changes (lines, bumps, or patches) on inside of cheeks and lips, tongue, or roof of the mouth
- O_2 Red areas on inside of cheeks and lips, tongue, or roof of the mouth
- O_3 Sores on inside of cheeks and lips, tongue, or roof of the mouth

A.7 <u>In the past month</u>, has the skin inside your mouth been more sensitive than normal to things like: toothpaste, spicy foods, acidic foods (such as orange juice or tomatoes), or carbonated beverages (such as soda, pop, or sparkling water)?

- O_0 No.
- O_1 Yes.

A.7b If yes, how much has your mouth sensitivity bothered you <u>in the past month</u>?

- O_0 Not at all
- O_1 A little bit
- O_2 Somewhat
- O_3 Quite a bit
- O_4 Very much

A.8 <u>In the past month</u>, have you had sores in your mouth?

- O_0 No.
- O_1 Yes.

A.8b If yes, how much have the sores in your mouth bothered you <u>in the past month</u>?

- O_0 Not at all
- O_1 A little bit
- O_2 Somewhat
- O_3 Quite a bit
- O_4 Very much

A.9 In the past month, has your mouth been dry?

- ○0 No.
- ○1 Yes.

A.9b If yes, how much has the dry mouth bothered you in the past month?

- ○0 Not at all
- ○1 A little bit
- ○2 Somewhat
- ○3 Quite a bit
- ○4 Very much

A.10 In the past month, has food tasted like it does *not* have normal flavor?

- ○0 No.
- ○1 Yes.

A.10b If yes, how much has food not having normal flavor bothered you in the past month?

- ○0 Not at all
- ○1 A little bit
- ○2 Somewhat
- ○3 Quite a bit
- ○4 Very much

A.11 Considering all aspects of your health, how important is the health of your mouth and teeth *to you*?

0	1	2	3	4	5	6	7	8	9	10
Not at all important										The most important

A.12 Considering all issues related to your transplant, how important are your mouth and teeth transplant issues *to you*?

0	1	2	3	4	5	6	7	8	9	10
Not at all important										The most important

Comments

YC1. Are there any other issues about the health of your mouth and teeth that you think we should know?

- ○0 No
- ○1 Yes

YC1.b If yes, do you think these issues are related to your transplant?

- ○0 No.
- ○1 Yes.
- ○9 I don't know.

Please explain:

YC2. Who completed this portion of the survey?

- ○1 Patient
- ○2 Parent or guardian
- ○3 Other, please explain: _____

Thank you for completing this survey.

POST-TRANSPLANT ORAL AND DENTAL HEALTH SURVEY: PARENT PORTION

B. This Section Asks Questions About Your Child's Dental Care.

B.1 Has your child had an opportunity to see a dentist in the past 12 months?

- ○0 No
- ○1 Yes

B.1b If yes, how many times?

- ○1 One time
- ○2 Two times
- ○3 Three or more times

B.1c If no, what made it hard to see a dentist? (check all that apply)

- ○1 I cannot find a dentist that takes my child's insurance.
- ○2 It is too expensive.
- ○3 I do not think it is important for my child at this time.
- ○4 The dentist that my child saw previously is not adequately trained to see him/her now.
- ○5 I was told that my child should not go to the dentist.
- ○6 I do not have time to take my child to the dentist.
- ○7 My child is anxious or fearful at the dentist.
- ○8 Other, please explain:

_____

B.2 Did you receive information on what to expect regarding your child's oral health (dental health) following your child's transplant?

- ○0 No
- ○1 Yes
- ○9 I don't know.

B.2b How prepared did you feel for your child's dental needs after transplant?

- ○0 Not at all prepared.
- ○1 Somewhat prepared.
- ○2 Very prepared.

B.3 How confident are you about knowing when your child should see a dentist?

- ○0 Not at all confident.
- ○1 Somewhat confident.
- ○2 Very confident.

B.4 Does your child have dental insurance?

- ○0 No
- ○1 Yes
- ○9 I don't know.

B.4b If yes, what type of *dental* insurance coverage does your child have?

- ○1 Government dental insurance (such as Medicaid).
- ○2 Private dental insurance.
- ○9 I don't know.

B.5 Does your child have medical insurance?

- ○0 No
- ○1 Yes
- ○9 I don't know.

B.5b If yes, what type of *medical* insurance does your child have?

- ○1 Government medical insurance (such as Medicaid).
- ○2 Private medical insurance.
- ○9 I don't know.

Parent Comments

PC.1 Are there any other issues about your child's oral or dental health that you think we should know?

- ○0 No
- ○1 Yes

PC1.b If yes, do you think these issues are related to your child's transplant?

- ○0 No.
- ○1 Yes.
- ○9 I don't know.

Please explain:

Over ➡

D. This Section Asks Questions About Your Child and Your Family.

D.1 What best describes your child's ethnic background?

- O_1 Hispanic or Latino (Mexican, Puerto Rican, Cuban, Central or South American descent)
- O_2 Not Hispanic or Latino

D.2 What best describes your child's racial background? (Select as many as apply to your child.)

- O_1 Native American or Alaska Native (including North, Central, or South American)
- O_2 African American/Black
- O_3 Asian (Cambodian, Chinese, Indian, Japanese, Korean, Malaysian, Pakistani, Filipino, Thai, Vietnamese)
- O_4 East Indian
- O_5 Native Hawaiian
- O_6 Pacific Islander
- O_7 White/Caucasian
- O_8 Other, **non-white**, please describe: _____

D.3 What is your relationship to your child?

- O_1 Mother (biologic or adoptive)
- O_2 Father (biologic or adoptive)
- O_3 Foster parent
- O_4 Grandparent
- O_5 Other, please explain: _____

D.4 Who completed this portion of the survey?

- O_1 Patient
- O_2 Parent or guardian of patient
- O_3 Other, please explain: _____

We appreciate the time you spent completing this survey.

Appendix C.

Adult Survey: ages 18+

Post-Transplant Oral and Dental Health Survey

Thank you for taking the time to answer the following questions and participate in our study of how having a bone marrow/stem cell transplant at a young age affects oral health quality of life.

It will take 5-10 minutes to fill out the survey.

We hope that you will feel comfortable sharing your thoughts with us. All of your answers will remain confidential. There are no "right" or "wrong" answers. Please feel free to write down any additional comments. However, if you wish to skip over questions, you may do so.

If you would like to talk to someone about this survey, please contact Dr. Brittany Dean at bensch@uw.edu or 971-260-0169.

POST-TRANSPLANT ORAL AND DENTAL HEALTH SURVEY

A. This Section Asks Questions About The Health of Your Mouth and Teeth.

A.1 In general, would you say the health of your mouth and teeth is:

Excellent	Very Good	Good	Fair	Poor
O_1	O_2	O_3	O_4	O_5

A.2 <u>In the past month</u>, have you had pain in your teeth?

- O_0 No.
- O_1 Yes.

A.2b If yes, how much has the pain in your teeth bothered you <u>in the past month</u>?

- O_0 Not at all
- O_1 A little bit
- O_2 Somewhat
- O_3 Quite a bit
- O_4 Very much

A.3 <u>In the past month</u>, has toothbrushing or flossing caused your gums to bleed?

- O_0 No.
- O_1 Yes.

A.3b If yes, how much has the bleeding with toothbrushing or flossing bothered you <u>in the past month</u>?

- O_0 Not at all
- O_1 A little bit
- O_2 Somewhat
- O_3 Quite a bit
- O_4 Very much

A.4 Do any of your teeth look smaller or a different shape?

- O_0 No.
- O_1 Yes.

A.4b If yes, how much has the size or shape of your teeth bothered you <u>in the past month</u>?

- O_0 Not at all
- O_1 A little bit
- O_2 Somewhat
- O_3 Quite a bit
- O_4 Very much

A.5 Are you missing any teeth because the teeth never developed?

- O_0 No.
- O_1 Yes.
- O_9 I don't know.

A.5b If yes, how much have the missing teeth bothered you <u>in the past month</u>?

- O_0 Not at all
- O_1 A little bit
- O_2 Somewhat
- O_3 Quite a bit
- O_4 Very much

A.6 Have you EVER been diagnosed with chronic graft versus host disease (cGVHD) in your mouth?

- O_0 No, I have never been diagnosed with mouth cGVHD.
- O_1 Yes, I have been diagnosed with mouth cGVHD but it has completely gone away (resolved).
- O_2 Yes, I have been diagnosed with mouth cGVHD and I have it currently.
- O_9 I don't know.

A.6b If you have mouth cGVHD <u>currently</u>, do you have (check all that apply):

- O_1 White changes (lines, bumps, or patches) on inside of cheeks and lips, tongue, or roof of the mouth
- O_2 Red areas on inside of cheeks and lips, tongue, or roof of the mouth
- O_3 Ulcers or sores on inside of cheeks and lips, tongue, or roof of the mouth

A.7 <u>In the past month</u>, has the skin (mucosa) inside your mouth been more sensitive than normal to things like: toothpaste, spices, acidic foods, carbonated beverages, etc.?

- O_0 No.
- O_1 Yes.

A.7b If yes, how much has your mouth sensitivity bothered you <u>in the past month</u>?

- O_0 Not at all
- O_1 A little bit
- O_2 Somewhat
- O_3 Quite a bit
- O_4 Very much

A.8 <u>In the past month</u>, have you had mouth sores or ulcers?

- O_0 No.
- O_1 Yes.

A.8b If yes, how much have your mouth sores or ulcers bothered you <u>in the past month</u>?

- O_0 Not at all
- O_1 A little bit
- O_2 Somewhat
- O_3 Quite a bit
- O_4 Very much

A.9 In the past month, has your mouth been dry?

- ○0 No.
- ○1 Yes.

A.9b If yes, how much has the dry mouth bothered you in the past month?

- ○0 Not at all
- ○1 A little bit
- ○2 Somewhat
- ○3 Quite a bit
- ○4 Very much

A.10 In the past month, has food tasted like it does *not* have normal flavor?

- ○0 No.
- ○1 Yes.

A.10b If yes, how much has food not having normal flavor bothered you in the past month?

- ○0 Not at all
- ○1 A little bit
- ○2 Somewhat
- ○3 Quite a bit
- ○4 Very much

A.11 Considering all aspects of your health, how important is your oral/dental health *to you*?

0	1	2	3	4	5	6	7	8	9	10
Not at all important										The most important

A.12 Considering all issues related to your transplant, how important are your oral/dental transplant issues *to you*?

0	1	2	3	4	5	6	7	8	9	10
Not at all important										The most important

B. This Section Asks Questions About Your Dental Care.

B.1 Have you had an opportunity to see a dentist in the past 12 months?

- O_0 No.
- O_1 Yes.

B.1b If yes, how many times?

- O_1 One time
- O_2 Two times
- O_3 Three or more times

B.1c If no, what made it hard to see a dentist? (check all that apply)

- O_1 I cannot find a dentist that takes my insurance.
- O_2 It is too expensive.
- O_3 I do not think it is important for me at this time.
- O_4 The dentist that I saw previously is not adequately trained to see me now.
- O_5 I was told that I should not go to the dentist.
- O_6 I do not have time to go to the dentist.
- O_7 I am anxious or fearful at the dentist.
- O_8 Other, please explain: _____

B.2 Did you receive information on what to expect regarding your post-transplant oral health (dental health)?

- O_0 No.
- O_1 Yes.
- O_9 I don't know.

B.2b How prepared did you feel for your dental needs after transplant?

- O_0 Not at all prepared.
- O_1 Somewhat prepared.
- O_2 Very prepared.

B.3 How confident are you about knowing when you should see a dentist?

- O_0 Not at all confident.
- O_1 Somewhat confident.
- O_2 Very confident.

B.4 Do you have dental insurance?

- O_0 No.
- O_1 Yes.
- O_9 I don't know.

B.4b If yes, what type of *dental* insurance do you have?

- O_1 Government dental insurance (such as Medicaid).
- O_2 Private dental insurance
- O_9 I don't know.

B.5 Do you have medical insurance?

- ○0 No.
- ○1 Yes.
- ○9 I don't know.

B.5b If yes, what type of *medical* insurance do you have?

- ○1 Government medical insurance (such as Medicaid).
- ○2 Private medical insurance
- ○9 I don't know.

Comments

C.1 Are there any other issues about your oral or dental health that you think we should know?

- ○0 No.
- ○1 Yes.

C.1b If yes, do you think these issues are related to your transplant?

- ○0 No.
- ○1 Yes.
- ○9 I don't know.

Please explain:

D. This Section Asks Questions About You and Your Family.

D.1 What best describes your ethnic background?

- ○1 Hispanic or Latino (Mexican, Puerto Rican, Cuban, Central or South American descent)
- ○2 Not Hispanic or Latino

D.2 What best describes your racial background? (Select as many as apply to you.)

- ○1 Native American or Alaska Native (including North, Central, or South American)
- ○2 African American/Black
- ○3 Asian (Cambodian, Chinese, Indian, Japanese, Korean, Malaysian, Pakistani, Filipino, Thai, Vietnamese)
- ○4 East Indian
- ○5 Native Hawaiian
- ○6 Pacific Islander
- ○7 White/Caucasian
- ○8 Other, **non-white**, please describe: _____

D.3 Who completed this survey?

- ○1 Patient
- ○2 Parent or guardian
- ○3 Other, please explain: _____

We appreciate the time you spent completing this survey.

Appendix D.

Invitation Email for Parent Survey: ages 2-7

Dear <parent_title> <parent_last_name>,

We are writing to ask if you would be willing to fill out a short electronic survey about <pt_first_name>. We are a research team made up of professionals within the Seattle Cancer Care Alliance. Our research focuses on how having a bone marrow or stem cell transplant at a young age affects the health of your mouth and teeth. Some people experience more dental problems because of the long-term effects of transplant. We hope that knowing which types of people experience which effects can help doctors and dentists to deliver better care to these patients.

The survey will take 5-10 minutes to complete and asks several questions about how your child's mouth and teeth influence how he or she feels. We will compare your answers to information from your child's medical chart to study how his or her diagnoses and treatment may have affected his or her mouth.

The information collected from you in this study will be kept strictly confidential and will not be included in your child's medical or dental record.

The risks associated with this research study may include discomfort or stress in answering questions about your child's oral health situation. Participation in this study is optional and your child's medical or dental care will not be affected whether or not you complete this survey. While neither you nor your child will benefit directly from this research study, we plan to learn from your answers how we can better help manage oral health needs for others who undergo bone marrow or stem cell transplantation.

Please use the following link to access the survey:
[survey-link] or,
[survey-url]

If we do not receive your response electronically, we will mail a paper copy to your home address, for your convenience. If you wish to opt out and prefer not to be contacted further, please go to the survey and choose the-opt out option in the first question.

Thank you very much for your time and consideration. If you have any questions about this survey, please contact Dr. Brittany Dean at bensch@uw.edu or 971-260-0169.

Sincerely,

Mark Schubert, DDS, MSD
Seattle Cancer Care Alliance

Ann Dahlberg, MD
Seattle Children's Hospital

Brittany Dean, DDS
UW School of Dentistry

Appendix E.

Invitation Email for Youth Survey: ages 8-17

Dear <parent_title> <parent_last_name>,

We are writing to ask if you and your child <pt_first_name> would be willing to fill out a short electronic survey included with this letter.

We are a research team made up of professionals within the Seattle Cancer Care Alliance. Our research focuses on how having a bone marrow or stem cell transplant at a young age affects the health of your mouth and teeth. Some people experience more dental problems because of the long-term effects of transplant. We hope that knowing which types of people have the most effects can help doctors and dentists to deliver better care to these patients.

The survey will take 5-10 minutes to complete. It asks several questions about how your child's mouth and teeth influence how he or she feels. We will compare your answers to information from your child's medical chart to study how his or her diagnoses and treatment may have affected his or her mouth. The information collected from you and your child in this study will be kept strictly confidential and will not be included in your child's medical or dental record.

The risks associated with this research study may include discomfort or stress in answering questions about your child's oral health situation. Participation in this study is optional and your child's medical or dental care will not be affected whether or not you complete this survey. While neither you nor your child will benefit directly from this research study, we plan to learn from your answers how we can better help manage oral health needs for others who undergo bone marrow or stem cell transplantation.

Please use the following link to access the survey:
[survey-link] or, [survey-url]

If we do not receive your response electronically, we will mail a paper copy to your home address, for your convenience. If you wish to opt out and prefer not to be contacted further, please go to the survey and choose the opt-out option in the first question.

Thank you very much for your time and consideration. If you have any questions about this survey, please contact Dr. Brittany Dean at bensch@uw.edu or 971-260-0169.

Sincerely,

Mark Schubert, DDS, MSD
Seattle Cancer Care Alliance

Ann Dahlberg, MD
Seattle Children's Hospital

Brittany Dean, DDS
UW School of Dentistry

Appendix F.

Invitation Email for Adult Survey: ages 18+

Dear <pt_title> <pt_last_name>,

We are writing to ask if you would be willing to fill out a short online survey.

We are a research team made up of professionals within the Seattle Cancer Care Alliance. Our research focuses on how having a bone marrow or stem cell transplant at a young age affects the health of your mouth and teeth. Some people experience more dental problems because of the long-term effects of transplant. We hope that knowing which types of people have the most effects can help doctors and dentists to deliver better care to these patients.

The survey will take 5-10 minutes to complete. It asks several questions about how your mouth and teeth influence how you feel. We will compare your answers to information from your medical chart to study how your diagnoses and treatment may have affected your mouth.

The information collected from you in this study will be kept strictly confidential and will not be included in your medical or dental record.

The risks associated with this research study may include discomfort or stress in answering questions about your oral health. Participation in this survey is optional. Your medical or dental care will not be affected whether or not you complete this survey. While you will not benefit directly from this research study, we plan to learn from your answers to help manage oral health needs for others in the future who undergo bone marrow or stem cell transplantation.

Please use the following link to access the survey:
[survey-link] or, [survey-url]

If we do not receive your response electronically, we will mail a paper copy to your home address, for your convenience. If you wish to opt out and prefer not to be contacted further, please go to the survey and choose the-opt out option in the first question.

Thank you very much for your time and consideration. If you have any questions about this survey, please contact Dr. Brittany Dean at bensch@uw.edu or 971-260-0169.

Sincerely,

Mark Schubert, DDS, MSD
Seattle Cancer Care Alliance

Ann Dahlberg, MD
Seattle Children's Hospital

Brittany Dean, DDS
UW School of Dentistry

Appendix G.

Informational Letter for Parent Survey: ages 2-7

Dear «parents»,

We are writing to ask if you would be willing to fill out the short survey about «first» included with this letter.

We are a research team made up of professionals within the Seattle Cancer Care Alliance. Our research focuses on how having a bone marrow or stem cell transplant at a young age affects the health of your mouth and teeth. Some people experience more dental problems because of the long-term effects of transplant. We hope that knowing which types of people experience which effects can help doctors and dentists to deliver better care to these patients.

The survey will take 5-10 minutes to complete and asks several questions about how your child's mouth and teeth influence how he or she feels. We will compare your answers to information from your child's medical chart to study how his or her diagnoses and treatment may have affected his or her mouth.

The information collected from you in this study will be kept strictly confidential and will not be included in your child's medical or dental record.

The risks associated with this research study may include discomfort or stress in answering questions about your child's oral health situation. Participation in this study is optional and your child's medical or dental care will not be affected whether or not you complete this survey. While neither you nor your child will benefit directly from this research study, we plan to learn from your answers how we can better help manage oral health needs for others who undergo bone marrow or stem cell transplantation.

If you agree to participate in this survey study, please complete the enclosed survey and return it to us with the self-addressed, stamped envelope included. Return the opt-out card in the envelope instead if you do not want to participate and do not want to be contacted further. Thank you very much for your time and consideration. If you have any questions about this survey, please contact Dr. Brittany Dean at bensch@uw.edu or 971-260-0169.

Sincerely,

Mark Schubert, DDS, MSD
Seattle Cancer Care Alliance

Ann Dahlberg, MD
Seattle Children's Hospital

Brittany Dean, DDS
UW School of Dentistry

Appendix H.

Informational Letter for Youth Survey: ages 8-17 (for youth patient)

Dear «first»,

We are writing to ask if you would be willing to fill out the short research survey included with this letter.

Some people experience more dental problems after having a bone marrow or stem cell transplant. We hope that our research will help us identify which types of people have the most problems in order to help doctors and dentists to take better care of these patients.

The survey will take 5-10 minutes to complete. It asks questions about how your mouth and teeth make you feel. There is also a portion for your parent or guardian to fill out about your dental care in the past. We will compare your answers to information from your medical chart to study how your past illness and treatment may have affected your mouth. We will not share your answers with other people.

You do not have to complete this survey. Some people may find it uncomfortable to answer questions about their mouth and teeth. It is OK to say yes or no.

This research will not help you now, but we hope it will teach us how to take better care of patients like you.

If you want to say "yes" to filling out the survey, please complete your section (*pages 1-4*) and have your parent or guardian complete the last section (*pages 5-7*) and then send the survey back to us in the envelope provided. Return the opt-out card in the envelope instead if you do not want to participate and do not want to be contacted further.

If you have any questions about this survey, you can email or call Dr. Brittany Dean at bensch@uw.edu or 971-260-0169.

Sincerely,

Mark Schubert, DDS, MSD
Seattle Cancer Care Alliance

Ann Dahlberg, MD
Seattle Children's Hospital

Brittany Dean, DDS
UW School of Dentistry

Appendix I.

Informational Letter for Youth Survey: ages 8-17 (for parent/guardian)

Dear «parents»,

We are writing to ask if you and your child «first» would be willing to fill out the short survey included with this letter.

We are a research team made up of professionals within the Seattle Cancer Care Alliance. Our research focuses on how having a bone marrow or stem cell transplant at a young age affects the health of your mouth and teeth. Some people experience more dental problems because of the long-term effects of transplant. We hope that knowing which types of people have the most effects can help doctors and dentists to deliver better care to these patients.

The survey will take 5-10 minutes to complete. It asks several questions about how your child's mouth and teeth influence how he or she feels. We will compare your answers to information from your child's medical chart to study how his or her diagnoses and treatment may have affected his or her mouth.

The information collected from you and your child in this study will be kept strictly confidential and will not be included in your child's medical or dental record.

The risks associated with this research study may include discomfort or stress in answering questions about your child's oral health situation. Participation in this study is optional and your child's medical or dental care will not be affected whether or not you complete this survey. While neither you nor your child will benefit directly from this research study, we plan to learn from your answers how we can better help manage oral health needs for others who undergo bone marrow or stem cell transplantation.

If you agree to participate in this survey study, please complete the enclosed survey (*pages 1-4 filled out by your child, pages 5-7 filled out by you*) and return it to us with the self-addressed, stamped envelope included. Return the opt-out card in the envelope instead if you do not want to participate and do not want to be contacted further.

Thank you very much for your time and consideration. If you have any questions about this survey, please contact Dr. Brittany Dean at bensch@uw.edu or 971-260-0169.

Sincerely,

Mark Schubert, DDS, MSD
Seattle Cancer Care Alliance

Ann Dahlberg, MD
Seattle Children's Hospital

Brittany Dean, DDS
UW School of Dentistry

Appendix J.

Informational Letter for Adult Survey: ages 18+

Dear «title» «last»,

We are writing to ask if you would be willing to fill out the short survey included with this letter.

We are a research team made up of professionals within the Seattle Cancer Care Alliance. Our research focuses on how having a bone marrow or stem cell transplant at a young age affects the health of your mouth and teeth. Some people experience more dental problems because of the long-term effects of transplant. We hope that knowing which types of people have the most effects can help doctors and dentists to deliver better care to these patients.

The survey will take 5-10 minutes to complete. It asks several questions about how your mouth and teeth influence how you feel. We will compare your answers to information from your medical chart to study how your diagnoses and treatment may have affected your mouth. The information collected from you in this study will be kept strictly confidential and will not be included in your medical or dental record.

The risks associated with this research study may include discomfort or stress in answering questions about your oral health. Participation in this survey is optional. Your medical or dental care will not be affected whether or not you complete this survey. While you will not benefit directly from this research study, we plan to learn from your answers to help manage oral health needs for others in the future who undergo bone marrow or stem cell transplantation.

If you agree to participate in the survey study, please complete the enclosed survey and return it to us with the self-addressed, stamped envelope included. Return the opt-out card in the envelope instead if you do not want to participate and do not want to be contacted further.

Thank you very much for your time and consideration. If you have any questions about this survey, please contact Dr. Brittany Dean at bensch@uw.edu or 971-260-0169.

Sincerely,

Mark Schubert, DDS, MSD
Seattle Cancer Care Alliance

Ann Dahlberg, MD
Seattle Children's Hospital

Brittany Dean, DDS
UW School of Dentistry

Appendix K.

Primary Disease Type by Group

		N	%
Disease group	**Disease**		
Non-malignant	**: Pancytopenia**	1	0.3
	AA: AA Aplastic anemia, NOS	36	9.4
	AA: AA Aplastic anemia,constitutional Fanconi's anemia	4	1.0
	AA: Congenital dyserythropoietic anemia	1	0.3
	ALD: Adrenoleukodystrophy	1	0.3
	BLACKFAN: Pure red cell anemia, chronic	4	1.0
	CGD: CGD Chronic Granulomatous Disease	7	1.8
	CIMMDIS: Hyperimmunoglobulin M syndrome	1	0.3
	CIMMDIS: Immune deficiency disorder, disease or syndrome	28	7.3
	CIMMDIS: Immunodeficiency with Thrombocytopenia and eczema	5	1.3
	HLH: Familial hemophagocytic histiocytosis	6	1.6
	HLH: Hemophagocytic lymphohistiocytosis	7	1.8
	JRA: Rheumatoid arthritis, juvenile	1	0.3
	MS: Multiple Sclerosis	1	0.3
	OTHER: Albers-Schoenberg Syndrome	2	0.5
	OTHER: Anemia, NOS	1	0.3
	OTHER: Congenital neutropenia	1	0.3
	OTHER: Dyskeratosis congenita	2	0.5
	OTHER: Glanzmann thromboasthenia	2	0.5
	OTHER: Lymphoproliferative Disease, NOS	3	0.8
	OTHER: Malignant histiocytosis	1	0.3
	OTHER: Shwachman-Diamond Syndrome	3	0.8
	OTHER: Thrombocytopenia	1	0.3
	PNH: PNH Paroxysmal nocturnal hemoglobinuria	3	0.8
	PVERA: Polycythemia Vera	1	0.3
	SICKLE: Hemoglobin S disease (Sickle cell)	10	2.6
	SS: Systemic Sclerosis, Progressive	2	0.5
	THALASSEM: Thalassemic Syndrome, NOS	3	0.8

		N	%
Solid tumor	**HD: HD Hodgkin's disease, NOS**	7	1.8
	HD: HD Hodgkin's disease, nodular sclerosis, NOS	11	2.9
	NBL: Neuroblastoma, NOS	38	9.9
	NHL: ML Malig. lymphoma non-Hodgkin's, NOS	5	1.3
	NHL: ML Malig. lymphoma, follicular, NOS	1	0.3
	NHL: ML Malig. lymphoma, lg. cell, diffuse	3	0.8
	NHL: ML Malig. lymphoma, lymphoblastic	3	0.8
	OTHER: Nephroblastoma, NOS	3	0.8
	OTHERCA: Germ Cell Tumor, NOS	3	0.8
	SARCOMA: SARC Ewing's Sarcoma	2	0.5
Leukemia/lymphoma	**ALL: ALL Acute lymphoblastic leukemia**	94	24.5
	ANL: AEL Erythroleukemia	1	0.3
	ANL: AML Acute megakaryoblastic leukemia	1	0.3
	ANL: AML Acute myeloid leukemia	36	9.4
	ANL: AMML Acute myelomonocytic leukemia	4	1.0
	ANL: AMOL Acute monocytic leukemia	2	0.5
	ANL: APL Acute promyelocytic leukemia	1	0.3
	ANL: Biphenotypic leukemia (AML vs ALL)	5	1.3
	CML: CML Chronic myeloid leukemia	7	1.8
	MDS: Chronic Myelomonocytic Leukemia, Juvenile (JMML)	3	0.8
	MDS: MDS Myelodysplastic syndrome (Preleukemia)	6	1.6
	MDS: Myeloproliferative disease,NOS	1	0.3
	MDS: RA Refractory Anemia, NOS	4	1.0
	MDS: RAEB Refractory anemia with excess blasts	1	0.3
	MDS: RARS Sideroblastic Anemia Acquired	1	0.3
	MDS: Refractory cytopenia with multilineage dysplasia	1	0.3
	OTHER: Large Granular Lymphocytic T-Cell Leukemia (LGLT)	1	0.3
All		383	100.0

Appendix L.

Conditioning Protocol by Group

		N	%
Myeloablative	**Conditioning regimen**		
No	**CLOFAR,TBI(200)**	1	0.3
	CLOFAR,TBI(300)	1	0.3
	CY	1	0.3
	CY,CAMP,FLU	1	0.3
	CY,FLU,H-TBI(400)	11	2.9
	CY,FLU,TBI(200)	7	1.8
	CY,FLU,TBI(300)	1	0.3
	CY,LI(1400),FLU,TBI(200)	1	0.3
	FLU,H-TBI(400)	5	1.3
	FLU,TBI(200)	3	0.8
	FLU,TBI(300)	1	0.3
	NONE	1	0.3

		N	%
Yes	**BU,CLOFAR**	1	0.3
	BU,CY	14	3.7
	BU,CY,ATG	15	3.9
	BU,CY,FLU,ATG	2	0.5
	BU,CY,L-PAM	2	0.5
	BU,CY,RITUX,ATG	1	0.3
	BU,CY,TEPA,FLU,ATG	2	0.5
	BU,FLU,ATG	1	0.3
	BU,L-PAM	5	1.3
	BU,L-PAM,TEPA	5	1.3
	CAMP,FLU	1	0.3
	CY	1	0.3
	CY,ATG	16	4.2
	CY,ATG,H-TBI(400)	1	0.3
	CY,ATG,H-TBI(600)	1	0.3
	CY,ATG,H-TBI(800)	2	0.5
	CY,ATG,TBI(200)	3	0.8
	CY,F-TBI(1320)	1	0.3

		N	%
	CY,FLU,ATG,TBI(200)	11	2.9
	CY,FLU,H-TBI(1320)	26	6.8
	CY,FLU,H-TBI(400)	1	0.3
	CY,H-TBI(1200)	5	1.3
	CY,H-TBI(1320)	30	7.8
	CY,LI(1000),H-TBI(1320)	1	0.3
	CY,LI(1080),FLU,H-TBI(1320)	1	0.3
	CY,LI(400),FLU,H-TBI(1320)	19	5.0
	CY,LI(400),H-TBI(1200)	2	0.5
	CY,LI(400),H-TBI(1320)	15	3.9
	CY,TEPA,FLU,F-TBI(400)	2	0.5
	CY,VP-16,H-TBI(1200)	6	1.6
	FLU,H-TBI(1200)	1	0.3
	FLU,H-TBI(400)	1	0.3
	H-TBI(1320)	3	0.8
	IFOS,TAXOL,CARBO	1	0.3
	L-PAM,ARA-C,BCNU,VP-16	9	2.3
	L-PAM,ARA-C,BCNU,VP-16,ATG	1	0.3
	L-PAM,CAMP,FLU	2	0.5
	L-PAM,TEPA,ARA-C,VP-16	1	0.3
	L-PAM,VP-16,CARBO	36	9.4
	LI(1400),TREO,FLU,TBI(200)	1	0.3
	LI(1600),TREO,FLU,TBI(200)	1	0.3
	LI(400),H-TBI(1200)	2	0.5
	LI(400),H-TBI(1320)	2	0.5
	MPRED,TREO,FLU,ATG,TBI(300)	1	0.3
	NONE	1	0.3
	TEPA,FLU,H-TBI(1320)	15	3.9
	TEPA,LI(400),FLU,H-TBI(1320)	6	1.6
	TEPA,VP-16,CARBO	1	0.3
	TREO,FLU	2	0.5
	TREO,FLU,ATG	43	11.2
	TREO,FLU,ATG,TBI(200)	1	0.3
	TREO,FLU,ATG,TBI(300)	2	0.5
	TREO,FLU,TBI(200)	22	5.7
	VP-16,TAXOL,CARBO	1	0.3
All		383	100.0