CCSS Analysis Concept Proposal

1. Title: Predictors of future quality of life in adolescent survivors of adolescent cancer

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3. Background and rationale:

Statistics from the National Cancer Institute show 5-year survival probability for all pediatric cancers combined to be 80%.[1] As survival rates increase and more pediatric cancer patients are surviving to adulthood, it is important not only to understand how the cancer experience impacts future quality of life, but also to know who is most at risk for poor quality of life. Many studies describe overall quality of life among survivors of childhood cancer,[2-13] however few attempt to actually predict who is at greatest risk for reporting poor health related quality of life (HRQOL).[14] This proposal differs from previous studies of HRQOL in CCSS survivors in that we will focus on those survivors diagnosed during adolescence. Our goal is to develop a practical tool for use by clinicians to identify those adolescents with cancer most at risk for a poor QOL outcome so they can be referred for preventive services.

Adolescence is characterized by great physiological and cognitive changes, and is considered a time of transition from dependence to independence.[15] These changes result in an increased concern with self image and contribute to the confusion and sensitivity that many adolescents experience.[15] This, in turn, often results in adolescents having great difficulty with situations in which they feel a lack of control.[16] Cancer, and its treatment, may be viewed as the ultimate loss of control and may result in increased anxiety and emotional distress that we hypothesize will continue in to adulthood and affect future HRQOL.

In addition to being a period of great change, adolescence is the stage during which a sense of identity is formed.[17] Psychologists Erikson[18] and Seltzer[19] assert that peer-group membership is necessary to healthy identity development since it allows the adolescent to decrease psychological dependence on their parents, yet retain a sense of belonging.[20] A cancer diagnosis may threaten peer-group membership, by denying the adolescent opportunity for membership physically, because s/he is undergoing treatment and therefore not able to attend school or social events, or emotionally because of perceived differences between the adolescent cancer patient and his/her “normal” peers. Limited interaction with peers may lead to a distorted sense of identity, and combined with physical deformity and/or other risk factors, may in turn, affect adult HRQOL.

The identification of risk factors for reporting poor HRQOL is important to designing appropriate interventions, however being able to predict who is at greatest risk for poor HRQOL is as, if not more, important. Identification of patients at highest risk for reporting poor HRQOL will allow clinicians to connect survivors of adolescent cancer with the appropriate resources and interventions in a timely manner, perhaps minimizing the impact of cancer and its treatment on the adolescent survivors' future quality of life.

4. Purpose/aims:

The primary aim of this manuscript is to develop two predictive models that can identify recently diagnosed adolescent cancer patients that are at risk for reporting poor mental and/or physical HRQOL. When validated, these predictive models will be used to develop a questionnaire, to be completed and scored by the health care provider, which asks about patient characteristics and treatment modalities. The resulting scores will identify those survivors at risk for reporting poor HRQOL and therefore allow the provider to connect survivors with appropriate resources.

5. Analysis framework:

Sample

Survivor participants, diagnosed when 10 to 18 years of age, who participated in the psycho-social portion of the 2003 Follow-Up survey and consented to medical record abstraction will be included in this study. Participants diagnosed with a second malignant neoplasm before the 2003 Follow-Up survey will be excluded so as to study only those characteristics related to the adolescent cancer experience.

Preliminary analyses show 2,203 participants completed both sections of the SF-36 on the 2003 Follow-Up survey, had not reported a second malignancy and were diagnosed between ages 10 and 18 years. Of these, 424 (19%) participants report poor mental HRQOL and 451 (20%) report poor physical HRQOL. For both outcomes, there are greater than four times the number of participants that do not report poor HRQOL, therefore we should have sufficient numbers for analyses.

Outcome

The outcome of interest in this study is self-reported health-related quality of life (HRQOL) as defined by the SF-36 (Follow-up 2). Two binary outcomes will be studied:

- Poor physical HRQOL (Physical component score ≤ 40)
- Poor mental HRQOL (Mental component score ≤ 40)

Independent (exploratory) variables

A. Diagnosis and treatment variables

- Subject characteristics
    - Sex [Female vs. Male]
    - Race [Black, Other vs. White (Other vs. White)]
    - Age at diagnosis [continuous]

- Cancer diagnosis [DIAGNOSE]

- Treatment
    - Surgery [MRAF]
        - Amputation
        - Other
        - None
    - Radiation [MRAF]
        - CRT
        - Chest
        - Other head
        - Neck
        - Abdomen
        - Spine
        - Pelvis
        - Limb
        - TBI
        - None
    - Chemotherapy[MRAF]
        - Anthracyclines [Y/N, cumulative dose, tertiles]
        - Alkylating agents [Y/N, cumulative dose, summed score]
        - Platinums [Y/N, cumulative dose, tertiles]
        - Bleomycin [Y/N, cumulative dose, tertiles]
        - Epipodophyllotoxins [Y/N, cumulative dose, tertiles]

Statistics

Descriptive statistics including frequencies, means and standard deviations, medians and ranges will be generated for the baseline demographic, diagnosis, treatment variables and outcome variables. Participants reporting poor mental and/or physical quality of health will be identified and the association between poor mental and physical HRQOL and demographic and treatment and disease related (pain, anxiety and disfigurement) variables will be studied using univariate logistic regression models. Mental and physical HRQOL will be modeled separately unless it is found that the strongest and most significant predictors are the same for both outcomes.

Various multiple logistic regression models will be generated based on the univariate results and the associated c-statistic and Receiver Operating Characteristic (ROC) curves compared. The c-statistic, corresponding to the area under the ROC curve (AUC), provides information about the model's accuracy or its ability to classify participants. An AUC or c-statistic of 1 indicates perfect ability to correctly classify a participant, whereas a c-statistic value of 0.5 indicates a model that is no better at classifying a participant than a coin flip.

Once the model with the highest c-statistic is identified, the internal validity of the model will be assessed with 10-fold cross-validation. Ten-fold cross validation was chosen because it has been found to be as accurate as bootstrapping with large samples[21] and is easily understood and implemented. The 10-fold cross-validation procedure is as follows: Participants will be divided, randomly into 10 approximately equal sized groups. The model above will be fit with 9

of the 10 groups (90% of the data) and applied to the remaining 10% of the data. If the predicted probability of being a case (reporting poor HRQOL) is greater than the predicted probability of being a control, the person will be categorized as "Model +" otherwise, if the predicted probability of being a control is greater than the predicted probability of being a case, the person will be categorized as "Model – ". A cross-tab of the truth (Poor HRQOL Y/N by SF-36) and the model's prediction will be produced (Figures 4a and b). This process will be repeated 10 times, with each of the 10 subsets serving once as the test set. The average cell values will be determined and used to calculate the model's sensitivity and specificity.

The model will then be externally validated with participants of the "Establishment of a lifetime cohort of adults surviving childhood cancer (SJLIFE)" study participants, diagnosed between the ages of 10 and 18, who have completed the SF-36 and have not had a second malignancy will be included in the validation set. The original model will be run and applied to this validation set. The model's accuracy, sensitivity and specificity will be assessed. A model with an accuracy of 80% and sensitivity >60% and/or specificity of >90% will be considered successful.

6. References

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Sample tables

Table 1: Characteristics of study population

	Survivors N (%)	Poor Mental HRQOL N (%)	Poor Physical HRQOL N (%)
Sex			
Male			
Female			
Race/Ethnicity			
White, non-Hispanic			
Black, non-Hispanic			
Hispanic			
Other			
Age at cancer diagnosis (years)			
Mean (SD)			
Range			
Cancer diagnosis			
Leukemia			
Central nervous system			
Hodgkin disease			
Non-Hodgkin lymphoma			
Wilms tumor			
Neuroblastoma			
Soft tissue sarcoma			
Bone cancer			
Treatment exposure			
Surgery			
Amputation			
Other Surgery			
None			
Chemotherapy			
Anthracyclines (Y/N)			
Mean (SD)			
Range			
Alkylating agent (Y/N)			
Mean (SD)			
Range			
Platinum (Y/N)			
Mean (SD)			
Range			
Bleomycin (Y/N)			
Mean (SD)			
Range			
Epipodophyllotoxins (Y/N)			
Mean (SD)			
Range			
Radiation			
CRT			
Chest			
Other head			
Neck			
Abdomen			
Spine			
Pelvis			
Limb			
TBI			
None			

Table 2: Univariate associations between poor mental/physical HRQOL demographic, cancer and treatment related characteristics

	Poor Mental HRQOL OR (95% CI)	Poor Physical HRQOL OR (95% CI)
Sex		
Male		
Female		
Race/Ethnicity		
White, non-Hispanic		
Black, non-Hispanic		
Hispanic		
Other		
Age at cancer diagnosis (years)		
Mean (SD)		
Range		
Cancer diagnosis		
Leukemia		
Central nervous system		
Hodgkin disease		
Non-Hodgkin lymphoma		
Wilms tumor		
Neuroblastoma		
Soft tissue sarcoma		
Bone cancer		
Treatment exposure		
Surgery		
Amputation		
Other Surgery		
None		
Chemotherapy		
Anthracyclines (Y/N)		
Mean (SD)		
Range		
Alkylating agent (Y/N)		
Mean (SD)		
Range		
Platinum (Y/N)		
Mean (SD)		
Range		
Bleomycin (Y/N)		
Mean (SD)		
Range		
Epipodophyllotoxins (Y/N)		
Mean (SD)		
Range		
Radiation		
CRT		
Chest		
Other head		
Neck		
Abdomen		
Spine		
Pelvis		
Limb		
TBI		
None		

Tables 3a and 3b: Results of multivariable predictive models

3a: Poor mental HRQOL

3b: Poor physical HRQOL

Figures 1a and 1b: ROC curves corresponding to multivariable predictive model

Figure 1a

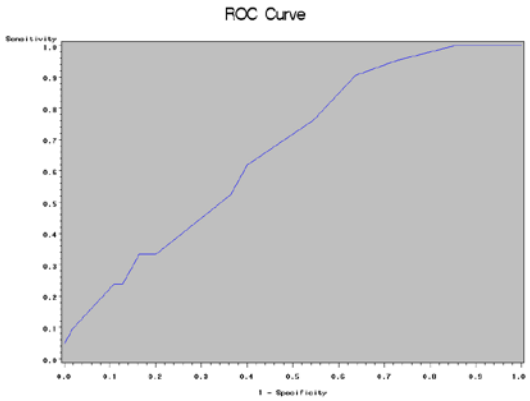

Figure 1b

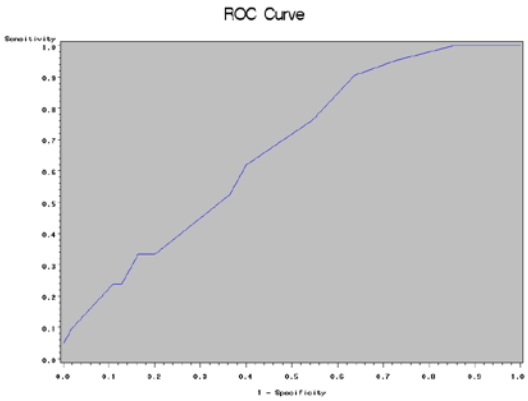

Table 4a and 4b: Classification tables resulting from 10-fold cross validation

4a:

Poor mental HRQOL

MODEL	+	-
+	TP	FP
-	FN	TN

Sensitivity = TP / (TP + FN)
Specificity = TN / (TN + FP)
Accuracy = TP + TN / N

4b:

Poor physical HRQOL

MODEL	+	-
+	TP	FP
-	FN	TN

Sensitivity = TP / (TP + FN)
Specificity = TN / (TN + FP)
Accuracy = TP + TN / N