Analysis Concept Proposal

a) *Study Title:* **The impact of chronic disease on health care utilization in the CCSS cohort**

b) *Working Group Investigators*

This proposed project will be developed through the **Cancer Control** (primary) and **Chronic Disease** (secondary) working groups.

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c) *Background and Rationale*

Several CCSS analyses have focused separately on the risk for chronic health conditions in survivors[1,2] and on the health care utilized by the survivor population.[3-6] As the population of survivors in the CCSS cohort ages and acquires more late effects of their cancer therapy, it is anticipated that their use of health services (physician visits, surveillance for second malignant neoplasms and other late effects, hospital admissions, and emergency room visits etc.) will increase. Although chronic disease has been included as a binary variable (none/mild/moderate vs. severe/life threatening) in previous health care utilization analyses, no analysis has examined associations between chronic disease status and health care utilization in detail.

A 2008 CCSS publication examined the receipt of "survivor-focused" care in the cohort. Of the 8,522 participants in that analysis, 89% reported that they had received some form of medical care in the preceding two years.[3] However, only 32% reported that they had received care focused on their prior cancer (survivor-focused care), and 18% reported that their care had included advice about screening or how to reduce their risk for late effects (risk-based survivor-focused care). Survivors with a *severe or life threatening chronic health condition* were more likely to have received some form of medical care (OR 1.3; 95% CI 1.0-1.4), as were those with moderate to extreme cancer pain. Risk factors for receiving no medical care included male gender, low household income, lower educational attainment and not having health insurance. Similarly, among survivors who had received some form of health care, those with *a severe or*

life threatening chronic health condition (OR 1.7; 95% CI 1.4-2.0), poorer emotional health, moderate to extreme cancer-related pain or anxiety, or poor physical health were more likely to report survivor-focused care (vs. general care). In contrast, survivors who were black, younger at diagnosis, older at interview, and without insurance were more likely to have received general rather than survivor-focused care. However, these analyses did not assess whether system specific chronic health conditions (e.g. cardiac, pulmonary) or the presence of multiple conditions impacted health care utilization. Further, the quantity of utilization (e.g. number of visits) and types of health care services accessed was not examined.

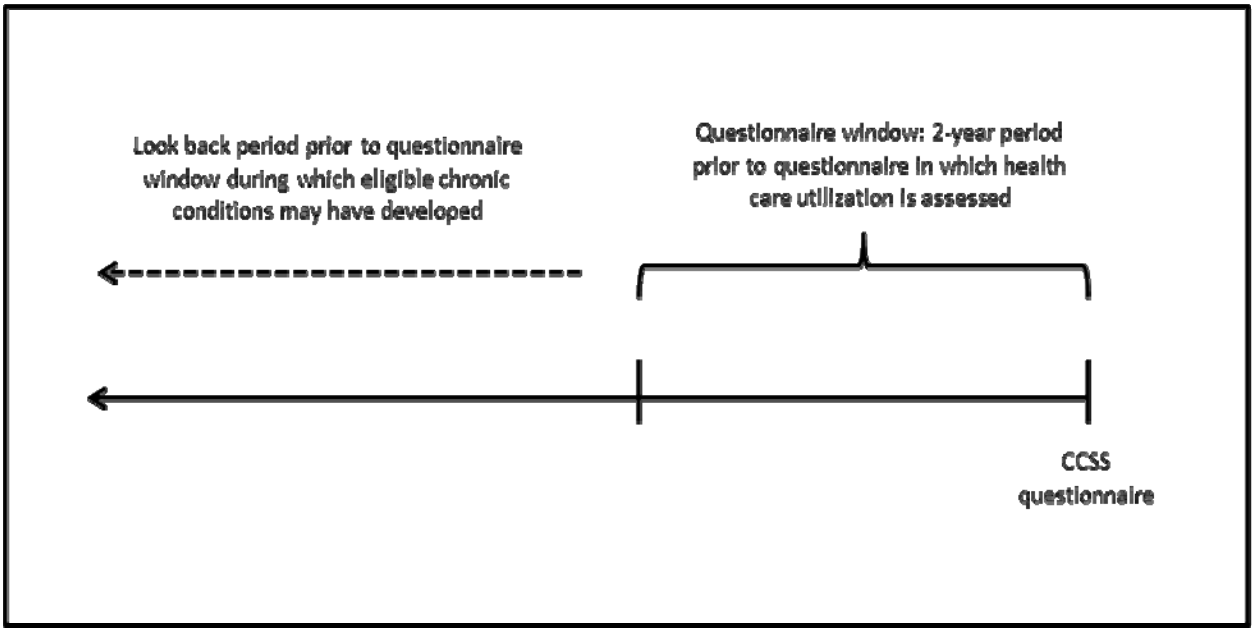
In prior CCSS analyses, chronic disease status did not appear to influence the use of cancer screening modalities recommended for the general population (i.e. those recommended by the US Preventive Services Task Force [USPSTF]). Female survivors in the CCSS cohort who reported a severe or life-threatening chronic health condition were no more likely to receive routine mammographic screening after age 40 (RR 1.05, 95% CI 0.76-1.49) or Pap smears (RR 0.93, 95% CI 0.81-1.06) than women with no, mild or moderate chronic conditions.[4] However, among survivors at increased risk for breast cancer, colorectal cancer or skin cancer as a result of their cancer therapy, having a severe/life-threatening condition was associated with better adherence to COG Guideline recommended colonoscopy, but not mammography or skin exam.

The population of survivors of childhood cancer alive in the US now exceeds 375,000.[7] As this population grows (and ages), survivors will place an increasing burden on the health care system. Understanding their health care needs will be important for the planning of specialized long-term follow-up clinics as well as for designing models of care that share follow-up between primary care practitioners and cancer centers. The present study aims to combine chronic disease and health care utilization pattern data from the original and expanded CCSS cohorts in order to explore associations between these variables.

d) *Specific Aims/Research Hypotheses*

Specific aim 1: To explore associations between the number, severity and type of chronic conditions in survivors and the volume of physician visits.

Hypothesis 1a: The number of physician visits over the two years preceding their most recent CCSS questionnaire will be higher among survivors who reported onset of one or more severe or life threatening (grade 3-4) chronic health conditions prior to the start of the two year time window



Hypothesis 1b: The number of physician visits over the two years preceding their most recent CCSS questionnaire will be correlated with the total number of chronic health conditions (any grade) as well as with the number of grade 3-4 health conditions that developed prior to the two year time window.

Exploratory aim 1: We will explore which organ systems affected by a chronic health condition are most likely to results in a higher number of physician visits. Organ systems considered will include cardiac, pulmonary, endocrine, neurologic, musculoskeletal and SMN.

Specific aim 2: To evaluate associations between the presence, number and type of chronic health conditions and the likelihood of reporting survivor-focused health care

Hypothesis 2a: Survivors who had developed a severe or life threatening chronic health condition (grade 3-4) prior to the two year window preceding their questionnaire will be more likely to report survivor-focused health care.

Hypothesis 2b: The likelihood of reporting survivor-focused health care over the two years preceding their most recent CCSS questionnaire will be correlated with the number of chronic health conditions (any grade) and the number of severe or life threatening health conditions (grade 3-4) reported by survivors prior to the two year time window.

Exploratory aim 2: We will determine which organ systems affected by a grade 3-4 chronic health condition are most likely to be associated with survivor focused health care. Organ

systems considered will include cardiac, pulmonary, endocrine, neurologic, musculoskeletal and SMN.

Specific aim 3: To explore the impact of the development of a severe or life threatening chronic health condition on the rates of hospitalization and emergency department use

Hypothesis 3a: Survivors who have developed a severe or life-threatening chronic health condition prior to the two year window preceding their questionnaire will report a greater number of hospital admissions over the two years preceding the questionnaire[1].

Hypothesis 3b: Survivors who have developed a severe or life-threatening chronic health condition prior to the two year window preceding their questionnaire will be more likely to report a visit to an emergency department over the two years preceding the questionnaire[2].

Specific aim 4: To explore the relationship between the development of any severe or life threatening chronic health condition and adherence with population cancer screening guidelines and the COG guidelines for surveillance in high-risk survivors

Hypothesis 4a: Female survivors who have developed a severe or life-threatening chronic health condition (other than a subsequent breast or cervical cancer) will be more likely to be compliant with recommendations for general population screening for breast and cervical cancer. Male and female survivors who have developed a severe or life-threatening chronic health condition (other than a subsequent colorectal cancer) will be more likely to be compliant with recommendations for general population screening for colorectal cancer.

Hypothesis 4b: Survivors who have developed a severe or chronic health condition will be more likely to be adherent to recommendations for surveillance for cardiac dysfunction, breast cancer, colorectal cancer and skin cancer (among survivors at high risk for these late effects who have not already developed one of these morbidities)

Analysis Framework

Sample: Original and expanded cohorts. We will only include participants in the original cohort who completed the 2007 questionnaire[3], along with participants in the expansion cohort who completed the baseline questionnaire.

[1] *Frequency of hospitalizations can only be assessed in the expansion cohort in which survivors report their actual number of hospital visits. For the combined cohort of original/expansion survivors, hospitalization will be assessed as a binary variable.*

[2] *This data is only available as a binary variable, thus frequency cannot be assessed.*

A. Dependent variables

PRIMARY OUTCOME:

i. Number of physician visits (B3 on 2007 Questionnaire and Expansion Baseline)

SECONDARY OUTCOMES

i. Survivor -focused care (B3/B4 on 2007 Questionnaire and Expansion Baseline)
ii. Hospitalizations (B6 – Expansion Baseline only)
iii. Emergency department or urgent care visit (B2 on 2007 Questionnaire and Expansion Baseline)
iv. High-risk surveillance (**Echocardiogram** [C1 on 2007 Questionnaire; O24 on Expansion Baseline]; **mammogram/breast MRI** [C5/6 on 2007 Questionnaire; O30 on Expansion Baseline]; **DEXA** [C2 on 2007 Questionnaire; O25 on Expansion Baseline]; **colonoscope/sigmoidoscope** [C4 2007 Questionnaire; not in Expansion Baseline])
v. Population screening (**FOB/scope** [C3, C4 2007 Questionnaire; not in Expansion Baseline]; **Pap smear** [C7 on 2007 Questionnaire; O28 on Expansion Baseline]; **mammogram** [C5 on 2007 Questionnaire; O30 on Expansion Baseline])

B. Independent variables

a. Disease variables

i. Cancer type

b. Treatment variables

i. Era of treatment (1970-79, 1980-89, 1990-99)
ii. Radiation (by field – head, chest, abdo/pelvis, other)
iii. Chemotherapy (yes/no AND anthracycline dose AND cyclophosphamide equivalent score)
iv. Surgery (yes/no)
v. HSCT (yes/no AND type)

c. Sociodemographic variables (as they were at the time of assessment of health care utilization)

i. Gender
ii. Age at treatment
iii. Attained age
iv. Race/ethnicity

[3] *Questionnaires addressing health care utilization differ between the several questionnaires completed by the original cohort. To ensure consistency, we will limit the analysis to those that completed the 2007 survey*

v. Annual household income
vi. Educational attainment
vii. Employment status
viii. Marital status
ix. Health insurance

d. Chronic disease status
i. Any grade (1-4), severe-life threatening (3-4)
ii. Number of chronic conditions
iii. Number of severe/life (3,4) threatening chronic conditions
iv. Grade 3-4 organ specific chronic diseases (SMN, cardiac, endocrine, pulmonary)

e. Health status
i. Perceived general health (L19 on 2007 Questionnaire/O21 Expansion)
ii. Mental health (BSI-18; L1-L18 on 2007 Questionnaire/K1-K18 on Expansion)
iii. Physical impairment /activity limitations (N22 and N23 2007 Questionnaire / O16 and O17 Expansion)
iv. Pain (L21 on 2007 Questionnaire; K19 on expansion)
v. Anxiety as a result of the previous cancer (L20 on 2007 Questionnaire; K20 on expansion)
vi. Concern about future health (O1 2007 questionnaire / V1 Expansion)

C. Data analysis plan

Specific aim 1

Survivors will be dichotomized between those with and without a grade 3-4 chronic health condition. The number of physician visits in the preceding two years will be categorized into 7 hierarchical levels (0 visits; 1-2; 3-4; 5-6; 7-10; 11-20; >20, as in the questionnaires). We plan to examine the relationship between grade 3-4 conditions (yes/no) and the frequency of physician visits using either logistic or ordered categorical regression depending on the distribution of the data. If a proportional odds model for ordered categorical regression is used, the assumption of proportional odds across numbers of physician visit categories will be assessed and if violated a general version of the model relaxing that assumption will be fit. Age at diagnosis, sex, attained age, race/ethnicity, and insurance status will be included as covariates in the model. Similar methods will be used to explore associations between the number of chronic health conditions (any grade) and physician visits, and the number of

grade 3-4 conditions and the number of physician visits. For each of total chronic conditions, and grade 3-4 chronic conditions, frequency will be categorized as: 0; 1-2; 3; ≥4

We may also consider including diagnosis and treatment modalities in the models with chronic conditions, assuming that chronic conditions are mediators of the association between diagnosis and/or treatment and number of hospitalizations. Non-linear approaches to mediation analysis that allow for inclusion of confounders and interactions between exposures (treatment, diagnosis) and mediators (chronic health conditions) will be utilized as described by Valeri and Vanderweele and using their published SAS macros.[8]

Specific aim 2

Medical care received in the two years preceding their most recent survey will be classified into one of three mutually exclusive levels, using the same classification system as prior CCSS health care utilization papers[3]:

(1) No health care;
(2) General medical care (one or more visits to a doctor or nurse, none of which were related to their prior cancer);
(3) Survivor-focused care (a medical visit related to the prior cancer, or one in which the survivor is counseled about how to reduce their risks or has surveillance tests ordered or discussed).

As with specific aim 1, we will assess the relationship between occurrence of a grade 3 or 4 health condition prior to 2 years before survey response and the maximum level of care reported to be received (i.e. none vs. general vs. survivor focused). Similarly, we will evaluate associations of both the number of chronic health conditions (grades 1-4) and the number of severe or life-threatening health conditions (grades 3-4) with the maximum level of care.

In order to examine the impact of specific grade 3-4 health conditions on the level of care received, as in our previous report, we will use three separate generalized linear models to determine the incremental risk of no care versus general care, no care versus survivor focused care, and general care versus survivor focused care as a function of specific chronic health conditions including cardiac, pulmonary, endocrine, musculoskeletal, neurologic and SMN. Models will be adjusted for age at diagnosis, sex, race/ethnicity, attained age and insurance status. Using similar methods to those described for aim 1, we will also explore the direct and indirect effects of diagnosis and/or treatment factors on levels of care and the degree to which chronic health conditions mediate this association.

Specific aim 3

a) We will examine the relationship between the presence of a grade 3-4 chronic health conditions, the number of health conditions (any grade) and the number of grade 3-4 chronic health conditions with the number of non-obstetric hospitalizations in the preceding 2 years (in the expansion cohort only) using Poisson regression models adjusted for age at diagnosis, sex, race/ethnicity, attained age and insurance status.
b) Similarly, we will examine the relationship between the presence of a grade 3-4 chronic health conditions, the number of health conditions (any grade) and the number of grade 3-4 chronic health conditions with the binary outcome of whether or not a survivor visited an emergency room or urgent care center in the preceding two years. Our analysis will utilize generalized linear models, with link function selected based on prevalence of the outcome (logit or log), controlling for age at diagnosis, sex, race/ethnicity, attained age and insurance status.

Again for this aim, we will explore the potential direct and indirect effects of diagnosis and/or treatment on hospitalization and emergency room/urgent care visits with chronic health conditions as potential mediators of this association.

Specific aim 4

Each subject will be classified into "Average Risk of an SMN" or "High risk of an SMN" based on their eligibility for screening and surveillance as defined in the table below – thus defining the screening they should be getting:

Table 1: Recommendations for screening and surveillance

Screening in survivors at AVERAGE risk of a SMN			
USPSTF recommended screening for the general (average risk) population	**Breast**	**Cervix**	
	Mammogram every 1 to 2 years for women aged 40 years or older	Pap smear every 3 years commencing at age 21 years	
Surveillance in survivors at HIGH risk of a SMN			
	Breast	**Colorectal**	**Skin**
Definition (COG) of high risk group	Female, ≥20 Gy radiation therapy to the chest	≥30 Gy radiation therapy to the abdomen, pelvis or spine	Any radiation therapy
COG recommended surveillance for survivors at high risk	Annual mammogram or MRI beginning 8 years after radiation or age 25 years, whichever occurs last	Colonoscopy every 5 years beginning at age 35 years	Annual dermatologic exam of irradiated areas

Subjects will also be identified as meeting recommendations for cardiac screening as per the COG Guidelines.

Table 2: Recommendations for cardiomyopathy surveillance

RECOMMENDED FREQUENCY OF ECHOCARDIOGRAM OR MUGA SCAN

Age at Treatment*	Radiation with Potential Impact to the Heart§	Anthracycline Dose†	Recommended Frequency
<1 year old	Yes	Any	Every year
	No	<200 mg/m²	Every 2 years
		≥200 mg/m²	Every year
1-4 years old	Yes	Any	Every year
	No	<100 mg/m²	Every 5 years
		≥100 to <300 mg/m²	Every 2 years
		≥300 mg/m²	Every year
≥5 years old	Yes	<300 mg/m²	Every 2 years
		≥300 mg/m²	Every year
	No	<200 mg/m²	Every 5 years
		≥200 to <300 mg/m²	Every 2 years
		≥300 mg/m²	Every year
Any age with decrease in serial function			Every year

*Age at time of first cardiotoxic therapy (anthracycline or radiation [see fields below], whichever was given first)
§See Section 71
†Based on doxorubicin isotoxic equivalent dose [see conversion factors in Section 28 "Info Link (Dose Conversion)"]

As with the analyses above, we will examine the relationship between presence of a grade 3-4 chronic health condition (as well as number of conditions, and number of grade 3-4 conditions) and compliance with outcomes defined by:

i. General population screening recommendations for cervical cancer and breast cancer (female only), and colorectal cancer (both sexes) among survivors who had not already developed one of these conditions and who meet the criteria outlined above for each screening type.
ii. COG surveillance guidelines (high risk) for breast cancer, colorectal cancer, skin cancer (see table 1 for eligibility) as well as anthracycline cardiomyopathy (see table 2 for eligibility) among patients at high risk who had not already developed one of these conditions.

For each screening type (and among only those patients for whom the specific screening or surveillance test is recommended) whether a subject obtained the recommended screening

will be determined and will define the binary outcome of compliance for that screening type. Generalized linear models with a log link function will be used to determine associations between the chronic condition measures and compliance with each type of screening, controlling for age at diagnosis, sex, race/ethnicity, attained age and insurance status. Since recommended screening is partially dependent on age, some analyses may be carried out stratified on current age.

References

1. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic Health Conditions in Adult Survivors of Childhood Cancer. N Engl J Med 2006;355:1572-82.

2. Armstrong GT, Kawashima T, Leisenring W, et al. Aging and risk of severe, disabling, life-threatening, and fatal events in the childhood cancer survivor study. J Clin Oncol 2014;32:1218-27.

3. Nathan PC, Greenberg ML, Ness KK, et al. Medical care in long-term survivors of childhood cancer: a report from the childhood cancer survivor study. J Clin Oncol 2008;26:4401-9.

4. Nathan PC, Ness KK, Mahoney MC, et al. Screening and surveillance for second malignant neoplasms in adult survivors of childhood cancer: a report from the childhood cancer survivor study. Ann Intern Med 2010;153:442-51.

5. Oeffinger KC, Mertens AC, Hudson MM, et al. Health care of young adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Ann Fam Med 2004;2:61-70.

6. Yeazel MW, Oeffinger KC, Gurney JG, et al. The cancer screening practices of adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Cancer 2004;100:631-40.

7. SEER Cancer Statistics Review, 1975-2010, based on November 2012 SEER data submission, posted to the SEER web site, April 2013. In: Howlader N, Noone AM, Krapcho M, et al., eds. Bethesda, MD: National Cancer Institute; 2013.

8. Valeri L, Vanderweele TJ. Mediation analysis allowing for exposure-mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros. Psychological methods 2013;18:137-50.

Table 1: Characteristics of the cohort

	Total n (%)
Cohort	
Baseline	
Expanded	
Age (median, range)	
At diagnosis	
At time of questionnaire	
Current age categories (years)	
<18	
18-24.9	
25-34.9	
35-44.9	
45-54.9	
≥55	
Gender	
Male	
Female	
Race/Ethnicity	
White	
Black	
Hispanic	
Other	
Treatment era	
1970-79	
1980-89	
1990-99	
Health Insurance status	
No, U.S.	
Yes, U.S.	
Private	
Public	
Canadian resident	
Annual household income	
< $40,000	
$40000-79,999	
$80,000 or greater	
Education	
< High school	
High school	
College graduate	
Employment status	
Employed or caring for home	
Looking for work or unable to work	
Student	
Cancer diagnosis	
Leukemia	
CNS tumor	
Hodgkin lymphoma	
Non-Hodgkin lymphoma	
Wilms tumor	
Neuroblastoma	

Sarcoma Bone tumor	
Treatment variables **Radiation therapy Yes/No** Brain Chest Not brain, not chest None RT status not known **Cardiotoxic therapies** Anthracyclines, no chest RT Chest RT, no anthracyclines Anthracyclines + chest RT No anthracyclines, no chest RT **Cyclophosphamide equivalent dose (mg/m2)** 0-<4000 4000-<8000 8000-<12000 1200-<16000 >+16000	

Table 2: Prevalence of chronic health conditions as of 2 years prior the completion of the questionnaire

	N(%)
Any grade 3-4 condition Yes No	
Any grade 1-4 condition Yes No	
Number of conditions – any grade (median, range)	
Number of conditions – grade 3-4 (median, range)	
Proportion with grade 3-4 condition involving: Cardiac SMN Pulmonary Endocrine	

Aim 1:

Table 3: Associations between chronic condition variables and subsequent number of physician visits based on separate proportional odds models for ordered categorical outcomes; each row of the table representing a separate adjusted model.

	Odds Ratio (95% CI)	p-value
Any grade 3-4 condition		
No		
Yes		
Any grade 1-4 condition		
No		
Yes		
Number of conditions (any grade)		
None		
1		
2		
3+		
Number of conditions (grades 3-4)		
None		
1		
2		
3+		
Any grade 3-4 condition of type:		
Cardiac		
No		
Yes		
SMN		
No		
Yes		
Pulmonary		
No		
Yes		
Endocrine		
No		
Yes		

*Adjusted for age at diagnosis, sex attained age, race/ethnicity, insurance status

Aim 2:

Table 4: Associations between chronic condition variables and type of medical care received (no care versus general care, no care versus survivor focused care, and general care versus survivor focused care), with each Odds Ratio (OR) of the table representing results from a separate adjusted logistic regression model.

	None vs general care		None vs. survivor focused care		General vs. Survivor focused care	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Any grade 3-4 condition No Yes						
Any grade 1-4 condition No Yes						
Number of conditions (any grade) None 1 2 3+						
Any grade 3-4 condition of type: Cardiac No Yes SMN No Yes Pulmonary No Yes Endocrine No Yes						

*Adjusted for age at diagnosis, sex attained age, race/ethnicity, insurance status

Aim 3:

Table 5: Associations between chronic condition variables and non-obstetric hospitalizations and emergency room/urgent care visits, with each Rate Ratio in the table representing a separate adjusted model. [Note: depending on distribution of hospital/ER visit counts, metric analyzed may be odds ratio or mean value]

	Non-Obstetric Hospitalizations		Emergency Room / Urgent care visits	
	Rate Ratio (95% CI)	p-value	Rate Ratio (95% CI)	p-value
Any grade 3-4 condition				
No				
Yes				
Any grade 1-4 condition				
No				
Yes				
Number of conditions (any grade)				
None				
1				
2				
3+				
Number of conditions (grades 3-4)				
None				
1				
2				
3+				
Any grade 3-4 condition of type:				
Cardiac				
No				
Yes				
SMN				
No				
Yes				
Pulmonary				
No				
Yes				
Endocrine				
No				
Yes				

*Adjusted for age at diagnosis, sex attained age, race/ethnicity, insurance status

Aim 4 : Associations between chronic condition variables and compliance with recommended screening or surveillance test (e.g. colorectal cancer screening, cardiomyopathy screening etc.) with each Odds Ratio (OR) of the table representing results from a separate adjusted logistic regression model.*

	Compliance with specific screening test	
	Odds ratio (95% CI)	p-value
Any grade 3-4 condition		
No		
Yes		
Any grade 1-4 condition		
No		
Yes		
Number of conditions (any grade)		
None		
1		
2		
3+		
Number of conditions (grades 3-4)		
None		
1		
2		
3+		
Any grade 3-4 condition of type:		
Cardiac		
No		
Yes		
SMN		
No		
Yes		
Pulmonary		
No		
Yes		
Endocrine		
No		
Yes		

*Adjusted for age at diagnosis, sex attained age, race/ethnicity, insurance status