1. **Study title:** Longitudinal Patterns of Late Effects in Adult Survivors of Childhood Brain Tumors

2. **Working group and investigators:** Psychology working group

The full investigator list includes:

- Thomas L. Hardie, EdD tlh63@drexel.edu
- Kevin G. Lynch, PhD lynch_k@mail.trc.upenn.edu
- Janet Deatrick, PhD deatrick@nursing.upenn.edu
- Jill Ginsberg, MD ginsbergji@email.chop.edu
- Wendy Hobbie, PNP, FAAN HOBBIE@email.chop.edu
- Elizabeth Wells, MD ewells@cnmc.org
- Greg Armstrong, MD greg.armstrong@stjude.org
- Wendy Leisenring, ScD wleisenr@fhcrc.org
- Leslie L. Robison, PhD Les.robison@stjude.org
- Kevin R. Krull, PhD kevin.krull@stjude.org
- Marilyn Stovall, PhD mstovall@mdanderson.org

3. **Background and rationale:** The overarching purpose of this study is to identify patterns (trajectories) in the attainment of adult social competence outcomes (e.g. education, employment, marriage) in adult survivors of pediatric brain tumors through time. Once these patterns (trajectories) are characterized, key tumor demographic/treatment data and late effects (previously reported in the CCSS cohort or from expert selection) will be used as predictors of trajectory membership to generate profiles that will guide surveillance strategies and proactive targeted treatments. The impact of disease and treatment on psychosocial developmental attainment (timely completion of adult tasks) is known to vary among survivors. Up to 50% of the survivors show significant deficits in neurocognitive skills, with some requiring extensive support in their activities of daily life, while others appear to progress normally (37% graduating from college and 44% working full-time)[1]. While each child has an individual course of development cast in time and presents with varying levels of strength in an individual domain of attainment, we postulate that their patterns will cluster into groups of survivors whose trajectories are similar to other members of their cluster (or latent class) , and are different from trajectories of survivors in other clusters. As noted above, the benefit of identifying clusters of survivors with similar responses to disease and late treatment effects through time (patterns of developmental attainment/delay) and developing profiles from the associated demographic/ clinical data is that these could be used to move care closer to the goal of individualized surveillance and interventions.

Adult development, the attainment of adult tasks and late effects

Survivors of pediatric brain tumors present with varying levels of developmental delays which are associated with neurocognitive deficits [2 3]. While a significant proportion of the survivors have alterations in their development resulting in their parents continuing to care for them, others have not, e.g. 44% are working full-time, 74% attend some college and 38% complete college. [4-6] Previous reports have demonstrated high correlations between neurocognitive function, as measured by the Childhood Cancer Survivor Study Neurocognitive Questionnaire, and attaining adult developmental tasks. [4 7] Additionally, changes in neurocognitive functioning have been associated with particular treatment exposures. These late treatment effects have been associated with frontal and temporal lobe radiation and gender [4 8].

Attainment of adult tasks is a surrogate measure of development and adaption in survivors. These tasks include socioeconomic outcomes of educational attainment, employment status, marital status and individual and household income. The attainment of adult tasks has been associated with neurocognitive functioning; that is with poorer task efficiency, emotional regulation, and memory has been associated with poorer educational performance and poor task efficiency, memory and organization were associated with never marrying. Impairment on all of the subscales was associated with income below $20,000 and lower levels of employment. Adult survivors of pediatric brain tumors (in aggregate) have lower rates of employment than do other cancer survivors [9]. Compared to their siblings, they have a five times greater risk of being unemployed in the previous twelve months and 14% reported never being employed [5 10].

Brain tumor survivors also experience reduced rates of marriage and if they do marry are more likely to divorce [9]. Interestingly, 62% percent of the CCSS cohort were never married, compared to 78% of brain tumor survivors[5].

While these delays in attainment of social competence have been well described cross-sectionally, clusters of patterns of development over time have not been characterized. The associations between physical and neurocognitive deficits linked to the delays in attainment of social competence can be non-linear in their appearance and affect a survivor's developmental course[7 8]. Trajectory data provides a more detailed understanding of potential interventional opportunities during development.

4. Specific aims/objectives/research hypotheses:

Aim a) To identify longitudinal patterns of psychosocial outcomes (education, employment, marriage and income) in adult survivors of CNS tumors;

Hypothesis a) Pediatric brain tumor survivors will aggregate into discrete groups based on the longitudinal patterns of psychosocial outcomes (education, employment, marriage and income) representing adult attainment.

Aim b) To explore the association among survivor patterns of adult attainment and disease characteristics and cancer treatments;

Hypothesis b) Tumor characteristics and treatment exposure will be predictors of pediatric brain tumor survivor cluster membership (latent trajectory) based on psychosocial attainment (from aim a).

Aim c) To examine the association between these survivor patterns of adult attainment and medical and psychological/neuropsychological late effects.

Hypothesis c) Pediatric brain tumor survivors' cluster membership will be predicted by late effects at the baseline time point.

Subject population: Adult survivors of pediatric brain tumors from the CCSS will be used to address the hypotheses. We propose the inclusion of survivors with the diagnoses of astrocytoma, medullo/PNET and other CNS tumors. Survivors from age 15 to 40 were included in the CCSS baseline survey; we will be restricting the age range for this study to 15 to 25 years at baseline. We are

restricting age to have valid outcome measures, e.g. young enough for high school and old enough for relationships. Prior publications and frequency data on the CCSS website provide support for variation in each of the domains of adult development. These cross-sectional reports do not provide enough detail to optimize the age range for the analyses proposed in this study. As such, the request for an expanded age range will provide a large enough sample with sufficient variation to support the shifting of the sample frame to develop trajectories.

5. Analysis framework:

Outcome of interest hypothesis a) Latent trajectories using the variables (listed below) across four waves of data for some and three for others.
Example of outcome(s) of interest: To address the aims and hypotheses, we are proposing the use of longitudinal data with co-occurring data in the survivors and educational attainment, marital status, employment status, and income which will be used to developmental clusters. Initially, longitudinal data from each domain, e.g. education, will be used to develop latent class trajectories resulting in independent models for each domain. These four models will provide information for the development of a multivariate model that will be used to develop latent clusters (trajectories) among survivors **(addressing hypothesis a)**.

Example of clusters (latent trajectories from Jackson 2000) which would be expected outputs [11] are displayed below and in tables 1, 2 and 3 and attached. The expected outputs will be displayed in a figure similar to Fig. 1, which will plot mean values for each of the domains and one for a multivariate model. Additionally, four additional figures for each domain will be provided. Additional tables will provide model fit and average latent class probabilities for most likely class membership.

Independent variables

The CCSS survey waves have addressed the domains of adult attainment with somewhat differing questions across the four time points. We are proposing the use of previously reported methods of dichotomizing and metrics used in prior CCSS reports, i.e. rubric (Kirchhoff 2010 & 2011) in employment, (Janson, 2009) in marital status, (Kirchhoff ,2011) and income (Ellenberg ,2009) [4 12-14]. Some of the domains of interest provide additional information which are time invariant, such as the number of special education services covariates in the proposed longitudinal models [5]. In addition, a limited number of covariates may included in the models. The above listed domains and covariates will be used to fit models to support hypothesis a.

1. Education measures at the baseline and three subsequent time points. Baseline (O1 through O4), 2000 survey (question 1), 2003 survey (question1) and 2007 survey (question A3.) These questions provide a consistent measure of education achievement across the time points. Education will be coded into four ordered categories: no high school degree, completed high school, some college, or completed college at each measurement point. These levels are consistent with previously reported educational attainment for brain tumor survivors [5] . Baseline questions O2-4 address the use of special educational services which are not measured at future points, are time invariant and will be used as covariates in the model.

2. Employment measures: Baseline (N12, O5, O6, & O8), 2000 survey (3, 3a, & 3b), 2003 survey (4, 5, 5a , 5b & N24), 2007 survey (A4, A5 A5a). The rubric applied by Kirchhoff (2010) was used as a baseline for the development of a dichotomous response for employment and will be implemented in this study [14]. Subjects will be classified as employed if they endorsed working during the last 12 months (baseline O5). Those who had not worked during the last 12 months will be divided into two levels of unemployment which will be defined based the survivor's endorsement of health-related unemployment for baseline, 2003 and 2007. The baseline question N12, 2003, N24 and 2007 question 4 endorsement of unable to work due to illness or disability will define health-related unemployment . In the 2000 question 3b, survivors were asked about employment at any time since 1995; those stating yes will be considered employed. Those answering that they did not work will be considered unemployed. In 2003 and 2007, participants were asked to select all categories that applied to their current employment status. The choices included: full-time (>30 hours per week) or part-time (<30 hours per week) employment; caring for home or family and not seeking work; retired; student; and other. Because participants were asked to choose all employment categories that applied, like Kirchoff, it will be "assumed that health status was the primary cause of unemployment for those who selected being unable to work because of illness or disability, unless they also reported being unemployed but seeking work. If this choice was selected, seeking work was considered the primary unemployment outcome. We considered participants unemployed by choice if they reported being a student, retired, caring for home or family, or otherwise unemployed but not seeking work" ([14] page 1016).

   Additionally, the Kirchhoff et.al. (2011) method (cited below) for categorizing occupation into four levels will be used as an additional dimension of employment. They report, of those with CNS tumor resections, 26% were in professional managerial roles, 28% in non-physical roles and 41% were unemployed [13].

   Occupational titles were acquired by questions at baseline and 2000, 2003 and 2007 and will be coded using the US Department of Labor Standard Occupational Classification (SOC) System (http://www.bls.gov/soc/). Consistent with prior coding of this dat,a military occupations will be excluded. "The SOC provide 23 categories including military survivor from which survivors will be coded. These then be further reduced to three catagories ''Professional/Managerial'' or Service/Blue Collar'' as outlined by Kirckoff (2011) paper.

3. Income measures: Income is measured at three time points and is missing on the 2000 survey. Measure of family income at $20,000 or below has been associated with psychological distress and physical inactivity in survivors [1 15]. This provides a threshold by which the data could be dichotomized for family data. Additionally, Ellenberg uses four income levels from <$19,000 to over $60,000 in 20,000 dollar increments with a fairly even distribution across the four levels [4]. We are proposing use of Ellenberg's strategy for family income in this study. CCSS survivors were more likely to earn <$20,000 and less likely to earn> $60,000 than their siblings [13]. This study will use above and below $20,000 to dichotomize personal income. We are requesting the following data: baseline (Q8, Q9) family and personal income, 2003 survey (S1, S2, S3), 2007 (A6,A7, & A8).

4. Marital Status: Baseline (L1 through L13), 2000 survey (2, 2a, & 2b), 2003 survey (2), 2007 Survey (M1, M2, M3). The analysis of the items will follow the rubric established by Janson, et.al. (2009) listed below.

"….. participants categorized themselves as single/never married, married, living as married, widowed, divorced, or separated/no longer living as married. Reponses were grouped into four outcomes: never-married, currently married, divorced, and ever divorced. Never-married was available from the 2003 (and 2007) survey. Subjects responding divorced or separated in the 2003 survey were defined as currently-divorced .... Cases who reported themselves as divorced or separated in any survey were classified as ever-divorced. It is possible that an individual responding married in consecutive surveys may have in fact been divorced and remarried. We anticipate that the number of divorce cases missed in this manner will be negligible……" (Janson (2009), page 2627). We will dichotomize on married/not married as well as use the four choices as ordinals/

Covariates

1. Age at Baseline A1
2. Gender Baseline A2
3. Age at Dx/Tx
4. Time since initial Dx/Tx

Data Analysis and Interpretation: To address the first specific aim, we will use latent class regression models in Mplus and or Latent Gold [16 17] to determine classes/clusters of cancer survivors based on the adult development outcome domains through time. First, as described above, we will follow algorithms described in prior analyses of CCSS data to create binary or ordinal variables corresponding to each of the attainment domains. For the ordinal variables, such as education, we may have to collapse them into binary variables to obtain stable estimates of the parameters of the latent class models. For each domain, we will use the Mplus or Latent Gold 4.5 program to fit a latent class regression model to the data [16]. For binary variables, this model is similar to a mixed effects logistic regression model for repeated binary outcomes, in that the log odds of a response of 1 for a subject to a given item at a given time point is related to a linear predictor containing fixed and random effects. In the latent class model, the random effect (i.e. random intercept) is assumed to follow a discrete distribution with a small number of points of support, rather than having a Normal distribution. The support points correspond to the clusters. To determine the number of clusters, we will follow the usual procedure for latent class analyses, where we successively fit models assuming 1, 2, 3, etc. clusters, and compare the fit of each model to the data using information criteria (AIC, BIC). We will choose the number of clusters that yields the best fit to the data. This best model will yield estimates of the conditional probability of a 1 (i.e. of success) for each item for each time point, as well as estimates of the probability of cluster membership for each subject. We will assign each subject to the cluster for which they have the highest estimated probability of membership. These analyses should yield interpretable classes, as they are based on sets of binary outcome variables.

These models will yield classifications for each domain. We will compare classifications across domains, and we expect to see one subset of people who have moderately high levels of success for all domains, and other subsets with success for some domains but not for others.

While the above description addresses the case of binary outcomes, we will attempt to run our analyses on ordinal variables, to retain as much information as possible. This type of analysis can be accommodated in Mplus or Latent Gold. The main difference from the analyses on binary responses, other than computational issues, is that now classes may be characterized in terms of additional odds

ratios and probabilities. We anticipate that the binary version of the analyses will yield similar classes to the analyses based on the ordinal response distributions, and that the analyses for Aims 2 and 3 will not be sensitive to how we use the items in the latent class analyses.

To allow for the variation in age at the first time point, we will include age, and time since cancer occurrence, as a covariate in the latent class regression models. These two variables are likely to be strongly correlated, so we anticipate including one or the other, rather than both. For each domain, we may restrict the age range of the subjects included in the analyses, to ensure that the responses are age appropriate. Thus, we may exclude subjects younger than 16, or 18, from the employment or marital status analyses. This decision will be made after an initial inspection of the data.

Aim b) To explore the association among these patterns and disease characteristics and cancer treatments;

Hypothesis b) Pediatric brain tumor survivor clusters (latent trajectories) based on psychosocial attainment (from aim a) will be associated with tumor characteristics and treatment exposure.

Outcome of interest for hypothesis b) The cluster membership will then be evaluated for its prediction by tumor type and treatment variables **(addressing hypothesis b)**.

The example below is taken from pilot data where the dependent variable is latent class membership of survivors and the predictors. Logistic regression results as in table 5. The number of reported tables is dependent on the outcomes of our bivariate efforts; there could be five pairs of these tables, one of each domain (education, marital status, etc) and a multivariate model including all the domains in a single latent class trajectory model.

Data Analysis and Interpretation: for Hypothesis b)

The cluster memberships from the above models will be used as outcome variables in the analyses for Aim b), where we will use mulitnominal logistic regression models to predict class membership from tumors characteristics, treatment characteristics, and subject characteristics. The selection of the treatment variables was completed following the recommendation of Harrell (1998) [18]. Following Harrell's recommended method, an expert clinician reviewer (Wendy Hobbie from The Children's Hospital of Philadelphia) selected from the treatment variables available and identified treatments (Tables 6 & 7)which were judged to be associated with variation in adult development, which were added to reported studies [4 5 14 19 20].

Independent variables: The coding for the treatment variables is consistent, if not identical to those listed in other CCSS prior publications [19 21 22].

Radiation Treatment

Regional head	Y/N
Regional treatment	categorized using the bain "4 seg diagram" attached and used in other CCSS studies [4].
Total Brain	Y/N
None	Y/N

Posterior Fossa

None	Y/N
< 30 Gy	Y/N
30-49	Y/N
50+	Y/N
Temporal Lobe	
None	Y/N
< 30 Gy	Y/N
30-49	Y/N
50+	Y/N
Frontal Lobe	
None	Y/N
< 30 Gy	Y/N
30-49	Y/N
50+	Y/N
Occipital Lobe	
None	Y/N
< 30 Gy	Y/N
30-49	Y/N
50+	Y/N

Chemotherapy

1. Busulfan Y/N, cumulative dose, tertiles]
2. Cyclophosphamide Y/N, cumulative dose, tertiles]
3. Ifosphamide Y/N, cumulative dose, tertiles]
4. Daunorubicin Y/N, cumulative dose, tertiles]
5. Doxorubicin Y/N, cumulative dose, tertiles]
6. Methotrexate Y/N, cumulative dose, tertiles]
7. Procarbazine Y/N, cumulative dose, tertiles]
8. Hydroxyurea Y/N, cumulative dose, tertiles]
9. Cisplantin Y/N, cumulative dose, tertiles]
10. Carboplatin Y/N, cumulative dose, tertiles]

Aim c) To examine the association between these selected neuropsychologic late effects and latent class trajectory membership.

Hypothesis c) Pediatric brain tumor survivors' cluster membership will be predicted by late effects at the baseline time point.

Outcome of interest hypothesis c) The cluster membership will then be evaluated for its association with selected late effects of tumors and treatment variables **(addressing hypothesis c)**. The selection of the late effects of tumors and/or tumor treatment variables was completed using the same method as outlined in the Outcome of interest hypothesis b) section above. The model fit and outcome tables

for this hypothesis will parallel those reported for hypothesis b), shown in Table 5. The primary difference in this hypothesis will be to use baseline late effects (Table 8) as predictors. As with hypothesis b), the number of reported tables is dependent on the outcomes of our bivariate efforts; there could be five pairs of these tables one of each domain (education, marital status, etc) and a multivariate model including all the domains in a single latent class trajectory model.

Independent Variables for hypothesis c), all questions are obtained from the baseline for use in a predictive model of cluster membership.

1. Would you say that your health is, Baseline question N.15
2. Hearing loss, Baseline question C. 1
3. Deafness, Baseline question C. 2
4. Legally blind Baseline question C.8
5. Underactive thyroid gland , Baseline question E.2
6. Deficiency of growth hormone, Baseline question E.8
7. Low sperm count, Baseline question E.15
8. Ever had a period , Baseline question E.15
9. Congestive heart failure, Baseline question F.4
10. Stroke, Baseline question F.9
11. Hepatitis, Baseline question H.4
12. Repeated seizures, Baseline question J.5
13. Problems with balance, Baseline question J.8
14. Tremors, Baseline question J.9
15. Amputation, Baseline question I.1
16. Heart surgery, Baseline question I.7 thru I 10 yes or no on any

Data Analysis and Interpretation: for Hypothesis c

For Hypothesis c) of the study, we will use multinomial logistic regression models to assess relationship between latent class membership as the dependent variable and the baseline (prior) late effects as predictors. We will perform these analyses separately for each late effect. We will repeat the analysis by combining all late effects into an overall sum (count) of late effects and use this as a predictor of latent class membership.

Figures and tables

Table 1: Demographics

Total population	N =, %
Male	N =, %
Female	N =, %
Race	N =, %
Age at diagnosis	M, SD
Current age	M, SD
Diagnosis	
astrocytoma	N =, %
medullo/PNET	N =, %
Other CNS tumors	N =, %
Education	Frequencies by survey wave
Employment	Frequencies by survey wave
Marital status	Frequencies by survey wave
Income family and personal	Frequencies by survey wave

Figure 1: Example of latent class trajectories From Jung 2008

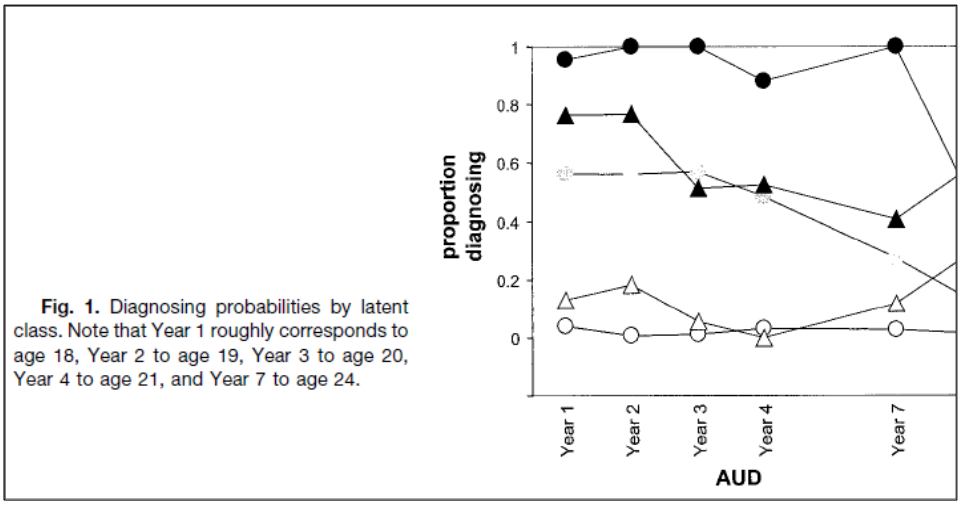

Fig. 1. Diagnosing probabilities by latent class. Note that Year 1 roughly corresponds to age 18, Year 2 to age 19, Year 3 to age 20, Year 4 to age 21, and Year 7 to age 24.

Table 2: Trajectory membership probabilities

Average Latent Class Probabilities For Most Likely Latent Class Membership (Row) by Latent Class (Column)

	1	2	3
1	**0.975**	0.012	0.014
2	0.055	**0.941**	0.003
3	0.030	0.000	**0.970**

Table 3: Model fit table for latent class trajectories

Models	ML	# of free parameters	AIC	BIC
1 latent class				
2 latent classes				
3 latent classes				
4 latent classes				

Table 4: Example for latent class trajectory model

	Estimate	S.E.	Est./S.E.	P-Value
Latent Class 1 trajectory				
Thresholds				
Baseline	-1.06	0.224	-0.473	0
2000	-0.021	0.203	-0.104	0.917
2003	0.328	0.172	1.911	0.056
2007	1.155	0.261	4.428	0
Latent Class 2 trajectory				
Thresholds				
Baseline				
2000	0.022	0.165	0.133	0.894
2003	0.961	0.196	4.899	0
2007	-1.143	0.238	-4.8	0
Categorical Latent Variables				
C#1 ON				
X	-2.454	0.738	-3.325	0.001
Intercepts				

C#	-0.048	0.335	-0.143	0.886

Table 5: Example for multinomial logistic regression for hypotheses b) and c)

Latent class membership				95% Confidence Interval for odds ratio)	
		Odd Ratio	Sig.	Lower Bound	Upper Bound
1	Intercept		0.016		
	Dxage	1.074	0.242	0.953	1.209
	School	1.553	0.73	0.127	18.996
	Childage	0.786	0.002	0.673	0.918
	[gender=F]	1.278	0.631	0.47	3.473
	[gender=M]	.	.	.	.
2	Intercept		0.001		
	Dxage	1.084	0.221	0.953	1.234
	l School	1.741	0.681	0.124	24.501
	Childage	1.521	0	1.24	1.865
	[gender=F]	0.584	0.365	0.182	1.872
	[gender=M]	.	.	.	.
3	Intercept		0.002		
	dxage	1.1	0.153	0.965	1.254
	School	18.845	0.007	2.195	161.762
	childage	0.804	0.011	0.68	0.951
	[gender=F]	1.192	0.75	0.405	3.513
	[gender=M]	.		.	.

Table 6: Radiation treatment frequencies

Regional head	N =, %
Total Brain	N =, %
None	N =, %
Posterior Fossa	

None	N =, %
< 30 Gy	N =, %
30-49	N =, %
50+	N =, %
Temporal Lobe	
None	N =, %
< 30 Gy	N =, %
30-49	N =, %
50+	N =, %
Frontal Lobe	
None	N =, %
< 30 Gy	N =, %
30-49	N =, %
50+	N =, %
Occipital Lobe	
None	N =, %
< 30 Gy	N =, %
30-49	N =, %
50+	N =, %
Brain 4 seg (from attached diagram)	
Segment 1	N=,%
Segment 2	N=,%
Segment 3	N=,%
Segment 4	N=,%

Table7: Chemotherapy frequencies

	N (%)	Cumulative dose	
Busulfan	N =, %	cumulative dose	tertiles]
Cyclophosphamide	N =, %	cumulative dose	tertiles]
Ifosphamide	N =, %	cumulative dose	tertiles]
Daunorubicin	N =, %	cumulative dose	tertiles]
Doxorubicin	N =, %	cumulative dose	tertiles]
Methotrexate	N =, %	cumulative dose	tertiles]
Procarbazine	N =, %	cumulative dose	tertiles]
Hydroxyurea	N =, %	cumulative dose	tertiles]
Cisplantin	N =, %	cumulative dose	tertiles]
Carboplatin	N =, %	cumulative dose	tertiles]

Table 8: Late effects frequencies

Would you say that your health is..	N =, %
Hearing loss	N =, %
Deafness	N =, %

Legally blind	N =, %
Underactive thyroid gland	N =, %
Deficiency of growth hormone	N =, %
Low sperm count	N =, %
Ever had a period	N =, %
Congestive heart failure	N =, %
Stroke	N =, %
Hepatitis	N =, %
Repeated seizures	N =, %
Problems with balance	N =, %
Tremors	N =, %
Amputation	N =, %
Heart surgery	N =, %

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FOR HYPOPHYSIS SEE PLATE 140