AWARD NUMBER: W81XWH-22-1-0666

TITLE: Assessment of Clonal Hematopoiesis and Its Relationship to Cardiovascular Disease in Hodgkin Lymphoma Survivors

PRINCIPAL INVESTIGATOR: Pamela Woodard, MD

CONTRACTING ORGANIZATION: Washington University, St. Louis, MO

REPORT DATE: August 2023

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

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5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Washington University
660 South Euclid Ave. and 510 S. Kingshighway
St. Louis, MO 631101010

The Rector & Visitors of the University of Virginia
1001 N. Emmet St.
Charlottesville, VA 22904-4195

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The funded project is proceeding forward without major difficulty. The proposal was approved by the Children's Oncology Group (COG), the DCP, and CIRB approval was obtained on. The study encompassing this research project (ALTE21C1) was activated within COG and COG member centers within the US have both agreed to participate and have proceeded with steps to activate the study at their institution . A webpage within the COG website has been constructed which contains the CIRB approved protocol and other resources to provide guidance, and answer questions for the participating centers. The workflows for certification of imaging centers for the cardiac MRI's has been launched and two centers have already been certified. The workflows for blood sample acquisition for clonal hematopoiesis have been defined and is ready to be executed once enrolled patients have begun participation in the study The committee members for the protocol meet monthly to address emerging issues, to enhance workflows and recruitment strategies. To date, there have been no major obstacles or delays in advancing this project toward its desired outcome.

15. SUBJECT TERMS

Late onset cardiac toxicity, Childhood cancer survivorship, Cardiac MRI, Clonal Hematopoiesis

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRDC
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1. INTRODUCTION:

The goal of this project is to establish the prevalence of therapy related clonal hematopoiesis (t-CH) in a population of Hodgkin's Disease survivors treated uniformly on a clinical trial (AHOD1331) with anthracyclines, a cardiotoxic agent. Secondly, we wish to see if patients possessing such t-CH demonstrate objective signs of cardiovascular disease (CVD) as measured by cardiac MRI (cMRI). Data supporting this observation will transform our approach toward CVD in childhood cancer survivors which will lead to studies to see if blocking the effects of t-CH can influence the development of CVD in childhood cancer survivors, a major source of mortality in this population.

2. KEYWORDS:

Clonal hematopoiesis, cardiovascular disease, childhood cancer survivors, Hodgkin Lymphoma, cardiac MRI. Anthracycline chemotherapy

3. ACCOMPLISHMENTS:

- **What were the major goals of the project?**

The major goals of the project are defined by the specific aims:

- **Specific Aim 1:** To assess the prevalence of participants in AHOD1331 with therapy-related clonal hematopoiesis (t-CH) possessing somatic mutations associated with cardiovascular disease (CVD) which are detected after Hodgkin Lymphoma therapy
- **Subtask 1 –** Obtain Institutional Review Board Approval: This study will be performed within the Children's Oncology Group,(COG), Protocol #: ALTE21C1, and thus IRB approval through the Central IRB (CIRB) utilized by COG was obtained (Washington University/Hayashi). All participating institutions routinely use this CIRB mechanism for COG studies and each institution must endorse the CIRB approval to enroll patients.
- **Subtask 2 -** CH analysis: Archived specimens from AHOD1331 and two specimens from blood samples obtained from enrolled study subjects one year apart from each other are available for use (University of Va./Walsh).
- **Specific Aim 2:** To assess participants of AHOD1331 with CH for the presence of absence of objective signs of CVD as measured by cardiac MRI (cMRI).
- **Subtask 1 -** Assess cMRI for CVD: cMRI obtained from enrolled subjects will be submitted to the radiology core (Washington University/Woodard). All cMRI will be evaluated by the partnering site PI and the presence of MRI findings consistent with CVD will be entered in the database.

- **Subtask 2 -** Collection of treatment data and clinical data for CVD risk factors Treatment data and clinical data including clinical assessments and laboratory assessments for CVD will be collected by the coordinating site (Washington University/Hayashi) and entered into the database in preparation for analysis.
- **Subtask 3 -** Analysis of Data: Data from the t-CH analysis and the radiologic findings will be complied along with the clinical data obtained from data collected in participation in AHOD1331 to assess a) whether t-CH emerge from therapy b) whether t-CH expands with time. c) whether patients possessing t-CH correlate with those possessing signs of CVD as documented by cMRI d) whether other specific patient characteristics (age, gender, race, etc.), or treatment variables (radiation) correlate with a higher incidence of t-CH with mutations associated with cardiovascular disease (secondary aims).

- **What was accomplished under these goals?**

Specific aim 1

- **Subtask 1:** Formal CIRB approval was obtained on January 4, 2023.
- **Subtask 2:** Workflows for two additional blood samples for CH analysis enrolled on the study have been refined and are available on the COG website and contained within the Protocol (ALTE21C1). Specimens will be retrieved as participants are enrolled. Enrollment will span the duration of the project, but it is expected to be completed within the first 36 months. The last specimen will be collected one year after the last patient is enrolled (each enrollee will have two specimens collected one year apart. CH analysis will be performed using all specimens collected for each enrolled subject together so that the quantitative changes in CH can be displayed over time.
- An exempt application was transitioned to a NON-UVA IRB application upon request from the UVA IRB HSR on 24 February 2023, given that samples processed by the UVa lab for clonal hematopoiesis analysis and quantification for this study involve only deidentified specimens. The paperwork has been completed and currently, we are awaiting NCI CIRB approval of the final paperwork which will then allow completion of the UVA local IRB protocol process."

Specific aim 2

- **Subtask 1:** Workflows for obtaining the cMRI are contained within the protocol. A certification process documenting that the participating centers can perform the cMRI according to protocol standards has been established as a Protocol Specific Requirement (PSR) and centers

receiving certification will receive a certificate documenting successful acquisition of this status and will be recorded on a central database for future reference. The protocol is officially activated; 2 centers have already been certified, and additional centers are at different stages in this process. There have been no difficulties in executing this process that would impede the timeline of completion of project.

- **Subtask 2**: The database for collecting specific data derived from the protocol has been generated and is live, and participating centers can now enter data from the patients they enroll into this database.
- **Subtask 3:** Demographic and therapy specific data from the research subjects when they participated in the original treatment study (AHOD1331) remains in the COG database specific for that study. Upon completion of enrollment and once all of the data from

What opportunities for training and professional development has the project provided?

Nothing To Report

How were the results disseminated to communities of interest?

Nothing to Report

What do you plan to do during the next reporting period to accomplish the goals?

The protocol was activated on 5/22/23. The centers with eligible patients have been contacted to raise awareness of the study and there has been universal enthusiasm for participation. A dedicated breakout session will be held at the Annual COG meeting in Atlanta, GA in September. We anticipate updates on the number of centers who have the study open, the number of enrollees, the number of cMRI's obtained and the number of blood samples obtained. We also expect to report the prevalence of cardiovascular disease in the enrolled subjects as documented by cMRI. Data on t-CH analysis will be shared once sufficient numbers of samples (including two samples obtained 1 year apart) are collected, allowing the trajectory of t-CH expansion to be assessed.

2. **IMPACT:**

- **What was the impact on the development of the principal discipline(s) of the project?**

  Nothing To Report

- **What was the impact on other disciplines?**

  Nothing To Report

- **What was the impact on technology transfer?**

  Nothing To Report

- **What was the impact on society beyond science and technology?**

  Nothing To Report

3. **CHANGES/PROBLEMS:**
   - **Changes in approach and reasons for change**

     There have been no significant changes to the project or its direction.

   - **Actual or anticipated problems or delays and actions or plans to resolve them**

     Protocol study startup is proceeding at all centers. There have been no significant problems or delays encountered to date.

   - **Changes that had a significant impact on expenditures**

     There have been no significant changes that have impacted expenditures.

   - **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

     Nothing To Report

   - **Significant changes in use or care of human subjects**

     Nothing To Report

   - **Significant changes in use or care of vertebrate animals.**

     Nothing To Report

   - **Significant changes in use of biohazards and/or select agents**

     Nothing To Report

4. **PRODUCTS:**
   - **Publications, conference papers, and presentations**

     - **Journal publications.**

       Nothing To Report

- **Books or other non-periodical, one-time publications.**

  Nothing To Report

- **Other publications, conference papers, and presentations.**

  Nothing To Report

- **Website(s) or other Internet site(s)**

  This study is listed on Clinical Trials.gov with the following URL:

  https://classic.clinicaltrials.gov/ct2/show/NCT05705531

- **Technologies or techniques**

  Nothing To Report

- **Inventions, patent applications, and/or licenses**

  Nothing To Report

- **Other Products**

  Nothing To Report

5. **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

   - **What individuals have worked on the project?**

Name:	Robert J. Hayashi, MD
Project Role:	Principal Investigator
Researcher Identifier (e.g. ORCID ID):	0000-0002-1140-1139
Nearest person month worked:	3
Contribution to Project:	no change
Funding Support:	W81XWH2210665

Name:	Kenneth Walsh, Ph.D.
Project Role:	Principal Investigator
Researcher Identifier (e.g. ORCID ID):	0000-0001-7580-2276

Nearest person month worked: 3
Contribution to Project: no change
Funding Support: W81XWH2210665

Name: Pam Woodard, MD
Project Role: Principal Investigator
Researcher Identifier (e.g. ORCID ID): 0000-0001-9012-0812
Nearest person month worked: 3
Contribution to Project: no change
Funding Support: W81XWH2210665

Name: Saro Armenian DO
Project Role: Study Committee Member
Researcher Identifier (e.g. ORCID ID): 0000-0003-2604-8603
Nearest person month worked: 1
Contribution to Project: no change
Funding Support: W81XWH2210665

Name: Sharon Castellino, MD
Project Role: Study Committee Member
Researcher Identifier (e.g. ORCID ID): 0000-0001-8367-2002
Nearest person month worked: 1
Contribution to Project: no change
Funding Support: W81XWH2210665

Name: Eric Chow MD
Project Role: Study Committee Member
Researcher Identifier (e.g. ORCID ID): 0000-0002-3665-1249
Nearest person month worked: 1

Contribution to Project: no change
Funding Support: W81XWH2210665

Name: David Hodgson MD
Project Role: Study Committee Member
Researcher Identifier (e.g. ORCID ID): 0000-0003-4687-4582
Nearest person month worked: 1
Contribution to Project: no change
Funding Support: W81XWH2210665

Name: Joshua Mitchell MD
Project Role: Study Committee Member
Researcher Identifier (e.g. ORCID ID): 0000-0001-7371-5742
Nearest person month worked: 1
Contribution to Project: no change
Funding Support: W81XWH2210665

Name: Aecha Ybarra MD
Project Role: Study Committee Member
Researcher Identifier (e.g. ORCID ID): 0000-0002-1813-407X
Nearest person month worked: 1
Contribution to Project: no change
Funding Support: W81XWH2210665

Name: Lisa Roth MD
Project Role: Study Committee Member
Researcher Identifier (e.g. ORCID ID): 0000-0002-6040-8644
Nearest person month worked: 1
Contribution to Project: no change

Funding Support: W81XWH2210665

Name: Caroline Mohrmann
Project Role: Study Committee Member
Researcher Identifier (e.g. ORCID ID): 0000-0002-1198-0433
Nearest person month worked: 1
Contribution to Project: no change
Funding Support: W81XWH2210665

Name: Jennifer Seelisch
Project Role: Principal Investigator
Researcher Identifier (e.g. ORCID ID): 0000-0002-2187-0051
Nearest person month worked: 2
Contribution to Project: no change
Funding Support: none

Name: Qinglin Pei
Project Role: Statistician
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 1
Contribution to Project: no change
Funding Support: COG

Name: Anna Gilmore
Project Role: Study Committee Member
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 2
Contribution to Project: Administrative support for protocol development and implementation
Funding Support: COG

Name: Tyler Brown

Project Role: Research Coordinator

Researcher Identifier (e.g. ORCID ID):

Nearest person month worked: 2

Contribution to Project: Administrative support for protocol development and implementation

Funding Support: COG

Name: Kara Felts

Project Role: Lead Clinical Research Associate

Researcher Identifier (e.g. ORCID ID):

Nearest person month worked: 3

Contribution to Project: no change

Funding Support: W81XWH2210665

Name: Lora Gallagher

Project Role: Clinical Research Coordinator

Researcher Identifier (e.g. ORCID ID):

Nearest person month worked: 3

Contribution to Project: cMRI coordination and site certification

Funding Support: W81XWH2210665

Name: Jie Zheng, PhD

Project Role: Co-Investigator

Researcher Identifier (e.g. ORCID ID): 0000-0002-2310-2996

Nearest person month worked: 4

Contribution to Project: cMRI protocol development and site certification

Funding Support: W81XWH2210665

Name:	Manish Aggarwal, MD
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	0000-0003-1073-0376
Nearest person month worked:	1
Contribution to Project:	cMRI protocol development and site certification
Funding Support:	W81XWH2210665

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

  No changes to report

- **What other organizations were involved as partners?**

  Organization Name: Children's Oncology Group (COG)

  Location of Organization: Seattle Children's Research Institute, Seattle Washington, Doug Hawkins, Chairman

  Partner's contribution to the project:

  - *Financial support; (Provides organizational, and infrastructure support for clinical trial execution.)*
  - *Collaboration* Provides statistical and protocol administrative support as part of the COG infrastructure*;*

  Organization Name: Public Health Institute

  Location of Organization: Oakland California

  Partner's contribution to the project:

  Collaboration : PHI provides administrative support for grants involving COG and assists in the disbursement of funds for per case reimbursement for this study.

  Organization Name: Division of Cancer Prevention, NCI

Location of Organization: Bethesda Maryland

Partner's contribution to the project:

- *Financial support;* Provides additional per case reimbursement from their budget to support the execution of this trial through the COG/PHI.

- *Collaboration* Oversees this and other clinical trials involving Cancer Control and Survivorship in the COG

6. **SPECIAL REPORTING REQUIREMENTS**

Inclusion Report

7. **APPENDICES:**

1. Inclusion Report
2. CIRB Approval
3. DCP Approval
4. Study Activation

OMB Number: 0925-0770
Expiration Date: 09/30/2024

PHS Inclusion Enrollment Report

1. * Inclusion Enrollment Report Title

Assessment of Clonal Hematopoiesis and Its Relationship to Cardiovascular Disease in Hodgkin Lymphoma Survivors

2. * Using an Existing Dataset or Resource ☐ Yes ☒ No

3. * Enrollment Location Type ☒ Domestic ☐ Foreign

4. Enrollment Country(ies)

USA: UNITED STATES

5. Enrollment Location(s)

Children's Oncology group sites in the US (124 centers with eligible institutions)

6. Comments

No enrollments to date.

Planned

Racial Categories	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		**Total**
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	0	0	0	0
White	0	0	0	0	0
More than One Race	0	0	0	0	0
Total	0	0	0	0	0

Cumulative (Actual)

Racial Categories	Ethnic Categories									
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			**Total**
	Female	**Male**	**Unknown/ Not Reported**	**Female**	**Male**	**Unknown/ Not Reported**	**Female**	**Male**	**Unknown/ Not Reported**	
American Indian/ Alaska Native	0	0	0	0	0	0	0	0	0	0
Asian	0	0	0	0	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0
Black or African American	0	0	0	0	0	0	0	0	0	0
White	0	0	0	0	0	0	0	0	0	0
More than One Race	0	0	0	0	0	0	0	0	0	0
Unknown or Not Reported	0	0	0	0	0	0	0	0	0	0
Total	0	0	0	0	0	0	0	0	0	0

Report 1 of 1

C›I›R›B
FOR THE NATIONAL CANCER INSTITUTE

CIRB Final Approval

Date: January 4, 2023

Study ID: ALTE21C1

Study Title: Assessment of Clonal Hematopoiesis and its Relationship to Cardiovascular Disease in Hodgkin Lymphoma Survivors

Protocol Version Date: 12/29/22

Study Chair: Robert Hayashi M.D.

On January 3, 2023, the NCI Pediatric CIRB reviewed the Study Chair's response dated December 29, 2022 and granted approval. The Study Chair provided this response as requested by the CIRB's previous review of ALTE21C1 at its meeting on December 8, 2022, at which time it was granted approval pending modification. The expedited review was conducted in accordance with the Federally-defined categories of expedited review stated in 45 CFR 46.110 (b)(1)(ii) and 21 CFR 56.110(b)(2).

CIRB approval for this study will expire on January 2, 2024.

The following documents were reviewed:

1. CIRB Application (PVD 12/29/22)
2. Consent Form (PVD 12/29/22)
3. Healthy Cardiac Lifestyle Survey (PVD 12/29/22)
4. Protocol Version Date 12/29/22
5. Study Chair Response to CIRB (PVD 12/29/22) dated 12/29/22

The NCI CIRB has approved this study for the enrollment of 230 participants.

The CIRB determined that this research satisfies the requirements of 45 CFR 46.404, and 21 CFR 50.51, described as research/clinical investigations not involving greater than minimal risk. The permission of at least one parent is required.

The CIRB has determined that assent of children age 7 and older is a necessary condition for proceeding with the research (per 45 CFR 46.408 and 21 CFR 50.55). For children younger than 7 years, assent is not a necessary condition for participating in the research (per 45 CFR 46.408(a) and 21 CFR 50.55 (a)), because their capacity is so limited. Principal Investigators are to document assent according to the local policies and procedures described in their Annual Principal Investigator Worksheet About Local Context.

In all cases, the CIRB expects that investigators will provide children with developmentally appropriate information about their diagnosis, treatment, and proposed research participation. In particular, investigators should explain the purpose as well as the design of the clinical trial, risks and benefits of participation, and offer an opportunity to ask questions.

As the Study Chair, you are responsible for reporting study-related activity to the CIRB.

The CIRB complies with the Federal regulations 45 CFR 46, 21 CFR 50, and 21 CFR 56.

Please note that the CIRB's review and approval of this research is not inclusive of prisoners.

If you have any questions regarding this review, please contact the Pediatric CIRB Coordinator at pediatriccirb@emmes.com.

cc: Jennifer Seelisch, MD
Anna Gilmore, BA, MPH
Lori Minasian, MD, FACP
Meg Mooney, MD
CTSU Protocol
CTSU Translation
Eric Chow M.D.
Michael Thomas BA
Bernard Parker, MD
Linda Parreco, RN

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20892

January 26, 2023

Brad Pollock, Ph.D.
Children's Oncology Group
Operations Center
440 E. Huntington Drive Suite 300
Arcadia, CA 91006

RE: Protocol Review: COG-ALTE21C1 entitled ***"Assessment of Clonal Hematopoiesis and its Relationship to Cardiovascular Disease in Hodgkin Lymphoma Survivors."***

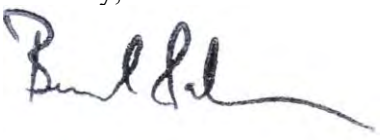
Review Decision: Approved with Recommendations

Dear Dr. Pollock:

Thank you for submitting the above protocol to the Cancer Prevention and Control Protocol Review Committee, Division of Cancer Prevention (DCP). The Protocol Review Committee is approving this cancer protocol. Attached is the CTSU recommendations.

Congratulations to you and your team on this accomplishment. We look forward to an interesting and successful trial

Sincerely,



Bernard W. Parker, M.D.
Medical Officer/Program Director
Community Oncology & Prevention Trials Research Group/DCP/NCI

CC: DCP Protocol Information Office
Worta McCaskill-Stevens, M.D., M.S, Chief of NCORP

CHILDREN'S ONCOLOGY GROUP

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A National Cancer Institute-funded group member of the National Clinical Trials Network

Memo

To: Principal Investigators and Clinical Research Associates

From: Anna Gilmore, Protocol Coordinator

Re: REVISED Study Activation

Study: **ALTE21C1**: *Assessment of Clonal Hematopoiesis and its Relationship to Cardiovascular Disease in Hodgkin Lymphoma Survivors*

Date: May 22, 2023 (REVISED May 26, 2023)

ALTE21C1 will be open for patient enrollment on Monday, **05/22/2023**. This study is open to all COG Institutions. *Please note that Canadian sites will not be able to activate ALTE21C1 until regulatory requirements for the Department of Defense (DOD) study grant are met. COG is currently working on procedures for these requirements and will post a memo once they are finalized.*

Site Reimbursement

Please refer to the protocol specific funding page on the CTSU members' website for funding information.

Study Specific Details

ALTE21C1 evaluates clonal hematopoiesis and cardiovascular disease in Hodgkin lymphoma survivors from the COG therapeutic trial, AHOD1331. Site-specific lists of AHOD1331 patients with available banked blood samples will be provided to guide selective local recruitment. Data and blood specimen collection for the two study time points can be completed during standard follow-up appointments, with a cardiac MRI (cMRI) submission once at baseline.

Protocol-Specific Requirements:
This study includes a Protocol Specific Requirement (PSR) for attestation of completion of site certification for cMRI performance. (See Section 9 and Appendix I of the protocol.) The *cMRI Site Certification* form with instructions is provided on the COG Protocol Web Page. The certification must be in place prior to your institution enrolling a patient on study.

Required Cardiac MRI (cMRI) Submission:
A site designated imaging specialist must complete technical training for collection of the study specific cMRI measures prior to first patient enrollment. Study-specific cMRI training materials and a technical guide will be made available on the protocol web page in the near future.

Study Enrollment and Data Submission

Study enrollment is accomplished via OPEN by going to https://www.ctsu.org and logging into the member's area using your CTEP IAM user name and password. Once in the member's area, click on the OPEN tab and then click on 'Connect to OPEN.' For questions regarding CTEP IAM accounts or access to the OPEN system, please contact the CTSU Helpdesk at ctsucontact@westat.com or call 1-888-823-5923 (9am ET to 6pm ET, excluding holidays).

After patient enrollment via CTSU OPEN, all data for this study will be submitted directly to the external coordinating centers. Refer to the Data Submission Schedule in the Case Report Forms packet on the COG website for specifics. Prior to initiating local recruitment, sites should email the coordinating center to receive their site-specific list of potentially eligible AHOD1331 candidates with confirmed available banked blood samples.

COG Eligibility Policy

Institutions are reminded of the COG policy regarding eligibility waivers: No patient will be entered on a COG clinical trial unless the institutional investigator confirms the patient meets all the criteria for study entry as stated in the protocol at the time study entry is attempted. Eligibility criteria cannot be waived.

Study Contacts

For registration/enrollment, data collection and data entry application questions, please contact:

Research Coordinator: Tyler Brown
Phone: (626) 241-1531
E-mail: TyBrown@childrensoncologygroup.org

For questions regarding external coordinating center data collection and submission, please contact:

Study CRA: Kara Felts
Phone: (314) 286-1177
E-mail: feltsk@wustl.edu

For patient related questions, please contact:

Study Chair: Robert J. Hayashi, MD
Phone: (314) 454-6018
E-mail: hayashi_r@wustl.edu

Study Vice Chair: Dr. Jennifer Seelisch, MD
Phone: (519) 685-8500 x52679
Email: jennifer.seelisch@lhsc.on.ca

For other protocol document questions, please contact:

Protocol Coordinator: Anna Gilmore
Phone: (626) 241-1521
E-mail: agilmore@childrensoncologygroup.org

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20892

January 26, 2023

Brad Pollock, Ph.D.
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440 E. Huntington Drive Suite 300
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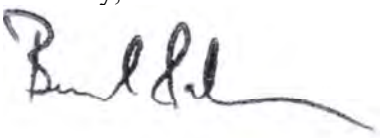

Bernard W. Parker, M.D.
Medical Officer/Program Director
Community Oncology & Prevention Trials Research Group/DCP/NCI

CC: DCP Protocol Information Office
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CHILDREN'S ONCOLOGY GROUP

ALTE21C1

Assessment of Clonal Hematopoiesis and its Relationship to Cardiovascular Disease in Hodgkin Lymphoma Survivors

A COG Groupwide Observational Study

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For Regulatory Requirements	**For patient enrollments:**	**For Data Submission**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at https://www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878) for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://open.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions by phone or email: 1-888-823-5923, or ctsucontact@westat.com.	After a patient enrollment via CTSU OPEN, data for this study will be submitted directly to the external Data Coordinating Center. Please see the Data Submission Schedule in the CRF packet for further instructions.
The most current version of the **study protocol** must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires log in with a CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).		
For clinical questions (i.e. patient eligibility or treatment-related) Contact the Study PI of the Lead Protocol Organization.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) Contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
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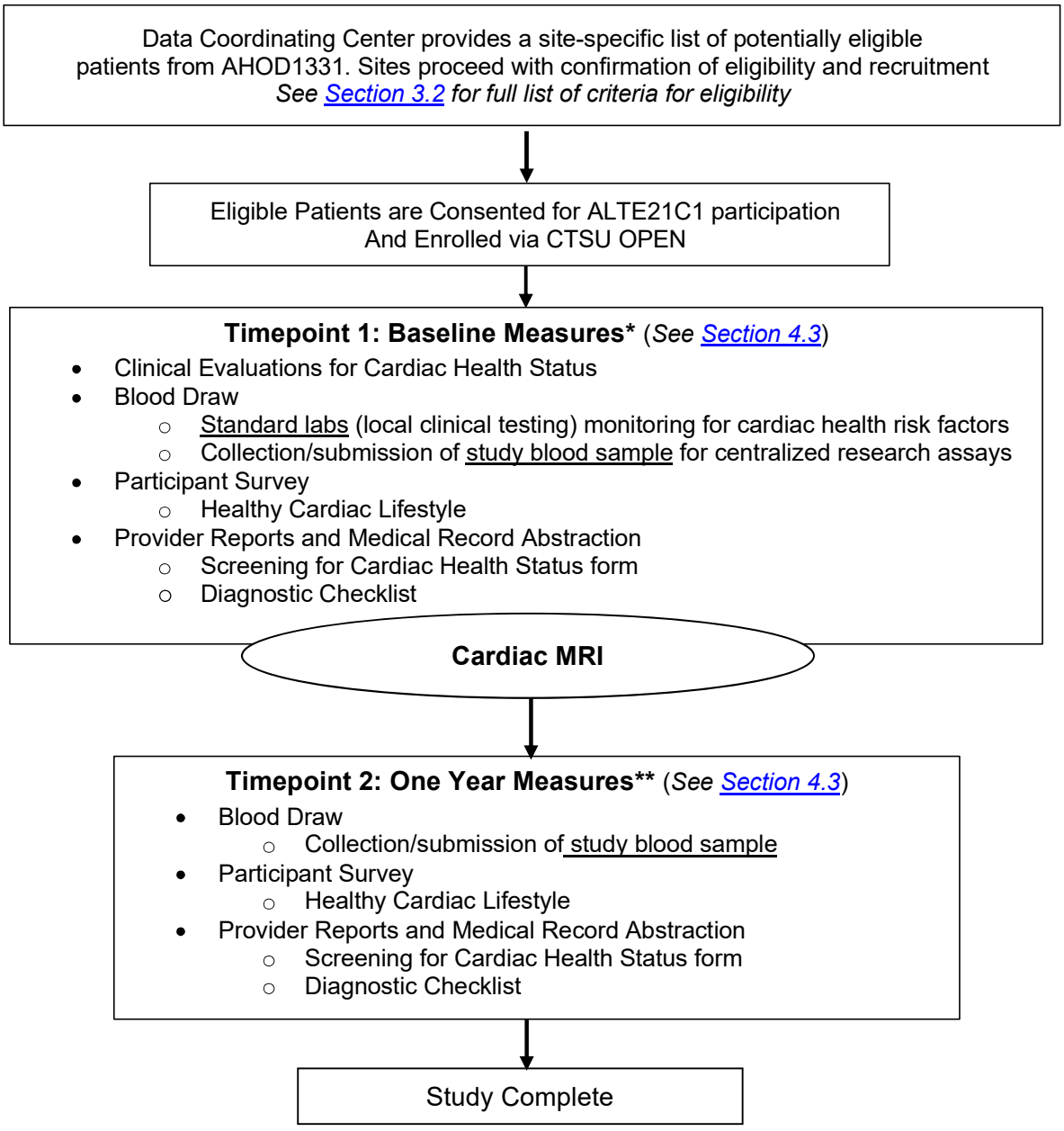
ABSTRACT

Cardiovascular disease (CVD) represents a significant source of mortality for childhood cancer survivors. Anthracycline chemotherapy exposure is a major risk factor which has been well described, but the exact mechanisms which account for the observed deterioration of heart function is still an active area of investigation. Clonal hematopoiesis (CH) of indeterminate potential, commonly referred to as "CHIP", is a common preleukemic condition that has been linked to CVD.[1-3] Therapy-related clonal hematopoiesis (t-CH) are clones that have been identified in some cancer survivors. Recent investigations suggest that t-CH possessing specific mutations, can be associated with the development of CVD. This study will capitalize on technologies that can detect the presence of t-CH at very low levels to determine whether such clones emerge from therapy, expand over time and whose presence correlate with early signs of CVD as detected by cardiac MRI. Participants from the recent COG trial, (AHOD1331) will be recruited for this study. Both freshly collected blood specimens and archived samples will be assessed for the presence of t-CH and a cardiac MRI will be obtained to assess the presence of CVD as it provides the most sensitive means of detecting early cardiac injury from anthracycline chemotherapy. Successful execution of this trial will help determine whether t-CH is associated with CVD in childhood Hodgkin Lymphoma patients.

EXPERIMENTAL DESIGN SCHEMA

Reminder: prior to the first patient enrollment, institutions must complete technical training for collection of the study specific cardiac MRI measures.

Recommendation: It is highly recommended that study measures occur during a scheduled standard of care follow up visit.



* **Timepoint 1 (Baseline) Measures** must be completed within one month after enrollment. An additional month of flexibility is permitted to obtain the cardiac MRI to accommodate clinical scheduling if needed.

** **Timepoint 2 (One Year) Measures** must be completed 12 ±3 months after the date of the Baseline study blood collection.

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

1.1.1 To assess the prevalence of participants in AHOD1331 with therapy-related clonal hematopoiesis (t-CH) possessing somatic mutations associated with cardiovascular disease (CVD) which are detected after Hodgkin Lymphoma therapy.

1.1.2 To assess participants of AHOD1331 with t-CH for the presence or absence of objective signs of CVD using cardiac MRI.

1.2 Secondary Aims

1.2.1 To assess whether participants in AHOD1331 with t-CH expand this population over time and possess objective findings of CVD.

1.2.2 To assess whether patients both with and without objective findings of CVD using cardiac MRI possess clinical risk factors for CVD.

1.3 Exploratory Aims

1.3.1 To assess the prevalence of patients receiving mediastinal radiation who have objective findings of CVD using cardiac MRI, that also possess t-CH with mutations associated with CVD.

1.3.2 To assess whether specific patient characteristics and treatment (age, gender, race, dexrazoxane usage, etc.) correlate with a higher incidence of t-CH with mutations associated with CVD.

1.3.3 To assess the effects of t-CH on CVD by considering other factors such as patient characteristics and clinical conditions associated with an elevated risk for CVD.

2.0 BACKGROUND

2.1 Introduction

Advancements in pediatric cancer therapy have increased the long-term cancer free survival to over 85%.[4, 5] Childhood cancer survivors (CCS) experience a variety of long-term side effects from cancer therapy, sometimes leading to early death. Cardiovascular disease (CVD) represents one of the most common causes of both early mortality and late mortality for CCS with standardized mortality ratios (SMR) of 21.7 (95% CI=10.4-45.6), 5-9 years from diagnosis, and 16.7 (95% CI=6.3-44.5), 10-19 years from diagnosis when compared to the general population.[6, 7] The risk for developing clinically significant CVD accumulates with time for CCS with 19.7% (17.6-21.7) of survivors developing CVD by 30 years from diagnosis.[8] Thus, early identification of patients at risk is needed to implement efforts to optimize cardiac health before severe declines occur.

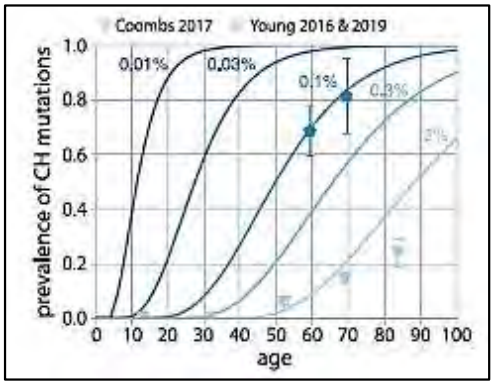


Figure 1 Predicted prevalence of CH mutations as a function of age with different detection thresholds (From CJ Watson et al. 2020 *Science* 367:1449)

Clonal hematopoiesis (CH) of indeterminate potential, commonly referred to as "CHIP", is a common preleukemic condition that has been linked to CVD.[1-3] In the original study of Jaiswal et al, clonal hematopoietic mutations were associated with a 1% per year increased risk of developing AML; however, heart disease was the most common cause of mortality in the 17,000 participants interrogated.[2, 9] While it is widely recognized that CH associated mutations are prevalent in elderly individuals, recent studies show that clonal expansions of hematopoietic cells are also prevalent in much younger individuals.

2.2 Clonal Hematopoiesis

Previous investigators have employed ultradeep, error-corrected sequencing that has allowed the detection of clonal events as low as 0.03% variant allele fraction (VAF).[10] Using these methods, Druley and colleagues have shown that clonal hematopoiesis is essentially ubiquitous by middle age, and an extension of these studies predicted that nascent clones would be prevalent in childhood and adolescent patients (Figure 1).[11]

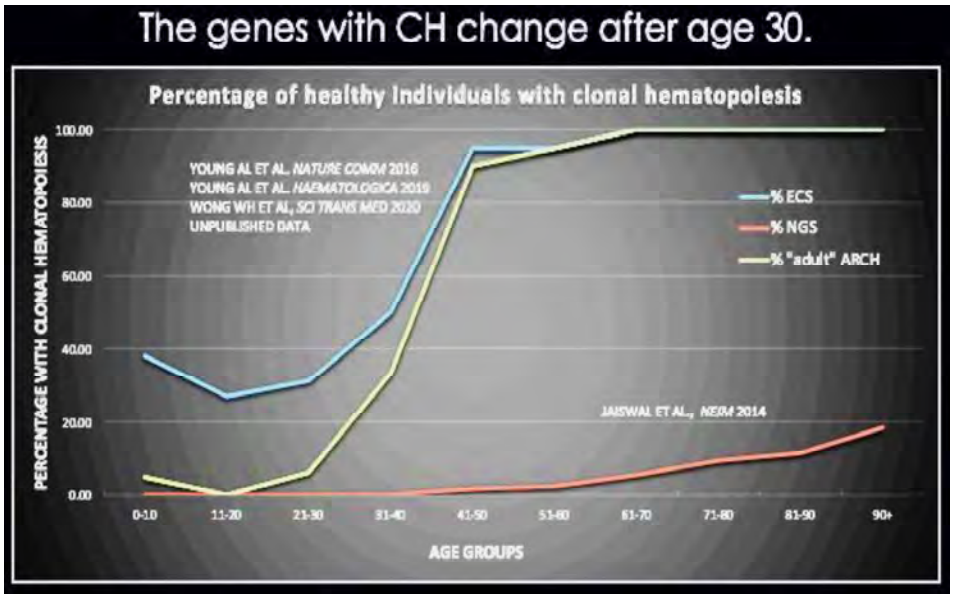


Figure 2: Demonstration of CH in healthy individuals from pediatrics to adulthood.
ECS = Error Corrected Sequencing
NGS = Next Generation Sequencing,
ARCH = Age Related Clonal Hematopoiesis

More recently, the Druley lab employed error-corrected sequencing to show that CH, is observed in >20% of otherwise healthy individuals from birth to young adulthood (Figure 2). In addition, members of this group have provided experimental evidence that CH attributed to mutations in *TET2*, *DNMT3A* and *Janus kinase 2* genes (i.e. $JAK2^{V617F}$) can causally contribute to CVD in various animal models by conferring pro-inflammatory phenotypes to the progeny leukocytes that are derived from the hematopoietic stem and progenitor cells (HSPC) clones.[12-16] Of particular significance for this study, the Zeiher group has published a series of reports showing that *relatively small VAF clones, that are much lower than the 2% VAF cutoff used to define "CHIP", are prognostic for poor outcome in heart failure*.[17-19] These reports, and others, have highlighted that the VAF threshold for "CHIP" is not biological, but dictated by the technical limitations of the exome sequencing employed. Thus, the significance of this study is derived in part from our ability to employ sensitive, error-corrected sequencing to study CH and CVD in CCS.

Exactly what drives clonal expansion of these mutations in some individuals and not others remain speculative. Clearly, advanced age leads to degradation of the bone marrow niche that will favor the expansion of mutant HSPC.[20] However, increasing evidence also suggests that environmental factors play a role in this process in younger individuals, perhaps by modulating the kinetics of clonal expansion or by altering the bone marrow niche to favor survival of the fittest HSPC clones. This hypothesis underlies the observation of elevated CH in cancer survivors that have been treated with genotoxic therapies. Therapy-related clonal hematopoiesis (t-CH) refers to the aberrant clonal expansions that are often detected in the blood of cancer survivors.[21, 22] This form of CH occurs as a result of the selective pressure that the genotoxic stress of radiation and/or chemotherapy exert on the HSPC. Mutations associated with t-CH can preferentially occur in genes that encode regulators of DNA-damage response (DDR) pathway, such as protein phosphatase, Mg2+/Mn2+ dependent 1D, (PPM1D), tumor protein 53 (*TP53*) and checkpoint kinase 2 (*CHEK2*).[23-27] A number of studies have shown that t-CH is associated with greater mortality. Gibson et al. reported that lymphoma patients with t-CH had significantly inferior overall survival including from CVD.[28] Coombs *et al*. reported that t-CH in patients with solid tumors is associated with reduced overall survival.[21, 24, 29] Takahashi *et al*.[30] and Gillis *et al*.[31] reported that the presence of t-CH in cancer patients significantly increased the risk of therapy-related myeloid neoplasm. Husby *et al*.[32] recently reported in five independent national registries that CH was not associated with inferior overall survival. However, patients with mutations in genes of the DNA repair pathway (PPM1D, TP53, RAD21, BRCC3) had a significant inferior overall survival on multivariate analysis.[32] Recent investigations by Walsh's group and others suggest that t-CH possessing specific mutations, can be associated with the development of CVD.[33-36]

Previous investigators have advanced work in a murine system supporting the premise of the proposed research. HSPC from *Trp53*-mutant mice were transferred into wild-type mice. Neutrophils derived from the t-CH were shown to infiltrate the hearts of these mice implicating them in the development of CVD. Doxorubicin treatment provided a selective advantage with expansion of the t-CH supporting the notion that cardiotoxic chemotherapy could also promote the expansion of t-CH which bore a mutation (Trp53 mut) associated with CVD. Finally, echocardiography demonstrated that this model resulted in clinical CVD supporting the notion that t-CH with mutations associated with CVD can expand in chemotherapy treated animals and lead to measurable signs of CVD.[33]

Recent advances in cardiac imaging have improved our ability to diagnose CVD at earlier stages. Cardiac MRI (cMRI) allows for the detection of cardiac strain and large vessel distensibility which can serve as early markers for both ventricular function and vascular disease.[37] To maximize the sensitivity to detect alterations in cardiac structures and function, we propose the use of the latest technological advances in cMRI imaging. It is expected that both myocardial strain and native myocardial T1 measurements will demonstrate early abnormalities preceding eventual decrease in myocardial systolic function as has been demonstrated in previous studies in CCS exposed to cardiotoxic agents.[38, 39]

2.3 Cardiac MRI to Detect Early Signs of Cardiovascular Disease

Evaluation of CCS in a single institution study in patients with prior exposure to cardiotoxic chemotherapy has supported the use of cMRI as a means of identifying patients with early signs of CVD. In this ongoing study, 30 subjects received anthracycline as their cardiotoxic chemotherapy. All thirty completed cMRI exams. Of these patients (16 male; average age, 15.7 ± 5.4 years; average BSA, 1.7±0.36 meters^2), using the definition of CVD that will be used in the protocol, (see Section 7.1), there were a total of 9 (30%) patients who had one

or more objective signs of CVD (mean years off therapy for the whole cohort was 7.88 years, s.d. = 5.63, range = 1.29-21.47, mean years off therapy of patients with abnormal cMRI 6.66 years, s.d.= 2.74 range = 1.29-17.92). Of note, of the 30 patients, one patient did not have a left ventricular ejection fraction (LVEF) calculation, and one patient did not have a global longitudinal strain (GLS) calculation because of suboptimal image quality.

Of these patients with abnormal cMRI's, 7 of 9 had abnormal GLS (average -16.3 ± 1.16%), 1 of 9 had abnormal left ventricular end diastolic volume (LVEDV)/BSA, and 4 of 9 had abnormal LVEF (average 51.8± 1.09%). Of the 4 patients who had abnormal LVEF, 3 also had abnormal GLS. Abnormal GLS has been shown to be a predictor of decreased LV systolic function.[39-41] While patients in this study have not been followed long enough to determine if those with decreased GLS will develop decreased systolic left ventricular function (deceased LVEF), 3 of 4 patients with abnormal LVEF, albeit mild, also had abnormal GLS. Based on these preliminary data, we hypothesize that cMRI can be used to detect early signs of cardiac injury from cancer therapy before symptoms develop or signs on conventional echocardiography are detected.

2.4 Methods for Risk Factor Assessment for CVD

Participants will be assessed for CVD risk factors at **Timepoint 1: Baseline** (within 1 month after enrollment) and **Timepoint 2: One Year** (12±3 months after the date of the Baseline study blood draw). Data collection for the study will be based on the "Simple 7" of CVD from the American Heart Association (Smoking status, Body Mass Index, Diet, Activity, Total Cholesterol, Blood Pressure, Fasting Glucose).[6]

Results of clinical exams and laboratory tests obtained as part of standard follow-up care will be abstracted and used to assess for metabolic syndrome (triglycerides, HDL-C). Recent studies have indicated that CCS possess conventional risk factors for CVD analogous to older, adult survivors.[42, 43] Presence of such risk factors, especially hypertension, has been shown to significantly increase the risk of subsequent CVD. In addition to assessing for traditional risk factors, we will also extract other important treatment factors including mediastinal radiation exposure and use of dexrazoxane, a therapy that can reduce the onset of heart failure when used in conjunction with anthracycline treatment. Data from these assessments will assist in providing a comprehensive clinical picture of the cardiac health status of the participants and their risk factors for CVD, which can be analyzed as to whether they correlate with any objective signs of CVD detected by cMRI.

At the two study time points, providers will complete and submit study forms with data regarding signs and symptoms of CVD: the *Screening for Cardiac Health Status* form, and *Diagnostic Checklist*. The *Diagnostic Checklist* is modeled after the form by the same name used by ALTE11C2, a COG protocol that prospectively assessed cardiovascular health among survivors of acute lymphoblastic leukemia, Hodgkin lymphoma, and osteosarcoma treated on dexrazoxane-containing pediatric clinical trials in the 1990s. ALTE11C2 enrolled 200 survivors from >70 COG sites for in-person cardiac (echocardiography) assessments. As part of that assessment, research personnel at COG sites submitted a comprehensive health history for each participant, providing data regarding major cardiovascular endpoints as well as related cardiovascular risk factors. The *Diagnostic Checklist* has been successfully implemented in COG and will support collection of relevant data to characterize CVD risk factors for the ALTE21C1 study population.

Participants, or their caregivers, will be asked to complete a *Healthy Cardiac Lifestyle Survey* at each of the two time points, with data used by the study to assess lifestyle factors related to cardiovascular health. Finally, participants will provide a blood sample at each time point for the protocol's t-CH studies.

Subject participation ends approximately 1 year after study entry upon study blood sampling and completion of the *Healthy Cardiac Lifestyle Survey*, and provider submission of data from the *Diagnostic Checklist* and *Screening for Cardiac Health Status* forms.

2.5 Overview

We hypothesize that *participants in AHOD1331 may be at risk for developing t-CH as a consequence of their Hodgkin Lymphoma treatment, and these clones may expand over time contributing to CVD that will be documented with cMRI*. This study will capitalize on the capture of a sizable population (participants of AHOD1331) who were treated with a uniform exposure of anthracycline.

Archived blood samples obtained prior to therapy initiation and at the end of therapy will be assessed for the presence of t-CH emerging from the therapy of AHOD1331. Subsequent samples will be collected in conjunction with cMRI imaging. Blood samples will be obtained at two study time points, separated by a year to assess whether t-CH expand with time and whether t-CH possessing mutations linked to CVD will correspond to those patients with objective signs of CVD demonstrated by cMRI. Additional data from patient surveys and basic laboratory tests will be used to characterize the CVD risk factors for these patients. This project will provide the opportunity to potentially clarify the role for t-CH and CVD in CCS and potentially provide a means of identifying high risk patients who could participate in interventions at an early stage of CVD development in an attempt to improve their long-term outcome.

3.0 STUDY ENROLLMENT PROCEDURES AND PATIENT ELIGIBILITY

3.1 Study Enrollment

3.1.1 Patient Registration

Prior to enrollment on this study, patients must have been enrolled on AHOD1331, and will already have been assigned a COG patient ID number. The same COG patient ID number should be used to enroll a patient on this study. This number is obtained via the Patient Registry module in OPEN once authorization for the release of protected health information (PHI) has been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with the registration, please refer to the online help. For additional help or information, please contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

In order for an institution to maintain COG membership requirements, every patient with a known or suspected neoplasm needs to be offered participation in APEC14B1, *Project:EveryChild A Registry, Eligibility Screening, Biology and Outcome Study*.

A Biopathology Center (BPC) number will be assigned as part of the registration process. Each patient will be assigned only one BPC number per COG Patient ID.

For additional information about the labeling of specimens please refer to the Pathology and/or Biology Guidelines in this protocol.

Please see Appendix I for detailed CTEP Registration Procedures for Investigators and Associates, and Cancer Trials Support Unit (CTSU) Registration Procedures including: how to download site registration documents; requirements for site registration, submission of regulatory documents and how to check your site's registration status.

3.1.2 IRB Approval

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an active CTEP status;
- active status at the site(s) on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating organization's roster;
- If using NCI CIRB, on the active NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;

- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- Lists all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements
Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all protocol-specific requirements (PSRs).

For information about the submission of IRB/REB approval documents and other regulatory documents as well as checking the status of study center registration packets, please see Appendix I.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org in order to receive further instruction and support. For general (non-regulatory) questions call the CTSU General Helpdesk at: 1-888-823-5923.

Note: Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review.

3.1.3 Study Enrollment

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

3.1.4 Timing

Reminder: Sites must complete technical training for collection of the study specific cardiac MRI (cMRI) measures prior to first patient enrollment. See Section 9.

Patients must be consented and enrolled through CTSU OPEN prior to performance of study measures. See specifics for the study measures in Section 4. Timepoint 1 (Baseline) Measures are to be performed within one month after enrollment, with the cMRI performed within 2 months of enrollment. Timepoint 2 (One Year) Measures are to be completed 12 ±3 months after the date of the Baseline study blood collection.

3.1.5 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this study.

3.2 Patient Eligibility Criteria

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived. All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record which will serve as the source document for verification at the time of audit.

Inclusion Criteria

3.2.1 Age

Patient must be ≥ 7 years of age at the time of enrollment (age to perform an MRI without sedation).

3.2.2 Treatment History
Enrolled and completed therapy on AHOD1331.

3.2.3 Disease status
Not known to have had a primary event (relapse/second malignancy/death).

Note: *Subjects enrolled and/or treated on AHOD1331 at another institution are eligible if they are now being followed at the current COG institution.*

3.2.4 Cardiac MRI Feasibility
Patient must have access to cardiac MRI at institution where receiving follow-up care and must be able to complete cardiac MRI without sedation.

Exclusion Criteria

3.2.5 Medical contraindication to undergoing a cardiac MRI.

3.2.6 Removed from AHOD1331 therapy prior to completing the AHOD1331 protocol specified treatment plan.

3.2.7 Received cancer therapy in addition to that of AHOD1331 (e.g., for disease progression or recurrence, or subsequent malignant neoplasm).

3.2.8 History of cardiovascular disease prior to enrollment on AHOD1331.

Regulatory Requirements

3.2.9 All patients and/or their parents or legal guardians must sign a written informed consent.

3.2.10 All institutional, FDA, and NCI requirements for human studies must be met.

4.0 STUDY PROCEDURES AND REQUIRED OBSERVATIONS

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol)

4.1 Training Requirements

A site designated imaging specialist must complete technical training for collection of the study specific cMRI measures prior to first patient enrollment. See Section 9 for further details.

4.2 Study Procedures

Reminder: patient eligibility requires prior enrollment and completion of protocol therapy on the AHOD1331 cancer therapeutic trial. In advance of local activation, sites can contact the Data Coordinating Center for access to a site-specific list (by COG ID) of candidates for local screening. After local approval for site registration, sites will be provided with a recruitment list of ***potentially eligible*** patients from AHOD1331 (site-specific and identified by COG ID). A confirmation of eligibility based on review of local medical records should be completed for each of the listed candidates prior to patient approach.

Note: the list of ***potentially eligible*** patients will be selective for patients with confirmation of available banked blood samples, which are required for study completion of planned protocol assays. Sites are asked to prioritize approach and enrollment of the participants on the provided lists. In case potentially eligible AHOD1331 patients are in local follow-up and were not included on the list, enrolling institutions are asked to confirm with the study team prior to proceeding with patient approach.

4.2.1 Recruitment

Each institution will follow the best recruitment strategy for their site and patients. Experience suggests that a combined mail, phone, and in-clinic approach is often superior to one dependent on only one method. Patient outreach prior to an annual visit is strongly recommended to allow for scheduling, as well as preparation of the patient/family for a potentially longer than routine visit. Patient remuneration (e.g., gift cards) will be distributed over the course of study participation.

4.2.2 Confirmation of Eligibility

Patients must be screened for eligibility to confirm that all criteria for inclusion are met (see Section 3.2) prior to enrollment on ALTE21C1. Patients may be screened and enrolled at the same visit; however, all screening procedures must be completed and reviewed prior to enrollment.

4.2.3 Consent and Enrollment

Consent, followed by enrollment via CTSU OPEN are completed by the treating institution.

4.2.4 Timing for Completion of Required Study Measures

Timepoint 1: Baseline measures should be completed as soon as possible and within 1 month of study enrollment. An additional month of flexibility is permitted for completion of the cMRI if necessary to accommodate clinical scheduling. Data

from the Baseline measures should be entered in the study's REDCap database within 10 weeks of enrollment.

Timepoint 2 One Year measures should be completed 12 ±3 months after the date of the Baseline study blood collection and data entered in the study's REDCap database within 10 weeks of collection.

All required observations are listed in Section 4.3. In the event of patient transfer, measures can be completed at another COG institution with the ALTE21C1 protocol open.

4.3 Required Study Observations

To evaluate clonal hematopoiesis and its relationship to cardiovascular disease in Hodgkin lymphoma clinical data, clinical measures, participant surveys, and specimens will be collected at Baseline and One Year time points. Study data are submitted via REDCap.

TABLE 1: STUDIES TO BE OBTAINED		Timepoint 1: Baseline[1]	Timepoint 2: One Year[2]
CVD Risk Factor Assessment (Section 4.4)	**Clinical Evaluations[3]**		
	History	X	
	Physical Exam with Vital Signs pulse, respiratory rate, blood pressure and BMI	X	
	Fasting clinical labs[3] cholesterol, triglycerides, HDL-C and blood glucose	X[4]	
	Provider Reports and Medical Record Abstraction[5]		
	Diagnostic Checklist	X	X
	Screening for Cardiac Health Status	X	X
Study Blood Specimen and Cardiac MRI (cMRI) (Section 4.5)	Peripheral Blood Specimen	X[4]	X
	Cardiac MRI	X	
Patient Self-Reporting (Section 4.6)	Healthy Cardiac Lifestyle Survey	X	X

1. Timepoint 1 Baseline Measures must be completed within one month (30 days) after enrollment. An additional month of flexibility is permitted to obtain the cardiac MRI in case required to accommodate clinical scheduling.
2. Timepoint 2 One Year Measures should be completed 12 ±3 months after the date of the Baseline study blood collection.
3. The Clinical Evaluations are expected to occur during a standard of care visit with the Fasting Clinical Lab results generated by the institution's local laboratory.
4. The Baseline study blood specimen should be drawn at the same appointment as the standard clinical labs, if feasible.
5. Data Submission via REDCap

4.4 Risk Factor Assessment for CVD

Clinical Evaluations at Baseline are expected to occur as part of a standard follow-up visit. The primary provider will complete a history and physical exam with vital signs to assess current medical status. Fasting laboratory tests (cholesterol, triglycerides, HDL-C and blood glucose) will be completed locally as per routine monitoring for cardiac health. Note: if feasible the study blood specimen should be drawn at the same appointment as the standard clinical labs.

Provider Reports and Medical Record Abstraction will be accomplished via care provider completion of the *Diagnostic Checklist* and *Screening for Cardiac Health Status* forms (available on the COG Study Web Page) with submission of these data via the study's secure REDCap database.

4.5 Study Blood Specimens and Cardiac MRI (cMRI)

4.5.1 Study Blood Sampling

Collection of a peripheral blood sample (3-5 mL) for the study's central analysis and t-CH quantitation is requested at each of the two study time points.

Sites are encouraged to schedule each study blood collection to coincide with standard of care labs. If feasible, the Baseline study blood sample should be collected during the same blood draw appointment as the standard clinical labs for which results are requested as part of the Risk Factor Assessment for CVD.

Study Blood Specimens for t-CH quantitation will be shipped to the study's central laboratory. For technical specifics, please consult the current version of the Study Blood Collection Guide provided with the Specimen Transmittal Form in the Case Report Forms packet on the COG Study Web Page.

4.5.1.1 Use of Previously Banked Specimens for CH Analysis

DNA will be retrieved from blood drawn and banked prior to initiation of therapy and at the end of therapy for the enrollees on ALTE21C1 who participated in biobanking through AHOD1331 or other COG specimen banking protocols. Specimens will be shipped to the central lab for CH analysis.

4.5.2 Cardiac MRI

The cMRI is obtained at Baseline and can be scheduled at a time convenient for the patient and families, preferably within one month of enrollment. However, an additional month of flexibility is permitted to obtain the cMRI if required to accommodate clinical scheduling. See Section 9 for technical requirements.

4.6 Patient Self Reporting

At each of the two study time points, participants will be asked to complete the *Healthy Cardiac Lifestyle Survey*, which will collect data used by the study to assess lifestyle factors related to cardiovascular health. The Survey is expected to take 10-15 minutes for participants to complete and is available on the COG Study Web Page.

For participants who are <18 years of age, participants may complete the survey independently or with their parent / primary caregiver's assistance. For participants who are ≥18 years of age, the survey will be completed by the patients themselves. It is preferred that the survey collection occur during the in-person clinic visit. However, it is permitted for the survey to be collected remotely, i.e., by mail, phone, videoconference, if an alternative is required for collection within required study time frame for the measure.

4.7 Follow-Up of Testing

Clinical test results will be managed by the primary team caring for the patient. It is recommended that patients with signs of CVD be encouraged to undergo an evaluation by a cardiologist according to institutional standards.

In case of positive findings of CVD during central review of the initial cMRI, providers will be encouraged to refer patients for evaluation by a cardiologist according to institutional standards. A study cardiologist will be available to assist in providing appropriate interpretation of the data relevant to standard of care recommendations for CVD management and the need of follow-up by a local cardiologist.

Results of analyses of the submitted blood specimen are for research purposes only and will not be shared directly with study participants or their providers.

See COG Late Effects Guidelines for recommended post treatment follow-up:
http://www.survivorshipguidelines.org/

Note: Follow-up data are expected to be submitted per the Case Report Forms (CRFs) schedule, until the patient meets Off Study Criteria (Section 5.2).

5.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

5.1 Criteria for Removal from Further Protocol Participation

a) Relapse or new cancer prior to completion of study evaluations.
b) Physician determines it is in participant's best interest.
c) Refusal of further participation by participant/parent/guardian.

Patients are to be followed until they meet the criteria for Off Study (see below).

5.2 Off Study Criteria

a) Death.
b) Lost to follow-up.
c) Unable to obtain or perform cardiac MRI imaging as required by the study (technical reasons, failure to perform scan without sedation, etc.).
d) Withdrawal of consent for any further data submission.
e) Completion of planned study assessments.

6.0 STATISTICAL CONSIDERATIONS

6.1 Primary Endpoint

The primary objectives are the demonstration that patients possessing CH and CH with mutations associated with CVD correlate with those patients with objective signs of CVD demonstrated by cMRI. Preliminary data from our institution at Washington University suggests that the prevalence of objective findings of CVD in anthracycline exposed CCS is as high as 30% (unpublished data). Preliminary data provided by investigators from this committee also demonstrated that CH can be detected in 15%-30% of children and young adults. We hypothesize that CH will be detected at a significantly higher rate in patients possessing objective signs of CVD demonstrated by cMRI, compared to those patients

lacking such findings. Additionally, we hypothesize that probability of CH with mutation will have positive association with the incidence of CVD.

6.2 Patient Accrual and Expected Duration of Trial

The total number of enrolled patients on AHOD1331 is 587. Of these, 398 are still in follow-up without a primary event (relapse/second malignancy/death) and have consented to blood/tissue sample research and future contact. We will strive for an accrual of **230**; the duration of the trial is expected to be four years.

The study will enroll up to 230 patients (58% of 398). With this sample size we have sufficient power (96.2%/88.2%) to detect 20% difference in CH rate for Aim 1.1.2 when the pooled CH is 15%/30%. Fewer patients will be needed to have sufficient power to detect the difference in CH with mutation rate for Aim 1.1.1. For example, when the difference for CH rate is 20% between abnormal cMRI and normal cMRI, only 115 evaluable patients (29% of the 398 patients) will be needed to have 82.1% power to detect 17.6% difference when the pooled CH rate is 15% and 88.2% to detect 23.6% difference when the pooled CH is 30%.

If accrual goals are not met, considerations will be raised in amending this proposal to include patients enrolled on AHOD0031. This study was the predecessor to AHOD1331 with very similar therapy and a comparable amount of doxorubicin (200-300 mg/m^2 depending upon response vs. 250 mg/m^2 for AHOD1331). There are currently 782 patients who would be eligible for this study, and this population could potentially allow us to fulfill our accrual goals if accrual from AHOD1331 falls below expectations.

6.3 Statistical Analysis Methods

6.3.1 Primary endpoints

The primary endpoints are the proportions of t-CH and t-CH with mutation for patients with or without CVD after Hodgkin Lymphoma therapy. The proportions will be compared with one-sided Z-Test with normal approximation and significance level 0.05.

We expect, based on our preliminary data noted above, to observe an abnormal cMRI frequency approximating 30%. **Table 2** lists the power calculation results for Aim 1.1.2. For instance, we would have > 80% power to detect a significantly higher prevalence of CH in patients with abnormal cMRI compared to those with normal cMRI using a one-sided Z-Test with normal approximation and significance level 0.05 when the accruing probability is 58% of the population still in follow up (n=230 out of 398) (**Table 2**). If the difference is greater, we can achieve the same power with a lower accrual rate or greater power with same accrual rate. It is also possible that the detection of CH may be lower than the projected 30%. If this study can enroll up to 230 patients, we would be sufficiently powered to observe a 20% difference for CH rate between 15% to 30%: the corresponding power is 96.2% or 88.2% when the pooled CH rate is 15% or 30% respectively.

Table 3 provides the power calculation for the Primary Aim 1.1.1 under the same assumption as in **Table 2**. The sample size is determined by the Primary Aim 1.1.2 and the sample size will be sufficient for Aim 1.1.1 to have the adequate power.

Table 2 Power calculations reflecting differences in CH between abnormal and normal cMRI findings						
Pooled prevalence of CH	15%			30%		
Difference in (%) CH detected Between Abnormal cMRI and Normal cMRI*	15%	20%	25%	15%	20%	25%
Power to detect a significance level of 0.05 with a 58% Accrual rate	83.0%	96.2%	99.5%	67.6%	88.2%	97.2%
Power to detect a significance level of 0.05 with a 40% Accrual rate	68.9%	88.2%	96.9%	52.6%	75.0%	90.0%
Power to detect a significance level of 0.05 with a 29% Accrual rate	55.0%	76.5%	90.4%	40.4%	60.8%	78.6%
*Abnormal cMRI = MRI demonstrating objective signs of CVD.						

Table 3 Power calculations reflecting differences in CH with mutation between abnormal and normal cMRI findings						
Pooled prevalence of CH	15%			30%		
Difference in (%) CH detected Between Abnormal cMRI and Normal cMRI*	15%	20%	25%	15%	20%	25%
Power to detect a significance level of 0.05 with a 58% Accrual rate	93.8%	97.9%	99.4%	97.6%	99.2%	99.8%
Difference in (%) CH with mutation Between Abnormal cMRI and Normal cMRI*	14.7%	17.6%	20.5%	20.7%	23.6%	26.5%
Power to detect a significance level of 0.05 with a 40% Accrual rate	84.0%	92.0%	96.4%	91.2%	95.7%	98.1%
Power to detect a significance level of 0.05 with a 29% Accrual rate	71.3%	82.1%	89.6%	80.7%	88.2%	93.2%
*Abnormal cMRI = MRI demonstrating objective signs of CVD.						

The frequency of mutations linked to CVD in pediatrics is unknown. Subsequent analysis will assess whether specific mutations possessed by CH correlate to those patients with abnormal cMRI's.

6.3.2 Secondary/Exploratory data analysis

All data for exploratory analysis will be presented in a descriptive manner. Subsequent analyses will be considered as exploratory, even if statistical tests will be used. Data will be presented as mean, medians, standard deviations and ranges for continuous variables and frequencies (% of group) for the categorical variables.

Secondary Aims

For Objective 1.2.1, we will use graphic analysis to reveal the time varying trend in the association between the expansion of CH over time and the presence/worsening of CVD signs and apply generalized estimating equation method (with each patient as cluster unit) to quantify this association while controlling for the potential correlation of repeated measurements within each patient.

For Objective 1.2.2, to determine if there is an association between the presence of CVD and the individual variables constituting the clinical profile, either parametric (e.g., independent t-test, χ^2-test, Pearson correlation coefficients) or non-parametric (e.g., Wilcoxon rank sum tests, Spearman's rank correlation coefficients) methods will be applied. Bootstrapping techniques might be used as a method of inference which does not rely on a specific underlying distribution. The statistical significance level will be set to 0.05 and all data analysis will be done using SAS statistical software (version 9.4).

Exploratory Aims
For Aim 1.3.1, the sample proportions and their exact 90% (Clopper-Pearson) confidence intervals are used to summarize the prevalence and nature of CVD, CH and CH with mutations associated with CVD for patients receiving mediastinal radiation.

For Aim 1.3.2 the specific patient characteristic and treatments (age, gender, race, dexrazoxane usage etc.) will be used to predict the incidence of t-CH with mutation rate. Comparisons will be conducted to compare the patient characteristic and treatments between the with and without mutation group. Regression model will be constructed to evaluate the effect of these patient characteristics and treatments on the incidence of t-CH with mutation rate, which will be presented by p-values, coefficients and their confidence intervals.

For Aim 1.3.3, the effects of t-CH on CVD will be evaluated by considering other covariates such as patient characteristics (age, gender, race, etc.) and clinical conditions (RT treatment with cardiac dosimetry, follow-up duration, etc.). A multivariable model will be constructed with CVD as the endpoint and t-CH as the explanatory variable together with other covariates such as patient characteristics and clinical conditions.

6.4 Gender and Minority Accrual Estimates

The gender and minority distribution of the study population is expected to be:

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian / Alaska Native	0	0	0	0	0
Asian	1	4	0	0	5
Native Hawaiian or Other Pacific Islander	0	2	0	0	2
Black or African American	14	11	2	2	29
White	63	72	15	25	175
More Than One Race	1	0	1	0	2
Total	**79**	**89**	**18**	**27**	**213**

INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian / Alaska Native	1	0	0	0	1
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	1	0	0	1
White	10	5	0	0	15
More Than One Race	0	0	0	0	0
Total	**11**	**6**	**0**	**0**	**17**

This distribution was derived from AHOD1331.

7.0 EVALUATION CRITERIA

7.1 Study Parameters: The cMRI image analysis

Parameters to be measured by cMRI: Deidentified study images will be transferred via HIPAA compliant cloud-based large file transfer system (e.g., WU Box) for central review for quality assessment and image analysis. The cMRI Core will ensure that parameters for the cMRI are uniform among centers and cross vendor platforms. Our cMRI Core team will analyze the data, including standard anatomical and functional metrics of all cardiac chambers, ejection fraction (EF), end diastolic volume (EDV), end systolic volume (ESV), cardiac output, myocardial mass, strain (global longitudinal [GLS], circumferential [GCS] and radial [GRS] strain), native T1 values, aortic flow and distensibility. Volumes, cardiac output, and myocardial mass will also be indexed to the body surface area (BSA) of the patient.

The primary outcome declaring the presence of objective signs of CVD will be the identification of one or more of the following abnormal thresholds:

1) Left Ventricular Ejection Fraction (LVEF), < 55%,
2) Global Longitudinal Strain (GLS) less negative than -18%,
3) Left Ventricular End Diastolic Volume indexed to body surface are (LVEDVi) > 85 mL:/meter^2.

In addition to the cMRI endpoints, T1 values will be assessed, and prolonged T1 values based on prior established data of normal values which were also utilized in generating the preliminary data at our institution in CCS cited above.[39-41] A T1MES phantom will be used to normalize T1 values across centers.[44] Phase contrast imaging a;pmg with heart rate and blood pressure taken at the time of cMRI will be used to assess aortic distensibility.[45] All image analysis will be performed at the image core center utilizing standard commercially available software.

7.2 CH Analysis:

To assess CH, genomic DNA isolated from blood will be analyzed by a targeted exon sequencing panel with ArcherDX/Invitae VariantPlex® Myeloid reagents for use with high-throughput next-generation sequencing. This anchored multiplex PCR protocol utilizes unidirectional gene-specific primers and molecular barcoded adapters that allow for post-sequencing error correction for quantitative calling of point mutations, structural mutations (indels, duplications) or copy number variants in target regions. A custom panel targets genes associated with myeloid malignancies, including the most prevalent age-related and therapy-related clonal hematopoiesis genes (e.g. *DNMT3A*, *TET2*, *ASXL1*, *TP53*, *PPM1D*, etc.). The panel requires 4 million reads per library to achieve a limit of detection goal of 1% variant allele frequency (VAF) at >93% of the bases targeted. This translates to approximately 80-90 libraries on a single Illumina NextSeq high-output sequencing cycles after correcting for PhiX control library. Deeper sequencing can drive the limit of detection even lower. Via the Archer Analysis Unlimited cloud-based computational software suite, sequencing results will be optimized for sensitivity and specificity using proprietary algorithms, enabling quantitative assessment of true variant calls from noise at every exonic location by employing a position-dependent variant calling algorithm that assigns a limit of VAF detection, *at the level of per-variant resolution*, by modeling noise at each position and for each base change. The assignment of position-specific limits of detection is superior to the static sensitivity thresholds employed in other studies (if applied at all), and it allows a rigorous assessment of variants, particularly the small VAF clones.

A clonal hematopoiesis-positive result will be defined by the presence of a cancer-associated somatic mutation (from the COSMIC database) in the blood of an individual with no known hematologic cancer or other clonal state, that is not represented as a germline polymorphism in the ClinVar database. These data will also be stratified on the basis of VAF, with a cutoff of 2% for canonical "CHIP", as well as large clones (e.g. VAF >10%), because some studies have shown that larger clones are associated with greater CVD risk.[2, 46] From this analysis we will be able to assess for the prevalence of CH bearing somatic mutations associated with CVD.

7.3 Risk Factor Assessment for CVD

Patients upon enrollment will be evaluated to assess their current medical status, (participant self-report: *Healthy Cardiac Lifestyle Survey*; and provider reporting: *Diagnostic Checklist*, *Screening for Cardiac Health Status*, history and physical exam) as it relates to cardiac health by the participating COG site. They will also obtain a fasting cholesterol, triglycerides, HDL-C and blood glucose at the time of initial blood draw for CH. Those demonstrating positive findings of CVD or those patients found to demonstrate signs of CVD on the initial study cMRI will be encouraged to be evaluated by a cardiologist according to institutional standards. Enrollees will repeat blood sampling for CH (no other labs) one year after the initial evaluation to assess for CH expansion with time. Subject participation ends upon participant completion of the second *Healthy Cardiac Lifestyle Survey* and provider submission of the *Diagnostic Checklist*, and *Screening for Cardiac Health Status*.

8.0 RECORDS AND REPORTING

After a patient enrollment via CTSU OPEN, data for this study will be submitted directly to the external Data Coordinating Center via REDCap. See the Case Report Forms posted on the COG web site with each protocol under *"Data Collection"*. A submission schedule is included.

8.1 Reporting

Demography Monitoring

Required submission of patient demographic data to NCI for this study will be submitted automatically via OPEN.

8.2 Reporting of Previously Unknown Conditions

This is an observational trial that will be collecting data from clinical assessments implemented locally and occurring as part of standard of care visits. There is a possibility previously undiagnosed conditions may be discovered among asymptomatic participants. This section lists those research assays that may have established clinical interpretations. *However, as most assays will be batched and centrally processed, any result will likely not be available to immediately influence clinical care*.

8.2.1 Cardiac MRI

Although local institutions may have in place a standard policy by which all cardiac MRIs are read locally, standard reports also will be generated after central review. The full reports will be made available to the participating institution (local PI or their designee) for quality improvement and quality assurance purposes. Given the complexity in communicating cMRI results, participants will not be provided results or report, but will be encouraged to discuss them with their physician.

8.22 CVD Risk Factor Assessment

Findings from this assessment (Section 4.4) including elements of the patient's history, physical exam and laboratory evaluations may indicate the presence of CVD or other medical conditions. Subsequent evaluations and management should follow standard institutional practices for good patient care.

9.0 CARDIAC MRI STUDIES REQUIRED AND GUIDELINES FOR OBTAINING

9.1 Participating MRI centers and Training Requirements

Centers with eligible patients should work in anticipation of obtaining cMRI scans for this study. A local representative with expertise/experience in cMRI should be designated for training to facilitate a smooth acquisition of the study (Section 9.3). Sites must complete technical training for collection of the study specific cardiac MRI (cMRI) measures prior to first patient enrollment.

Requests for descriptions of MRI scanners and associated software will be distributed to participating centers to ensure optimal data collection. Phantoms and test scans will be sent to the designated contact/s at participating institutions to ensure that optimal imaging will be obtained.

9.2 The cMRI data acquisition

Using cMRI basic myocardial function, myocardial strain, abnormal signal for early diffuse myocardial fibrosis, and aortic distensibility will be assessed. The basic cMRI examination will include short and long axis bright blood cine imaging and imaging in the short axis to obtain myocardial T1 values.[45] An aortic phase contrast/flow quantification sequence and systolic/diastolic blood pressure will be obtained at the time of imaging in order to calculate aortic distensibility. Aortic distensibility will be examined as it has been shown to decrease after treatment with certain chemotherapeutic agents, with potential to lead to hypertension. To make this the safest examination possible, no intravenous gadolinium-based contrast agents will be administered. The MRI examination at all times will be obtained without sedation. Sequences that are optimally acquired with breath hold will be obtained with breath hold when possible but will be obtained free-breathing using multiple averages in patients unable to hold their breath.

The length of the overall examination is approximately 45 minutes in length. Sequence parameters are displayed in Table 4.

Table 4 The cMRI Protocol Imaging Parameters*				
Sequences	**Cine long-axis (SSFP)**	**Cine short-axis (SSFP) stack**	**Native T1 map**	**Phase Contrast/Flow quantification**
Field of view read (mm)	350	350	440	330
Field of view phase (mm)	350	350	352	248
Slice thickness (mm)	6	8	5	6
Slice number	1	12	1	1
Acquired pixel size (mm2)	1.8x1.8	1.8 x 1.8	1.4 x 1.4	1.7 x 1.7
Matrix size (read x phase)	192 x192	192 x 192	320 x 256	192 x 144
Temporal resolution (ms)	39.8	39.3	None	40
Phase	25	25	None	13
TR (ms)/TE (ms)	2.84/1.21	2.81/1.20	2.9/1.01	4.0/2.21
Averages	1	1	1	---
Number of T1/mode	None	None	Pre-contrast: MOLLI-5-3-3	None
K-space lines/RR	14	14	128	5
Parallel Imaging (GRAPPA/ARC) factor	2	2	2	2
Velocity encoding (cm/s)	None	None	None	150
Partial Fourier	None	None	7/8	None
Bandwidth (Hz/Px)	930	930	1116	606
Spin-Locking frequency	None	None	None	None
Scan time (s)	9 sec	3 min	8 sec	6 sec
Flip angle	33	33	35	20
* Parameters may vary slightly across scanner vendors. For cine and flow quantification imaging, FOV will be based upon patient size.				

The primary outcome measures used for this analysis will consist of the following.

Table 5: cMRI study endpoints		
Primary assessment	**Measurement**	**Threshold for declaring abnormal function**
LV systolic function	Left Ventricular Ejection Fraction (LVEF)	<55%
	Global Longitudinal Strain (GLS),	>-18%
LV diastolic volume	Left Ventricular End Diastolic Volume (LVEDV)	>85mL/Meter ^{2}

9.2.1 Record-keeping of derived imaging data

After processing, the deidentified cardiac MR images will be transferred via the Washington University (WU) HIPAA-compliant network to Central Neuroimaging Data Archive (CDNA).

CNDA is a resource for managing study data collected by the WU research community. CNDA implements a number of features and procedures to ensure the security and integrity of the data it hosts and full HIPAA compliance. All data coming into and out of the CNDA are transmitted over secure channels using SSL. All data are stored on a ZFS raidz2 storage system with disaster recovery and offsite backup. Snapshots of the relational database are taken nightly, enabling reconstruction of the database from any time point in the study. Access to study data is restricted to authorized users who are assigned specific access privileges (create, read, edit, delete) according to their role in the study. All logins and access to data are tracked in the internal audit system. Derived numerical data will stored within WU REDCap, a commercially available, secure, web-based application for building and managing online databases.

9.3 The Cardiac MRI Core and Local Training Requirements

The Cardiac MRI Core located within the Center for Clinical Imaging Research (CCIR) at Washington University is led by Pamela K. Woodard, MD, FACR, FSCMR, CCIR Director. She and the physicist for the Core, Jie Zheng, PhD, have been performing cardiac MRI research together since 1995. Manish Aggarwal, MD and Dr. Woodard have worked together for 3 years in the interpretation of clinical cardiac MRI at St. Louis Children's Hospital (SLCH). Dr. Woodard is the Head of Cardiac CT/MRI for both SLCH and Barnes-Jewish Hospital. This group led by Dr. Woodard has been the cardiac MRI processing core for a number of pediatric and oncological trials, including the Cardiac Biomarkers in Pediatric Cardiomyopathy (PCM Biomarkers)[47] and the PROactive Evaluation of Function to Avoid CardioToxicity (PROACT) trials.[48]

The Cardiac MRI Core will perform the functions of:

a) providing the cardiac MR protocol and instruction to participating sites	9.3.1
b) site/scanner qualification,	9.3.2
c) quality assurance of images and assurance of homogeneity among sites,	9.3.3
d) assurance of deidentification and HIPAA compliance,	9.3.4
e) processing of cardiac MRI scans,	9.3.5
f) record-keeping of derived imaging data,	9.3.6
g) HIPAA compliant storage of processed imaging data.	

9.3.1 Providing the cardiac MR protocol and instruction to participating sites

The Cardiac MRI Core will provide electronic transfer of the cardiac MRI protocol to the participating sites for upload onto their scanner to ensure protocol homogeneity. Sites will be queried for their suitability for participating in the study, to include information on scanner field strength, vendor, platform, gating capability, and available surface coils. The Cardiac MRI Core at WU has relationships with the Research and Development and Applications groups of the major vendors (Siemens, GE, Philips, etc.) to assist in this process. In addition to Dr. Zheng, a Siemens physicist is available on-site. The Cardiac MRI Core will develop an imaging guide to instruct centers in the performance of the examination, to include parameters and scan plane set up. Participation in an instructional Webinar/Zoom meeting will be required for the scanning technologist/imaging site investigator at all sites, during which these individuals will have the opportunity to ask questions and familiarize themselves with the protocol.

9.3.2 Site/scanner qualification

Prior to the onset of scanning research participants, each center will be required to provide the Cardiac MRI Core with a test scan for site/scanner qualification. Each site will be asked to perform the non contrast enhanced cMRI examination on a normal volunteer on the scanner they intend to use for the study. This test scan is to demonstrate site proficiency in performing the scan to include completeness, image quality, and adequate deidentification. Scanners will be calibrated for T1 measurements using a T1MES phantom.[44, 49] (Will be shipped to center if not available at the participating site).

9.3.3 Quality assurance of images and assurance of homogeneity among sites

Each site will be provided with transmittal forms to accompany each cMRI scan transfer. The technologist performing the scan will be required to list the series number of each sequence scanned and the number of images in each sequence. This transmittal form will be reviewed and reconciled with the series and number of images in each series transferred to ensure all images have been received. A member of the Core will also review each set of images for image quality to include adequate signal and absence of respiratory or cardiac motion. If images are sub-optimal, a member of the Core will contact the site technologist to provide remedial instruction for improvement in subsequent scan performance. Only cMRI examinations of diagnostic quality will be included in the analyzed data set.

9.3.4 Assurance of deidentification and HIPAA compliance

Deidentified cMRI scans will be transferred via HIPAA compliant cloud-based large file transfer system (WU Box) for central review for quality assessment and image analysis. A member of the Cardiac MRI Core will review each examination to ensure that each data set is completely deidentified in both the image alpha-numerics and DICOM header information. To do this, we will assess the data set using the XNAT Data Client (https://wiki.xnat.org/xnat-tools/xnat-desktop-client-dxm). If not fully deidentified, we will use XNAT to fully deidentify the DICOM data. Using XNAT we are able to visually review each individual series for "burned-in" protected health information (PHI) and to specify blocks of voxels for removal from the image.

9.3.5 Processing of cardiac MRI scans

Deidentified cMRI images will be processed for cardiovascular imaging biomarkers including left and right ventricular ejection fraction (EF), end diastolic volume (EDV), end systolic volume (ESV), cardiac output, and myocardial mass. Left ventricular strain, (global longitudinal [GLS], circumferential [GCS] and radial [GRS] strain), left ventricular myocardial native T1 values, aortic flow and distensibility. Volumes, cardiac output, and myocardial mass will also be indexed to the body surface area (BSA) of the patient. Processing will be performed utilizing commercial software, which supports the analyses of segmentation for cardiac function quantification (LVEF, RVEF, LVEDV, RVEDV, LVESV, RVSV, LVSV, RVSV, Cardiac output, Myocardial mass, myocardial T1 maps, among other functions), analysis of myocardial strain (global and segmental longitudinal, circumferential, radial) via feature tracking of standard steady state free precession (SSFP) cine images, and the analyses of velocity and flow from velocity-encoded flow quantification sequences. The software is housed on a secure HIPAA-compliant server in the CCIR on the WU HIPAA-compliant network. Data on this server, post-processing, will be transferred to CNDA for intermediate and long-term storage.

9.3.6 Record-keeping of derived imaging data

After processing, the deidentified cMRI images will be transferred via the WU HIPAA-compliant network to CNDA. CNDA is a resource for managing study data collected by the WU research community. CNDA implements a number of features and procedures to ensure the security and integrity of the data it hosts and full HIPAA compliance. All data coming into and out of the CNDA are transmitted over secure channels using SSL. All data are stored on a ZFS raidz2 storage system with disaster recovery and offsite backup. Snapshots of the relational database are

taken nightly, enabling reconstruction of the database from any time point in the study. Access to study data is restricted to authorized users who are assigned specific access privileges (create, read, edit, delete) according to their role in the study. All logins and access to data are tracked in the internal audit system. Derived numerical data will stored within WU REDCap, a commercially available, secure, web-based application for building and managing online databases.

APPENDIX I: CTEP AND CTSU REGISTRATION PROCEDURES

INVESTIGATOR AND RESEARCH ASSOCIATE REGISTRATION WITH CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at . For questions, please contact the RCR ***Help Desk*** by email at RCRHelpDesk@nih.gov.

CTSU REGISTRATION PROCEDURES

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Protocol-Specific Requirements For ALTE21C1 Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- Attestation of completion of site certification for cMRI performance.

Submitting Regulatory Documents:
Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the *Regulatory* section and select *Regulatory Submission*.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878) or CTSURegHelp@coccg.org in order to receive further instruction and support.

Checking Your Site's Registration Status
Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration; and*
- Enter the site's 5-character CTEP Institution Code and click on Go.
  - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

Data Submission / Data Reporting
Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.
Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as a Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

APPENDIX II: YOUTH INFORMATION SHEETS

INFORMATION SHEET REGARDING RESEARCH STUDY ALTE21C1
(for children from 7 through 13 years of age)

We want to tell you all about this study. You and your family can decide if you want to be in it. Ask questions if you don't understand.

1. What is the name of the study? A Study About How Blood Cell Growth Patterns Relate to Heart Health After Treatment for Hodgkin Lymphoma

2. Who is in charge of the study? The study is being done by Children's Oncology Group and is being done at other hospitals.

3. What is the study about? We are asking you to take part in a research study because you had Hodgkin lymphoma. A research study is when doctors work together to try out new ways to help people. In this study we are trying to learn how patterns in blood cell growth might be related to heart health problems that can happen in some children after treatment for Hodgkin lymphoma. We hope this information will tell us more about how to provide heart health follow-up care in patients after cancer treatments.

4. What will happen to me in the study?
   i. A survey about heart health
   Children who are part of this study will answer questions on a survey about heart health with the help of their parent(s).

   ii. Blood samples for research
   Children will also be asked to give a small amount of blood (a teaspoonful or less) two times, once now and once about a year from now. The extra blood would be taken during a regular follow-up visit so you will not have to make a special trip to the doctor.

   iii. An MRI of the heart
   You would be asked to have a special scan called a cardiac MRI to see how your heart health is doing.

   iv. Review of past medical record information
   We will also collect information from your medical records to learn about the treatment you received for the Hodgkin lymphoma and heart health history.

If you choose to enroll on this study, you will be eligible to receive a gift card for your participation in the study.

Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is that your doctor may learn more about how Hodgkin lymphoma treatment may affect your heart health over time. If your doctor and other doctors understand that better, they may be able to improve follow-up care for children after they finish cancer treatment, but we don't know for sure if there is any benefit of being part of this study.

Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." The risks to you from this study are possible pain, bruising, bleeding or infection

at the site of the needle stick. The cardiac MRI scan takes about 45 minutes to complete so you may feel bored or uncomfortable during the scan. Other things may happen to you that we don't yet know about.

5. Do I have to be in the study? You and your family can choose to be part of this study or not. You and your family can also decide to stop being in this study at any time once you start. The doctors and nurses will still take care of you. If you have any questions or don't like what is happening, please tell your parent, the doctor or nurse.

INFORMATION SHEET REGARDING RESEARCH STUDY ALTE21C1
(for teens from 14 through 17 years of age)

We want to tell you all about this study. You and your family can decide if you want to be in it. Ask questions if you don't understand.

1. What is the name of the study? A Study About How Blood Cell Growth Patterns Relate to Heart Health After Treatment for Hodgkin Lymphoma

2. Who is in charge of the study? The study is being done by Children's Oncology Group and is being done at other hospitals.

3. What is the study about? We are asking you to take part in a research study because you had Hodgkin lymphoma. A research study is when doctors work together to try out new ways to help people. In this study we are trying to learn how patterns in blood cell growth might be related to heart health problems that can happen in some children and teens after finishing treatment for Hodgkin lymphoma. We hope this information will tell us more about how to prevent or find heart problems earlier in patients during follow-up care after cancer treatment.

4. What will happen to me in the study?
   i. A survey about heart health
   Children and teens who are part of this study will fill out a survey with questions about heart health (with the help of their parent(s) if preferred).

   ii. Blood samples for research
   Children and teens will also be asked to give a small amount of blood (a teaspoonful or less) two times, once now and once about a year from now. The extra blood would be taken during a regular follow-up visit so you will not have to make a special trip to the doctor.

   iii. An MRI of the heart
   You would be asked to have a special scan called a cardiac MRI to see how your heart health is doing.

   iv. Review of past medical record information
   We will also collect information from your medical records to learn about the treatment you received for the Hodgkin lymphoma and about your heart health history.

Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is that your doctor may learn more about how Hodgkin lymphoma treatment may affect your heart health over time. If your doctor and other doctors understand that better, they may be able to improve follow-up care for you and for other children and teens after they finish cancer treatment, but we don't know for sure if there is any benefit of being part of this study.

Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." The risks to you from this study are possible pain, bruising, bleeding or infection at the site of the needle stick. The cardiac MRI scan takes about 45 minutes to complete. You may feel bored or uncomfortable during the scan. Your doctor will talk to you about other risks related to the cardiac MRI scan. Other things may happen to you that we don't yet know about.

5. Will I be paid to be in this study? If you choose to enroll on this study, you will be eligible to receive a gift card for your participation in the study.

6. Do I have to be in the study? You and your family can choose to be part of this study or not. You and your family can also decide to stop being in this study at any time once you start. The doctors and nurses will still take care of you. If you have any questions or don't like what is happening, please tell your parent, the doctor or nurse.

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This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Institutions must use the sections of this document that are in bold type in their entirety. Editorial changes to these sections may be made as long as they do not change information or intent. If the local IRB insists on making deletions or more substantive modifications to any of the sections in bold type, they must be justified in writing by the investigator at the time of the institutional audit.

SAMPLE RESEARCH INFORMED CONSENT/PARENTAL PERMISSION FORM

ALTE21C1, *Assessment of Clonal Hematopoiesis and its Relationship to Cardiovascular Disease in Hodgkin Lymphoma Survivors*

Study title for study participants: a study about how blood cell growth patterns relate to heart health after treatment for Hodgkin lymphoma

If you are a parent or legal guardian of a child who may take part in this study, permission from you is required. The assent (agreement) of your child may also be required. When we say "you" in this consent form, we mean you or your child; "we" means the doctors and other staff.

Overview

You are being asked to take part in this research study because you completed treatment for Hodgkin lymphoma (also known as Hodgkin disease) while taking part in in a previous treatment study called AHOD1331.

Taking part in this study is voluntary. You may choose not to be in this study. If you decide not to be in this study, you will not be penalized and you will not lose any benefits to which you are entitled. You will still receive medical care.

Incredible progress has been made in curing Hodgkin lymphoma. With this success has come greater awareness that in some patients, cancer treatment at a young age may lead to later complications, including problems with heart health. The main goal of this study is to see if checking for blood cell growth patterns called therapy-related clonal hematopoiesis (t-CH) can help tell us who might be at risk for heart health problems after Hodgkin lymphoma treatment.

Taking part in this study involves providing a sample of blood for research and completing a brief survey about heart health during two routine clinic appointments, one at baseline and a second about a year later. Taking part involves having a fasting blood test for markers of heart health and a special scan of the heart called a cardiac MRI. Finally, taking part involves giving permission for information from your medical charts to be shared with the study researchers. The study takes about one year to complete.

We hope that this study will help you personally, but we do not know if it will. The potential benefits to you associated with participation in this study are described in the section Are there benefits to taking part in the study?

You have a choice about participating in this research study or not.

The rest of this form provides detailed information about the study and what to expect should you decide to participate.

Why am I being invited to take part in this study?

You are being asked to take part in this research study because you completed treatment for a diagnosis of Hodgkin lymphoma (also known as Hodgkin disease) while taking part in the study AHOD1331.

This is a research study that looks at the effects of different kinds of treatments on health in human patients. This study has public funding from the National Cancer Institute (NCI), part of the National Institutes of Health (NIH) in the United States Department of Health and Human Services. This research study is also funded by the U.S. Department of Defense (DoD).

This study is organized by Children's Oncology Group (COG). COG is an international research group that conducts clinical trials for children with cancer. More than 200 hospitals are members of COG.

It is common to enroll children, adolescents and young adults after treatment for cancer in a study that seeks to improve cancer treatment over time. Research studies include only people who choose to take part. You have a choice between participating in this research study or not.

Please take your time to make your decision. You may want to discuss it with your family and friends. We encourage parents to include their child in the discussion and decision to the extent that the child is able to understand and take part.

What is the current standard of care after cancer treatment?

The current standard of care for children and young adults after completing treatment for Hodgkin lymphoma is to receive regular checkups that include screening for potential heart health problems.

Why is this study being done?

Treatment for Hodgkin lymphoma at an early age may lead to later heart complications in some, but not all, patients. Therapy-related Clonal hematopoiesis (t-CH) happens when a cell that usually makes many different types of blood cells starts repeating just one type of blood cell with a DNA pattern different from other blood cells. A blood test can be used to measure t-CH. Scientists have noticed a possible link between heart complications after cancer treatment and specific patterns in t-CH. Study researchers want to learn more about t-CH and whether measuring t-CH in the blood might help identify patients with a higher likelihood of developing heart complications after treatment for Hodgkin lymphoma. If doctors know who may be at greater risk for developing later heart complications, then they can more closely monitor those patients to prevent or detect heart complications early.

The overall goals of this study are to:

- **Learn how patterns of t-CH in the blood relate to the likelihood of later heart health complications in children and young adults who have completed treatment for Hodgkin lymphoma.**

- **See how factors such as cancer treatment history, lifestyle, and individual traits such as age, gender, or race may relate to t-CH and clinical measures of heart health in children, adolescents and young adults after treatment for Hodgkin lymphoma.**

What will happen on this study that is research?

Taking part in this study involves two study visits (at Baseline and One Year later). The study visits can be coordinated with routine clinic appointments. At the two study visits, you will be asked to provide a blood sample and fill out a brief survey about heart health. Taking part in the study also involves having a special scan of the heart called a cardiac MRI (just once, at baseline) and giving permission for information from your medical charts to be shared with the study researchers.

Study Tests and Procedures

The following tests and procedures will be done once for the study as part of the Baseline study visit. These are considered standard follow-up care and may be done even if you do not take part in this study.

- **Physical examination,** checking your height and weight, heart rate, breathing rate, and blood pressure.
- **Medical history**, which includes questions about how you are feeling and about any symptoms related to heart health.

The following tests and procedures will be done because you are part of this study. If you were not in the study, you would probably not have these tests and procedures.

Fasting Blood Test
At or around the same time as the Baseline study visit, you will be asked to have a blood draw for clinical testing for markers used to monitor heart health such as blood cholesterol levels and blood glucose. You will be asked to fast for about 10 hours prior to the blood draw. Doctors routinely use these tests as part of standard of care to diagnose or monitor problems with the heart. Having the blood tests done for the specific purposes of the study is considered research. This institution will receive some money for completing the blood tests for the study. You will not be asked to pay for the study's clinical blood tests.

Cardiac Magnetic Resonance Imaging (cMRI) Scan
At or around the same time as the Baseline study visit, you will be asked to have a scan of your heart called a cardiac MRI (cMRI). Doctors routinely use cMRI scanning as part of standard of care to diagnose or monitor problems with the heart. Having a cMRI scan for the specific purposes of the study is considered research. This institution will receive some money for completing the cMRI for the study. You will not be asked to pay for the cMRI.

For the study cMRI, you are asked to lie face up on a flat surface that is then rolled into a long tubular machine called an MRI scanner. The machine uses magnets and radio waves to capture a detailed image of your heart. While in the machine, you may be asked to hold very still or hold your breath for periods of time. The cMRI scanning process is expected to take about 45 minutes.

MRI scanning is a non-invasive (does not involve surgery) way for doctors to see what is going on inside the body. An MRI scan does not expose the body to radiation the way an X-ray does. Since the MRI scanner uses magnets, it can attract or move (pull on) objects that contain metal. You should alert your doctor if you have any type of metal implant in your body from previous surgeries to be sure it is safe for you to have a cMRI. Your doctor will talk to you about this and how to prepare for the cMRI. Please see "Risks of cMRI scan" below for more information and the risks of cMRI.

Central Review of cMRI Results

The cMRI scans will be sent to a central review center. The results of these central reviews will not be returned to you personally, but a summary report will be provided to your doctor within several months of your study visit. Your doctor will decide whether there is any information in the central review report that would be important to discuss with you.

Heart Health Survey

At each of the two study visits, you will be asked to complete a brief survey that includes questions about lifestyle factors that affect heart health, such as smoking history, exercise, and diet. The survey should take about 10-15 minutes to complete.

Blood Samples for Research

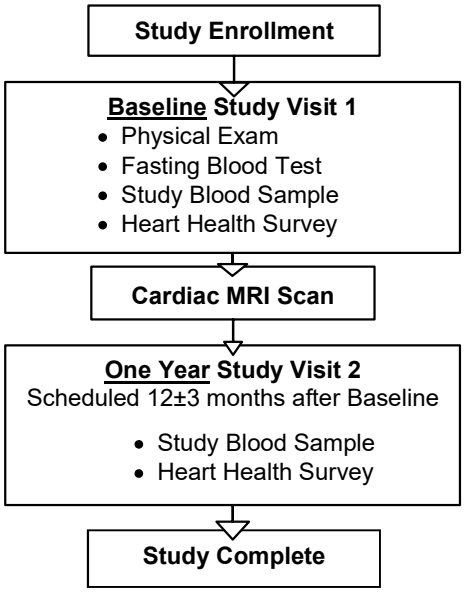
We would like to collect a small blood sample (5 mL, 1 teaspoon) at each of the two study visits. The blood can be taken during other routine blood tests and would not require any extra needle sticks. The blood samples will be sent to the study laboratory and used to research how t-CH may relate to heart health.

We are also asking your permission to use part of leftover (banked) samples of your blood that you originally provided for the AHOD1331 study or samples that you may have provided for another COG study with biobanking. Your blood samples from the past will be tested for t-CH and compared to t-CH in blood samples collected at the Baseline and One Year time points for this study. The study researchers want to learn how t-CH patterns change over time and look at differences in t-CH in the blood before and after treatment for Hodgkin lymphoma.

Research on the blood specimens is very unlikely to discover results that are important to your current or future health. Neither you nor your study doctor will be notified or given reports or other information about research that is done using your samples, unless something is discovered that could directly affect your health. If that happens, your study doctor will be notified and will decide whether and how to contact you.

Your samples and information will not be sold to third parties.

Diagram of Study
This chart shows the steps for taking part in this study.



What side effects or risks can I expect from being in the study?

You may lose time at school, work, or home and spend more time in the hospital or doctor's office than usual. You may be asked sensitive or private questions that you usually do not discuss.

The most common risks related to drawing blood from your arm are brief pain and maybe a bruise, infection or bleeding. Care will be taken to avoid these complications.

As with any study involving data collection, there is the possibility of a breach of confidentiality of the data. Every precaution will be taken to secure participants' personal information to ensure confidentiality. Each participant will be given a study code number. During the study, this number will be used instead of names and other private information.

Risks of cMRI scan
The cMRI scan may be harmful if you have metal implants in your body. Your doctor or clinic staff may ask you to complete a standard questionnaire to screen for certain types of metal implants. If you have a device such as a pacemaker, bone hardware, or a device in your uterus, there may be risks unique to that device or risks particular to the device's location in your body. Your doctor will review the type of device you have and inform you of risks specific to the device. In general, these risks could be:

- Heating or movement of the device
- Device malfunction
- Damage to the tissue that surrounds the device.

If you have a skin tattoo, including cosmetic tattoos (eye-liner, lip-liner), you could experience the following:

- Irritation, swelling, or heating in the area of the tattoo
- In rare instances, a primary or secondary burn.

If you have a tattoo, your doctor or clinic staff may offer you a cold, wet washcloth to put over the tattoo to reduce this risk.

You may feel warm during the scan.

You may feel a slight tingling in your arms or legs during the scan due to magnetic field changes.

You may be uncomfortable inside the MRI scanner if you do not like to be in closed spaces ("claustrophobia"). During the procedure, you will be able to talk with the staff through a speaker system. You can tell them to stop the scan at any time. The MRI procedure performed during the MRI scan produces a loud hammering noise. Staff may provide earplugs if needed. You may also experience discomfort from lying on the imaging table, although we will make every effort to minimize any discomfort. If you have a pre-existing back, joint, or muscle problem, the time required to lie on the imaging table may worsen this condition.

With an MRI, there is the rare possibility of a skin burn. This risk is increased if you have a tattoo.

In addition to the risks described above, there may be unknown risks, or risks that we did not anticipate, associated with being in this study.

Are there benefits to taking part in the study?

We hope this study will help you personally, but we do not know if it will.

As some of the research test results have clinical significance, you may find out about previously unknown conditions. Your study doctor will receive a report of the central review of the cMRI results.

Information learned from this study may benefit other patients in the future.

What other options are there?

You may choose not to participate in this study.

How many people will take part in the study?

The total number of people enrolled in this study is expected to be about 230.

How long is the study?

It will take about one year to finish your part in the study.

You can stop taking part in the study at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study doctor and your regular doctor first.

Your doctor or the study doctor may decide to take you off this study:

- if he/she believes that it is in your best interest

- if your disease comes back during the time you are taking part in the study

What about privacy?

We will do our best to make sure that the personal information in your medical record will be kept private. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. The Children's Oncology Group has a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the Children's Oncology Group will do their best to make sure that any information that goes out to others will not identify who you are. Information about this Certificate of Confidentiality is included in **Attachment 1**.

Organizations that may look at and/or copy your research or medical records for research, quality assurance, and data analysis include groups such as:

- **Children's Oncology Group and research partners**
- **Representatives of the National Cancer Institute (NCI), Food and Drug Administration (FDA), and other U.S. and international governmental regulatory agencies involved in overseeing research.**
- **The U.S. Department of Defense (DoD)**
- **The Institutional Review Board of this hospital**
- **National Cancer Institute Central Institutional Review Board (CIRB)**
- **Site of Data Coordinating Center for COG**

In addition to storing data in the study database, data from publicly funded studies may also be shared broadly for future research with protections for your privacy. The goal of this data sharing is to make more research possible that may improve people's health. Your study records may be stored and shared for future use in public databases. However, your name and other personal information will not be used.

Some types of future research may include looking at your information and information from other patients to see who had side effects across many studies or comparing new study data with older study data. However, right now we don't know what research may be done in the future using your information. This means that:

- You will not be asked if you agree to take part in the specific future research studies using your health information.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your information.

What are the costs?

You will not pay for the study blood samples collection, storage, or testing. Also, you will not pay for completing the cMRI scan for the study.

Taking part in this study may lead to added costs for you or your insurance company. There are no plans for the study to pay for medical treatment. Please ask about any expected added costs or insurance problems. Staff will be able to assist you with this.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury. However, by signing this form, you are not giving up any legal rights to seek to obtain compensation for injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://www.cancer.gov/clinicaltrials/learningabout.

If you choose to enroll on this study, this institution will receive some money from the Children's Oncology Group to support the cost of doing the research.

If you choose to enroll on this study, you will also be eligible to receive a gift card for your participation in the study.

The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

What are my rights as a participant?

Taking part in this study is voluntary. You may choose not to be in this study. If you decide not to be in this study, you will not be penalized, and you will not lose any benefits to which you are entitled. You will still receive medical care.

You can decide to stop being in the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. Your doctor will still take care of you.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study. A committee outside of COG closely monitors study reports and notifies COG if changes must be made to the study.

Whom do I call if I have questions or problems?

For questions about the study or if you have a research related problem or if you think you have been injured in this study, you may contact Dr. *XXXX* or your doctor at *XXXX*.

If you have any questions about your rights as a research participant or any problems that you feel you cannot discuss with the investigators, you may call *XXXX* Institutional Review Board (IRB) Administrator at *XXXX*.

If you have any questions or concerns that you feel you would like to discuss with someone who is not on the research team, you may also call the Patient Advocate at *XXXX*.

Where can I get more information?

The COG Family Handbook for Children with Cancer has information about specific cancers, tests, treatment side effects and their management, adjusting to cancer, and resources. Your doctor can get you this Handbook, or you can get it at https://www.childrensoncologygroup.org/index.php/cog-family-handbook.

Visit the NCI's Web site at http://www.cancer.gov.

If you are in the United States, you may call the NCI's *Cancer Information Service* at: 1-800-4-CANCER (1-800-422-6237).

Information about long term follow-up after cancer treatment can be found at: http://www.survivorshipguidelines.org/.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

You will get a copy of this form. You may also ask for a copy of the protocol (full study plan).

Signature

I have been given a copy of all _____ pages of this form. The form includes 1 attachment.

I have reviewed the information and have had my questions answered.
I agree to take part in this study.

Participant_____Date _____

Parent/Guardian_____Date _____

Parent/Guardian_____Date _____

Physician/PNP/PA or designee
obtaining consent_____Date _____

Attachment 1

Certificate of Confidentiality

The Children's Oncology Group is covered by a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act.

The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

For ALTE21C1 Data Submission

After a patient enrollment via CTSU OPEN, all data for this study will be submitted directly to the external Data Coordinating Center.

A Data Submission Schedule in the CRF packet will be provided in the near future with further instructions.

ELIGIBILITY			
Question (Element)	**Valid Value**	**Edit checks & validations**	**SDC USE ONLY**
STRATIFICATION			
ALTE21C1 Stratum:*	[] - Stratum 1: All patients	1. Required	3577921 COGStratFactTp
ALTE21C1 Treatment:*	[] - Not applicable	1. Default	3333730 TxAssTp
Treatment Start Date:* *Enrollment date by default, as no therapeutic treatment is administered for this trial.*	DD/MMM/YYYY	1. Pre-filled with enrollment date 2. Non-editable field	657 TX_PROJECTED_BEGDT
PROTOCOL VERSION			
Which protocol version was patient consented to at study enrollment?*	[] - Original (Activation)	1. DENOTE: AMD# 2. Required	4433614 CncSdyPrtVsTp
AGE			
Is the patient greater than or equal to 7 years of age at time of study enrollment? * *Per protocol section 3.2.1* *Help Text: 7 years of age is the minimum age to perform an MRI without sedation*	[] - Yes [] - No	1. Required 2. Must be Yes 3. Query if age < 7 years	3104501 PtAgeinRangeatStudyEnr
TREATMENT HISTORY			
Has the patient enrolled and completed therapy on AHOD1331?* *Per protocol section 3.2.2*	[] - Yes [] - No	1. Required 2. Must be Yes 3. Cross validate against AHOD1331 enrollment.	4399812 PtNwDxIND
DISEASE STATUS			

Question (Element)	Valid Value	Edit checks & validations	SDC USE ONLY
Is the patient not known to have had a primary event (relapse/second malignancy/death)?* *Per protocol section 3.2.3* ***Note:*** *Subjects enrolled and/or treated on AHOD1331 at another institution are eligible if they are now being followed at the current COG institution.*	[] - Yes [] - No	1. Required 2. Must be Yes	12486331 PRM_EVNT_UNK_OCC_IND
CARDIAC MRI FEASIBILITY			
Does the patient have access to cardiac MRI at institution where receiving follow-up care and must be able to complete cardiac MRI without sedation?* *Per protocol section 3.2.4*	[] - Yes [] - No	1. Required 2. Must be Yes	12495866 MRI_SED_ASMNT_IND
EXCLUSION CRITERIA			
Does the patient have a medical contraindication to undergoing a cardiac MRI?* *Per protocol section 3.2.5*	[] - Yes [] - No	1. Required 2. Must be No	12501417 MRI_MED_CONTRA_ASMNT_IND
Was the patient removed from AHOD1331 therapy prior to completing the AHOD1331 protocol specified treatment plan?* *Per protocol section 3.2.6*	[] - Yes [] - No	1. Required 2. Must be No	2192740 PT_OTX_IND
Did the patient receive cancer therapy for disease progression or recurrence, or subsequent malignant neoplasm, in addition to that of AHOD1331?* *Per protocol section 3.2.7*	[] - Yes [] - No	1. Required 2. Must be No	2763213 CA_TX_RCV_IND

Question (Element)	Valid Value	Edit checks & validations	SDC USE ONLY
Does the patient have a history of cardiovascular disease prior to enrollment on AHOD1331?* *Per protocol section 3.2.8*	[] - Yes [] - No	1. Required 2. Must be No	3587220 HxIndCdcDsz
REGULATORY REQUIREMENTS			
Date informed consent signed:*	DD/MMM/YYYY	1. Required 2. Date must be >= DOB and <= today	656 ICF_SIG_DT
Have all institutional, FDA, and NCI requirements for human studies been met?*	[] - Yes [] - No	1. Required 2. Must be Yes	2006153 STUDY_COMP_REQ_IND_2
COMMENTS			
Comments:			797 RSCH_COMMENTS_TXT

Enrollment Healthy Cardiac Lifestyle Survey

COG ID _____

Smoking History / Antecedentes de tabaquismo / Historique de tabagisme

Do you currently smoke and have you ever smoked (tobacco) cigarettes? /

¿Fuma actualmente y alguna vez ha fumado cigarrillos (tabaco)? /

Fumez-vous actuellement et avez-vous déjà fumé des cigarettes (du tabac)?

- ◯ Yes, I am a current smoker. / Sí, actualmente soy fumador./ Oui, je fume actuellement
- ◯ No, I don't currently smoke. I quit less than a year ago. / No, actualmente no fumo. Lo dejé hace menos de un año./ Non, je ne fume pas actuellement. J'ai arrêté il y a moins d'un an.
- ◯ No, I don't currently smoke. I quit more than a year ago. / No, actualmente no fumo. Lo dejé hace más de un año./ Non, je ne fume pas actuellement. J'ai arrêté il y a plus d'un an.
- ◯ No, I never smoked OR I smoked a few times but less than 100 cigarettes in total during my whole life. / No, nunca he fumado O he fumado algunas veces, pero menos de 100 cigarrillos en total durante toda mi vida./ Non, je n'ai jamais fumé OU j'ai fumé quelques fois mais moins de 100 cigarettes au total durant toute ma vie.
- ◯ Prefer not to answer / Prefiero no contestar/ Je préfère ne pas répondre

If you have ever smoked, how many cigarettes (tobacco) per day did you or do you smoke? /

Si ha fumado alguna vez, ¿cuántos cigarrillos (tabaco) al día fumaba o fuma?/

Si vous avez déjà fumé, combien de cigarettes (tabac) avez-vous fumées ou fumez-vous par jour?

- ◯ Never smoked OR smoked less than 100 cigarettes in total in my whole life. / Nunca he fumado O he fumado menos de 100 cigarrillos en total en toda mi vida. / Je n'ai jamais fumé ou j'ai fumé moins de 100 cigarettes au total au cours de ma vie.
- ◯ Less than 1 cigarette per day / occasionally smoked for _____ years / Menos de 1 cigarrillo al día o he fumado ocasionalmente durante _____ años / Moins d'une cigarette par jour / fumeur occasionnel depuis _____ ans
- ◯ 1-10 cigarettes per day (10 cigarettes = ½ pack) for _____ years / De 1 a 10 cigarrillos al día (10 cigarrillos = ½ paquete) durante _____ años / 1-10 cigarettes par jour (10 cigarettes = ½ paquet) pendant _____ ans
- ◯ 11-20 cigarettes per day (20 cigarettes = 1 pack) for _____years / De 11 a 20 cigarrillos al día (20 cigarrillos = 1 paquete) durante _____años / 11-20 cigarettes par jour (20 cigarettes = 1 paquet) pendant _____ans
- ◯ 21-30 cigarettes per day (30 cigarettes = 1 ½ packs) for _____years / De 21 a 30 cigarrillos al día (30 cigarrillos = 1 ½ paquetes) durante _____años / 21-30 cigarettes par jour (30 cigarettes = 1½ paquets) pendant _____ans
- ◯ 31-40 cigarettes per day (40 cigarettes = 2 packs) for _____years / De 31 a 40 cigarrillos al día (40 cigarrillos = 2 paquetes) durante _____años / 31-40 cigarettes par jour (40 cigarettes = 2 paquets) pendant _____ans
- ◯ More than 41 cigarettes per day (more than 2 packs) for _____years / Más de 41 cigarrillos al día (más de 2 paquetes) durante _____años / Plus de 41 cigarettes par jour (plus de 2 paquets) pendant _____ans
- ◯ Prefer not to answer / Prefiero no contestar / Je préfère ne pas répondre

Number of years smoked / durante _____ años / depuis _____ ans

_____

Physical Activity / Actividad física / Activité physique

How many days in a usual week do you do moderate physical activity?
(A person doing moderate physical activity can usually talk, but not sing, during the activity.) /

¿Cuántos días a la semana suele realizar una actividad física moderada? _____días por semana
(Por lo general, una persona que realiza una actividad física moderada puede hablar, pero no cantar, durante la actividad.) /

Combien de jours par semaine pratiquez-vous une activité physique modérée? _____ jours par semaine
(Une personne pratiquant une activité physique modérée peut généralement parler, mais pas chanter, pendant l'activité.)

- ◯ 0
- ◯ 1
- ◯ 2
- ◯ 3
- ◯ 4
- ◯ 5
- ◯ 6
- ◯ 7

(# of days per week / días por semana / jours par semaine)

On the days you do moderate physical activity, about how many minutes do you exercise? / Los días que realiza una actividad física moderada, ¿cuántos minutos se ejercita aproximadamente? / Les jours où vous pratiquez une activité physique modérée, pendant combien de minutes environ faites-vous de l'exercice?	_____ (# of minutes of exercise on days of moderate activity/ minutos de ejercicio los días de actividad moderada/ minutes d'exercice les jours d'activité modérée)
How many days in a usual week do you do vigorous physical activity? (A person doing vigorous physical activity usually cannot say more than a few words before pausing for a breath.) / ¿Cuántos días a la semana suele realizar una actividad física vigorosa? (Por lo general, una persona que realiza una actividad física vigorosa no puede decir más de unas pocas palabras antes de hacer una pausa para respirar.) / Combien de jours par semaine pratiquez-vous une activité physique intense? (Une personne pratiquant une activité physique intense ne peut généralement pas dire plus de quelques mots avant de s'arrêter pour respirer.)	◯ 0 ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7 (# of days per week / días por semana / jours par semaine)
On the days you do vigorous physical activity, about how many minutes do you exercise? / Los días que realiza una actividad física vigorosa, ¿cuántos minutos se ejercita aproximadamente?/ Les jours où vous pratiquez une activité physique intense, pendant combien de minutes environ faites-vous de l'exercice?	_____ (# of minutes of exercise on days of vigorous activity/ minutos de ejercicio los días de actividad vigorosa/ Nombre de minutes d'exercice les jours d'activité intense)

Diet History / Historial dietético / Historique de l'alimentation

How many cups of fruits and vegetables do you eat in an average day?

One cup of fruit = 1 banana, 1 apple, 15 grapes, or ½ cup raisins
One cup of vegetables = 1 ear of corn, 1 potato, 2 cups cooked greens, 1 cup uncooked greens, 2 celery stalks, or 12 baby carrots /

¿Cuántas tazas de fruta y verdura consume en un día promedio?

Una taza de fruta = 1 plátano, 1 manzana, 15 uvas o ½ taza de pasas
Una taza de verduras = 1 elote, 1 papa, 2 tazas de verduras cocidas, 1 taza de verduras crudas, 2 tallos de apio o 12 zanahorias baby /

Combien de tasses de fruits et légumes mangez-vous en moyenne par jour?

Une tasse de fruits = 1 banane, 1 pomme, 15 raisins ou ½ tasse de raisins secs
Une tasse de légumes = 1 épi de maïs, 1 pomme de terre, 2 tasses de légumes verts cuits, 1 tasse de légumes verts non cuits, 2 branches de céleri ou 12 petites carottes

- ◯ Less than 4 / Menos de 4 ½ tazas / Moins de 4½ tasses
- ◯ 4 ½ cups or more / 4 ½ tazas o más / 4½ tasses ou plus
- ◯ I don't know / No sé / Je ne sais pas
- ◯ Prefer not to answer / Prefiero no contestar / Je préfère ne pas répondre

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Do you eat 2 servings or more of fish weekly?
(One serving of fish is approximately 3.5 ounces, approximately the size of a deck of cards.) /

¿Consume dos o más porciones de pescado a la semana?
(Una porción de pescado es alrededor de 100 gramos, aproximadamente del tamaño de una baraja.) /

Consommez-vous au moins deux portions de poisson par semaine?
(Une portion de poisson représente environ 3,5 onces, soit à peu près la taille d'un jeu de cartes.)

- ◯ Yes / Sí / Oui
- ◯ No / No / Non
- ◯ I don't know / No sé / Je ne sais pas
- ◯ Prefer not to answer / Prefiero no contestar / Je préfère ne pas répondre

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Do you eat 3 or more servings of whole grains daily?
(Whole grain foods include whole wheat or rye bread, brown or wild rice, whole-wheat pasta, bran flakes or whole-grain cereals, and oatmeal) /

¿Consume tres o más porciones de granos integrales al día?
(Los alimentos integrales incluyen el pan integral o de centeno, el arroz integral o silvestre, la pasta integral, las hojuelas de salvado o los cereales integrales y la avena) /

Consommez-vous au moins 3 portions de céréales complètes par jour?
(Les aliments à base de céréales complètes comprennent le pain de blé entier ou de seigle, le riz brun ou sauvage, les pâtes de blé entier, les flocons de son ou les céréales complètes, et les flocons d'avoine)

- ◯ Yes / Sí / Oui
- ◯ No / No / Non
- ◯ I don't know / No sé / Je ne sais pas
- ◯ Prefer not to answer / Prefiero no contestar / Je préfère ne pas répondre

Do you drink less than 36 ounces (4 ½ cups) of beverages with added sugar weekly?
(Beverages with added sugar include: regular soft drinks, fruit drinks (fruit aides and fruit punch), and sweet tea.) /

¿Toma menos de 1 litro (4 ½ tazas) de bebidas con azúcar añadida a la semana?
(Las bebidas con azúcar añadida incluyen: refrescos normales, bebidas de frutas (con fruta añadida y ponche de frutas) y té dulce.) /

Buvez-vous moins de 36 onces (4½ tasses) de boissons contenant des sucres ajoutés par semaine?
(Les boissons contenant des sucres ajoutés comprennent : les boissons gazeuses ordinaires, les boissons aux fruits (aides aux fruits et punchs aux fruits) et le thé sucré.)

- ◯ Yes / Sí / Oui
- ◯ No / No / Non
- ◯ I don't know / No sé / Je ne sais pas
- ◯ Prefer not to answer / Prefiero no contestar / Je préfère ne pas répondre

Do you eat 1,500 milligrams or less of sodium daily?

If you don't track your daily sodium intake by reading the food label, to answer "yes" you should do at least two
of the following:
(1) Avoid eating pre-packaged processed food or eat low-sodium versions.
(2) Avoid eating out or ask for low-sodium preparations.
(3) Cook at home without adding salt. /

¿Consume 1500 miligramos o menos de sodio al día?

Si no realiza un seguimiento de su ingesta diaria de sodio leyendo la etiqueta de los alimentos, para responder "sí" debe hacer al menos dos de las siguientes acciones:
(1) Evitar el consumo de alimentos procesados preenvasados u optar por las versiones bajas en sodio.
(2) Evitar comer fuera de casa o pedir que los alimentos se preparen con bajo contenido de sodio.
(3) Cocinar en casa sin añadir sal. /

Consommez-vous 1 500 milligrammes ou moins de sodium par jour?

Si vous ne contrôlez pas votre consommation quotidienne de sodium en lisant les étiquettes des produits alimentaires, pour répondre >, vous devez faire au moins deux des choses suivantes :
(1) Évitez de consommer des aliments transformés préemballés ou optez pour des versions à faible teneur en sodium.
(2) Évitez de manger au restaurant ou demandez des préparations à faible teneur en sodium.
(3) Cuisinez à la maison sans ajouter de sel.

- ◯ Yes / Sí / Oui
- ◯ No / No / Non
- ◯ I don't know / No sé / Je ne sais pas
- ◯ Prefer not to answer / Prefiero no contestar / Je préfère ne pas répondre

Enrollment Screening for Cardiac Health Status

History	
Do you have any shortness of breath with or without exertion?	◯ yes ◯ no
Any chest pain or tightness?	◯ yes ◯ no
Any edema/swelling/ or recent weight change?	◯ yes ◯ no
Any limitation in activity?	◯ yes ◯ no
Any fatigue?	◯ yes ◯ no
Physical Exam	
Any jugular venous distension (JVD)?	◯ yes ◯ no
Crackles on auscultation of the lung exam?	◯ yes ◯ no
S3?	◯ yes ◯ no
Cardiac murmurs	◯ yes ◯ no
Lower extremity edema?	◯ yes ◯ no
History of:	
Labs: any elevation of BNP > 100 or NT-Pro BNP > 125	◯ yes ◯ no
Enlarged cardiac size on CXR?	◯ yes ◯ no
Any confirmed abnormality on ECG?	◯ yes ◯ no
Abnormality on MRI including LVEF, LVEDD (indexed), LVESV (indexed), GLS, RVEF, Myostrain?	◯ yes ◯ no

Symptomatic HF? Definition: at least one item in two of the following three categories including symptoms of HF (paroxysmal nocturnal dyspnea, shortness of breath, swelling, orthopnea or weight gain), physical exam findings (presence of jugular venous distension, lung crackles, edema or S3 heart sound) and diagnostic testing (pulmonary edema on chest x-ray or elevated brain natriuretic peptide (BNP) >100 pg/ml or N-terminal BNP (NTproBNP) > 125 pg/ml)	◯ yes ◯ no
Grading	◯ Grade 2: symptoms with mild to moderate activity or exertion ◯ Grade 3: symptoms at rest or minimal exertion requiring intervention ◯ Grade 4: life-threatening consequences requiring urgent intervention
Acute coronary syndrome Definition: Required to have 2/3 of either troponin elevation, chest pain, and ECG changes	◯ yes ◯ no
Grading	◯ Grade 2: symptomatic, progressive angina with normal cardiac enzymes and hemodynamically stable ◯ Grade 3: symptomatic, unstable angina and/or acute myocardial infarction with abnormal cardiac enzymes and hemodynamically stable

Enrollment Specimen Transmittal form

COG ID	_____
BPC ID	_____
Date sample collected	_____
Time sample collected	_____
Institution name	_____
Sender Name	_____
Sender Phone	_____
Sender Email	_____
FedEx Tracking Number	_____
Shipment Date	_____
Collection Tube Volume	_____ (mL)

Cmri Site Crf

cMRI Session ID	_____
Date of cMRI Study	_____
Weight at time of scan. (kg)	_____
Height at time of scan. (cm)	_____
Systolic Blood Pressure (SBP).	_____
Diastolic Blood Pressuer (DBP).	_____
Heart Rate	_____
Scanner Vendor	_____
Scanner Field Strength	◯ 1.5 Tesla ◯ 3 Tesla
Scanner Platform	_____
Notes	_____

1 yr Follow up Healthy Cardiac Lifestyle Survey

Smoking History / Antecedentes de tabaquismo / Historique de tabagisme

Do you currently smoke and have you ever smoked (tobacco) cigarettes? /
¿Fuma actualmente y alguna vez ha fumado cigarrillos (tabaco)? /
Fumez-vous actuellement et avez-vous déjà fumé des cigarettes (du tabac)?

- ◯ Yes, I am a current smoker. / Sí, actualmente soy fumador./ Oui, je fume actuellement
- ◯ No, I don't currently smoke. I quit less than a year ago. / No, actualmente no fumo. Lo dejé hace menos de un año./ Non, je ne fume pas actuellement. J'ai arrêté il y a moins d'un an.
- ◯ No, I don't currently smoke. I quit more than a year ago. / No, actualmente no fumo. Lo dejé hace más de un año./ Non, je ne fume pas actuellement. J'ai arrêté il y a plus d'un an.
- ◯ No, I never smoked OR I smoked a few times but less than 100 cigarettes in total during my whole life. / No, nunca he fumado O he fumado algunas veces, pero menos de 100 cigarrillos en total durante toda mi vida./ Non, je n'ai jamais fumé OU j'ai fumé quelques fois mais moins de 100 cigarettes au total durant toute ma vie.
- ◯ Prefer not to answer / Prefiero no contestar/ Je préfère ne pas répondre

If you have ever smoked, how many cigarettes (tobacco) per day did you or do you smoke? /
Si ha fumado alguna vez, ¿cuántos cigarrillos (tabaco) al día fumaba o fuma?/
Si vous avez déjà fumé, combien de cigarettes (tabac) avez-vous fumées ou fumez-vous par jour?

- ◯ Never smoked OR smoked less than 100 cigarettes in total in my whole life. / Nunca he fumado O he fumado menos de 100 cigarrillos en total en toda mi vida. / Je n'ai jamais fumé ou j'ai fumé moins de 100 cigarettes au total au cours de ma vie.
- ◯ Less than 1 cigarette per day / occasionally smoked for _____ years / Menos de 1 cigarrillo al día o he fumado ocasionalmente durante _____ años / Moins d'une cigarette par jour / fumeur occasionnel depuis _____ ans
- ◯ 1-10 cigarettes per day (10 cigarettes = ½ pack) for _____ years / De 1 a 10 cigarrillos al día (10 cigarrillos = ½ paquete) durante _____ años / 1-10 cigarettes par jour (10 cigarettes = ½ paquet) pendant _____ ans
- ◯ 11-20 cigarettes per day (20 cigarettes = 1 pack) for _____years / De 11 a 20 cigarrillos al día (20 cigarrillos = 1 paquete) durante _____años / 11-20 cigarettes par jour (20 cigarettes = 1 paquet) pendant _____ans
- ◯ 21-30 cigarettes per day (30 cigarettes = 1 ½ packs) for _____years / De 21 a 30 cigarrillos al día (30 cigarrillos = 1 ½ paquetes) durante _____años / 21-30 cigarettes par jour (30 cigarettes = 1½ paquets) pendant _____ans
- ◯ 31-40 cigarettes per day (40 cigarettes = 2 packs) for _____years / De 31 a 40 cigarrillos al día (40 cigarrillos = 2 paquetes) durante _____años / 31-40 cigarettes par jour (40 cigarettes = 2 paquets) pendant _____ans
- ◯ More than 41 cigarettes per day (more than 2 packs) for _____years / Más de 41 cigarrillos al día (más de 2 paquetes) durante _____años / Plus de 41 cigarettes par jour (plus de 2 paquets) pendant _____ans
- ◯ Prefer not to answer / Prefiero no contestar / Je préfère ne pas répondre

Number of years smoked / durante _____ años / depuis _____ ans

_____

Physical Activity / Actividad física / Activité physique

How many days in a usual week do you do moderate physical activity?
(A person doing moderate physical activity can usually talk, but not sing, during the activity.) /

¿Cuántos días a la semana suele realizar una actividad física moderada? _____días por semana
(Por lo general, una persona que realiza una actividad física moderada puede hablar, pero no cantar, durante la actividad.) /

Combien de jours par semaine pratiquez-vous une activité physique modérée? _____ jours par semaine
(Une personne pratiquant une activité physique modérée peut généralement parler, mais pas chanter, pendant l'activité.)

- ◯ 0
- ◯ 1
- ◯ 2
- ◯ 3
- ◯ 4
- ◯ 5
- ◯ 6
- ◯ 7

(# of days per week / días por semana / jours par semaine)

On the days you do moderate physical activity, about how many minutes do you exercise? / Los días que realiza una actividad física moderada, ¿cuántos minutos se ejercita aproximadamente? / Les jours où vous pratiquez une activité physique modérée, pendant combien de minutes environ faites-vous de l'exercice?	_____ (# of minutes of exercise on days of moderate activity/ minutos de ejercicio los días de actividad moderada/ minutes d'exercice les jours d'activité modérée)
How many days in a usual week do you do vigorous physical activity? (A person doing vigorous physical activity usually cannot say more than a few words before pausing for a breath.) / ¿Cuántos días a la semana suele realizar una actividad física vigorosa? (Por lo general, una persona que realiza una actividad física vigorosa no puede decir más de unas pocas palabras antes de hacer una pausa para respirar.) / Combien de jours par semaine pratiquez-vous une activité physique intense? (Une personne pratiquant une activité physique intense ne peut généralement pas dire plus de quelques mots avant de s'arrêter pour respirer.)	◯ 0 ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7 (# of days per week / días por semana / jours par semaine)
On the days you do vigorous physical activity, about how many minutes do you exercise? / Los días que realiza una actividad física vigorosa, ¿cuántos minutos se ejercita aproximadamente?/ Les jours où vous pratiquez une activité physique intense, pendant combien de minutes environ faites-vous de l'exercice?	_____ (# of minutes of exercise on days of vigorous activity/ minutos de ejercicio los días de actividad vigorosa/ Nombre de minutes d'exercice les jours d'activité intense)

Diet History / Historial dietético / Historique de l'alimentation

How many cups of fruits and vegetables do you eat in an average day?

One cup of fruit = 1 banana, 1 apple, 15 grapes, or ½ cup raisins
One cup of vegetables = 1 ear of corn, 1 potato, 2 cups cooked greens, 1 cup uncooked greens, 2 celery stalks, or 12 baby carrots /

¿Cuántas tazas de fruta y verdura consume en un día promedio?

Una taza de fruta = 1 plátano, 1 manzana, 15 uvas o ½ taza de pasas
Una taza de verduras = 1 elote, 1 papa, 2 tazas de verduras cocidas, 1 taza de verduras crudas, 2 tallos de apio o 12 zanahorias baby /

Combien de tasses de fruits et légumes mangez-vous en moyenne par jour?

Une tasse de fruits = 1 banane, 1 pomme, 15 raisins ou ½ tasse de raisins secs
Une tasse de légumes = 1 épi de maïs, 1 pomme de terre, 2 tasses de légumes verts cuits, 1 tasse de légumes verts non cuits, 2 branches de céleri ou 12 petites carottes

- ◯ Less than 4 / Menos de 4 ½ tazas / Moins de 4½ tasses
- ◯ 4 ½ cups or more / 4 ½ tazas o más / 4½ tasses ou plus
- ◯ I don't know / No sé / Je ne sais pas
- ◯ Prefer not to answer / Prefiero no contestar / Je préfère ne pas répondre

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Do you eat 2 servings or more of fish weekly?
(One serving of fish is approximately 3.5 ounces, approximately the size of a deck of cards.) /

¿Consume dos o más porciones de pescado a la semana?
(Una porción de pescado es alrededor de 100 gramos, aproximadamente del tamaño de una baraja.) /

Consommez-vous au moins deux portions de poisson par semaine?
(Une portion de poisson représente environ 3,5 onces, soit à peu près la taille d'un jeu de cartes.)

- ◯ Yes / Sí / Oui
- ◯ No / No / Non
- ◯ I don't know / No sé / Je ne sais pas
- ◯ Prefer not to answer / Prefiero no contestar / Je préfère ne pas répondre

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Do you eat 3 or more servings of whole grains daily?
(Whole grain foods include whole wheat or rye bread, brown or wild rice, whole-wheat pasta, bran flakes or whole-grain cereals, and oatmeal) /

¿Consume tres o más porciones de granos integrales al día?
(Los alimentos integrales incluyen el pan integral o de centeno, el arroz integral o silvestre, la pasta integral, las hojuelas de salvado o los cereales integrales y la avena) /

Consommez-vous au moins 3 portions de céréales complètes par jour?
(Les aliments à base de céréales complètes comprennent le pain de blé entier ou de seigle, le riz brun ou sauvage, les pâtes de blé entier, les flocons de son ou les céréales complètes, et les flocons d'avoine)

- ◯ Yes / Sí / Oui
- ◯ No / No / Non
- ◯ I don't know / No sé / Je ne sais pas
- ◯ Prefer not to answer / Prefiero no contestar / Je préfère ne pas répondre

Do you drink less than 36 ounces (4 ½ cups) of beverages with added sugar weekly?
(Beverages with added sugar include: regular soft drinks, fruit drinks (fruit aides and fruit punch), and sweet tea.) /

¿Toma menos de 1 litro (4 ½ tazas) de bebidas con azúcar añadida a la semana?
(Las bebidas con azúcar añadida incluyen: refrescos normales, bebidas de frutas (con fruta añadida y ponche de frutas) y té dulce.) /

Buvez-vous moins de 36 onces (4½ tasses) de boissons contenant des sucres ajoutés par semaine?
(Les boissons contenant des sucres ajoutés comprennent : les boissons gazeuses ordinaires, les boissons aux fruits (aides aux fruits et punchs aux fruits) et le thé sucré.)

- ◯ Yes / Sí / Oui
- ◯ No / No / Non
- ◯ I don't know / No sé / Je ne sais pas
- ◯ Prefer not to answer / Prefiero no contestar / Je préfère ne pas répondre

Do you eat 1,500 milligrams or less of sodium daily?

If you don't track your daily sodium intake by reading the food label, to answer "yes" you should do at least two
of the following:
(1) Avoid eating pre-packaged processed food or eat low-sodium versions.
(2) Avoid eating out or ask for low-sodium preparations.
(3) Cook at home without adding salt.

¿Consume 1500 miligramos o menos de sodio al día?

Si no realiza un seguimiento de su ingesta diaria de sodio leyendo la etiqueta de los alimentos, para responder "sí" debe hacer al menos dos de las siguientes acciones:
(1) Evitar el consumo de alimentos procesados preenvasados u optar por las versiones bajas en sodio.
(2) Evitar comer fuera de casa o pedir que los alimentos se preparen con bajo contenido de sodio.
(3) Cocinar en casa sin añadir sal. /

Consommez-vous 1 500 milligrammes ou moins de sodium par jour?

Si vous ne contrôlez pas votre consommation quotidienne de sodium en lisant les étiquettes des produits alimentaires, pour répondre >, vous devez faire au moins deux des choses suivantes :
(1) Évitez de consommer des aliments transformés préemballés ou optez pour des versions à faible teneur en sodium.
(2) Évitez de manger au restaurant ou demandez des préparations à faible teneur en sodium.
(3) Cuisinez à la maison sans ajouter de sel.

- ◯ Yes / Sí / Oui
- ◯ No / No / Non
- ◯ I don't know / No sé / Je ne sais pas
- ◯ Prefer not to answer / Prefiero no contestar / Je préfère ne pas répondre

1 yr Follow up Screening for Cardiac Health Status

Do you have any shortness of breath with or without exertion?	◯ yes ◯ no
Any chest pain or tightness?	◯ yes ◯ no
Any edema/swelling/ or recent weight change?	◯ yes ◯ no
Any limitation in activity?	◯ yes ◯ no
Any fatigue?	◯ yes ◯ no
Any jugular venous distension (JVD)?	◯ yes ◯ no
Crackles on auscultation of the lung exam?	◯ yes ◯ no
S3?	◯ yes ◯ no
Cardiac murmurs?	◯ yes ◯ no
Lower extremity edema?	◯ yes ◯ no
Labs: any elevation of BNP > 100 or NT-Pro BNP > 125?	◯ yes ◯ no
Enlarged cardiac size on CXR?	◯ yes ◯ no
Any confirmed abnormality on ECG?	◯ yes ◯ no
Abnormality on MRI including LVEF, LVEDD (indexed), LVESV (indexed), GLS, RVEF, Myostrain?	◯ yes ◯ no

Symptomatic HF? Definition: at least one item in two of the following three categories including symptoms of HF (paroxysmal nocturnal dyspnea, shortness of breath, swelling, orthopnea or weight gain), physical exam findings (presence of jugular venous distension, lung crackles, edema or S3 heart sound) and diagnostic testing (pulmonary edema on chest x-ray or elevated brain natriuretic peptide (BNP) >100 pg/ml or N-terminal BNP (NTproBNP) > 125 pg/ml)	◯ yes ◯ no
Grading	◯ Grade 2: symptoms with mild to moderate activity or exertion ◯ Grade 3: symptoms at rest or minimal exertion requiring intervention ◯ Grade 4: life-threatening consequences requiring urgent intervention
Acute coronary syndrome Definition: Required to have 2/3 of either troponin elevation, chest pain, and ECG changes	◯ yes ◯ no
Grading	◯ Grade 2: symptomatic, progressive angina with normal cardiac enzymes and hemodynamically stable ◯ Grade 3: symptomatic, unstable angina and/or acute myocardial infarction with abnormal cardiac enzymes and hemodynamically stable

1 yr Follow up Specimen Transmittal form

COG ID Number	_____
BPC ID Number	_____
Date Sample Collected	_____
Time Sample Collected	_____
Institution Name	_____
Sender Name	_____
Sender Phone	_____
Sender Email	_____
FedEx Tracking Number	_____
Shipment Date	_____
Collection Tube Volume	_____ (mL)

STUDY CHAIR ELIGIBILITY REVIEW			
This form is required to be submitted for all INELIGIBLE patients by the study chair.			
Question (Element)	**Valid Value**	**Edit checks**	**SDC USE Only**
Is the patient eligible?*	[] - Yes [] - No	1. Query if blank 2. Query if Yes 3. Email to SS, DM if NO	1235 PT_ELIG_IND
PATIENT ELIGIBILITY			
Reason patient did not meet eligibility criteria: *Check all that apply.*	[] - Disease type or histology [] - Patient characteristics [] - Prior therapy [] - Stage, extent of disease [] - Timing of enrollment [] - Other	1. Query if blank and above is No 2. Query if answered and above is Yes 3. Email to COGQA if selected	3370583 PT_INELIG_Rsn_A1 PT_INELIG_Rsn_A2 PT_INELIG_Rsn_A3 PT_INELIG_Rsn_A4 PT_INELIG_Rsn_A5 PT_INELIG_Rsn_A6
If Other, specify:	Text field	1. Query if answered and above is NOT 'Other' 2. Query if blank and above is 'Other'	3373489 PT_INELIG_ELIG_SPEC
Ineligibility information source: *Check all that apply.*	[] - Audit [] - Institutional report [] - Other	1. Query if blank and Elig is No 2. Query if answered and Elig is Yes	3370590 Pati_Info_Inel_Info_Type_A1 Pati_Info_Inel_Info_Type_A2 Pati_Info_Inel_Info_Type_A3
If Other, specify:	Text field	1. Query if answered and above is NOT 'Other' 2. Query if blank and above is 'Other'	3373485 Pati_Data_Inel_SPEC
COMMENTS			
Comments:			797 RSCH_COMMENTS_TXT