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**Clinical Research Protocol**

# TRIPLE-A PILOT: Actively intercepting ADT-induced metabolic aberrations in newly diagnosed prostate cancer

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| RG Number: | 1121348 |
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| Indication | Androgen Deprivation Therapy + RT, prostate cancer |
| Study sites | Fred Hutchinson Cancer Center<br>Veterans Affairs Puget Sound Health Care System<br>University of Washington |
| Funding Organization: | National Cancer Institute, SPORE Pilot P50 CA097186-18 |
| Principal Investigators: | Marian L. Neuhouser, PhD (FHCRC)<br>Jonathan Wright, MD (VAPSHCS) |

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|---|---|
| **TITLE** | Triple-A Pilot Study |
| **SPONSOR** | P50 CA097186-18 |
| **FUNDING ORGANIZATION** | National Cancer Institute |
| **NUMBER OF SITES** | 2: Fred Hutchinson Cancer Center, Veterans Affairs Puget Sound Healthcare System |
| **RATIONALE** | National Guidelines specify that one treatment option for newly diagnosed intermediate and high-risk prostate cancer patients is external beam radiation therapy (RT) plus 6-24 months of concomitant androgen deprivation therapy (ADT). This standard of care combination therapy demonstrates significant survival benefits. ADT effectively slows the growth of prostate cancer cells, thereby enhancing the therapeutic effectiveness of RT. Despite the clinical gains, ADT leads to an array of side effects including insulin resistance, dyslipidemia, weight gain, increased visceral fat mass coupled with increased muscle wasting/sarcopenia, and quality of life deterioration. These metabolic and physiologic changes begin rapidly within the first few months of ADT use and place patients at increased risk of new co-morbidities such as diabetes, cerebrovascular disease, coronary artery disease, venous thromboembolism and sudden cardiac death. Identifying translational approaches to attenuate these ADT metabolic aberrations have not been rigorously tested, leaving a gap in determining patient treatment options. This proposal pilot tests a comprehensive nutrition and physical activity intervention initiated concurrently with RT+ADT in newly diagnosed intermediate and high-risk prostate cancer patients to determine whether the intervention intercepts the abrupt metabolic and physiologic changes caused by ADT. |
| **STUDY DESIGN** | This is a pilot randomized controlled trial to investigate the effects of a 6-month nutrition and physical activity intervention on blood measures of lipids and insulin resistance, and anthropometry, body composition, and patient reported outcomes in newly diagnosed intermediate and high-risk prostate cancer patients undergoing RT+ADT. |
| **PRIMARY OBJECTIVE** | The study has the following primary **specific aims**:<br>1. Examine intervention effects on ADT-induced insulin resistance measured by HOMA-IR;<br>2. Examine intervention effects on ADT-induced changes in anthropometry and body composition; |
| **SECONDARY OBJECTIVES** | Exploratory aims:<br>1. Explore intervention effects on blood lipids (triglycerides and total, HDL- and LDL-cholesterol) and hemoglobin A1c;<br>2. Explore intervention effects on patient reported outcomes.<br>3. Explore intervention effects on the gut microbiome |
| **NUMBER OF SUBJECTS** | 20 |
| **SUBJECT SELECTION CRITERIA:**<br>**Inclusion Criteria** | <u>Inclusion Criteria:</u><br>1. Males aged 40or older with newly diagnosed D'Amico risk category intermediate or high-risk prostate cancer; |

| | |
|---|---|
| | 2. Primary treatment is external beam radiation therapy with androgen deprivation therapy [Zoladex, Lupron, Degarelix, and other luteinizing hormone-releasing hormone (LHRH)-directed therapies];<br>3. Physically able to undertake an exercise program. |
| **SUBJECT SELECTION CRITERIA:**<br>**Exclusion Criteria** | Exclusion Criteria:<br>1. Advanced, metastatic disease;<br>2. Planning to join a commercial/structured diet change or fitness program;<br>3. Have significant pre-existing T2D (poor glycemic control while on medication, Hemoglobin A1c ≥ 10) or significant pre-existing CVD (myocardial infarction or stroke within prior six months);<br>4. Physician confirmed cognitive impairment or alcohol/narcotic abuse; |
| **DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY** | Subjects will participate in the study for 6 months.<br>The total duration of the study is expected to be 1.5 years |
| **PRIMARY ENPOINTS** | **Primary Aim 1:** Compare intervention effect HOMA-IR levels relative to baseline in intervention and control participants.<br>**Primary Aim 2:** Compare intervention effect on weight, waist circumference, fat mass and lean mass relative to baseline in intervention and control participants. |
| **SECONDARY ENDPOINTS** | **Exploratory Aims.** We will explore the intervention effect on blood lipids and HbA1c, and whether the intervention induces patient reported outcomes (PROs)-specifically quality of life and fatigue differences between the intervention and control arms |
| **STATISTICS**<br>**Primary Analysis Plan** | Linear regression models will test the intervention effects on ADT-induced changes in HOMA-IR (**Aim 1**), body composition (**Aim 2**) and metabolic biomarkers, PRO measures and gut microbiome (**Exploratory aims**). Separate models will be fit for each outcome measure, with an indicator variable for study arm (intervention/control) and adjustment for the respective baseline metabolic biomarker, body composition or PRO measure. Further adjustment for biomarkers that may have shared biology (i.e., total and LDL cholesterol) and for medication use that could affect biomarker concentrations will be considered. We expect most potential confounding variables will be evenly distributed between arms at randomization, but this assumption will be checked prior to analysis. Analyses will follow an intent-to-treat approach. |
| **Rationale for Number of Subjects** | We have set a sample size of 10 in each of the intervention and control arms for this pilot study, which will provide preliminary data to support an R01. |

## 1. BACKGROUND

Prostate cancer represents 19% of all new cancers in men with an age-adjusted incidence rate of 109/100,000.[1] Many prostate cancers are low risk, localized tumors where the 5-year relative survival rate is 99% even without treatment.[1] However, at least a third of prostate cancers present at diagnosis as intermediate to high-risk disease and a 2018 report noted a recent increase in incidence of these more aggressive tumors.[2,3] The National Comprehensive Cancer Network (NCCN)[4] Guidelines, the American Urological Association (AUA), the American Society for Radiation Oncology (ASTRO) and the Society of Urologic Oncology (SUO) all specify that these patients should receive curative-intent, multimodal treatment consisting of radiation therapy (RT) + at least six months of ADT.[5-8] The RT+ADT combination therapy gives clinically important improvements in biochemical-free survival and disease-free survival over RT alone.[9,10]

**Table 1. Expected changes in blood biomarker and body composition measures due to initiation of ADT**

| Measure | % change from ADT initiation |
|---|---|
| **Blood biomarkers** | |
| HbA1c, % | + 1.3 - 4.7% |
| HOMA-IR | +11.6% |
| Total cholesterol, mg/dl | + 0 - 9.0% |
| LDL cholesterol, mg/dl | +0 - 7.3% |
| HDL cholesterol, mg/dl | +7.6 - 11.3% |
| Triglycerides, mg/dl | +13.3 - 36.0% |
| **Body composition markers** | |
| Weight, kg | +1.8 - 2.4% |
| Waist circumference, cm | +1.4 - 3.9% |
| Total fat mass, kg | +11.0 - 12.0% |
| Total lean mass, kg | -2.5 - (-3.6)% |

ADT effectively slows the growth of prostate cancer cells, thereby enhancing therapeutic effectiveness of RT.[4,5,11] Despite clinical gains, ADT induces rapid shifts in metabolic health including dyslipidemia, insulin resistance, and shifts in body composition favoring fat mass deposition and lean mass loss.[12-28] Further, many patients report quality of life deterioration, particularly from increased fatigue and loss of vitality.[29-32] These ADT metabolic changes occur rapidly, within 2-3 months of starting ADT[33] and persist even after cessation of ADT.[34,35] **Table 1** summarizes these consistently observed changes from observational studies and meta analyses.[12,15-17,19,30,36-40] Nearly all patients, even those with pre-ADT healthy weight and blood profiles, will experience some of these shifts, demonstrating a need for intervention.

Our overall research and clinical goals are to intercept or prevent the constellation of dyslipidemia, insulin resistance, weight gain and body composition shifts in these patients. These conditions are harder to treat than prevent since the body quickly becomes refractory to weight loss after a large gain has occurred. A small number of RCTs tested resistance or strength exercise during ADT and yielded modest improvements in overall muscle mass, fitness, quality of life and fatigue.[41-44] However, most have been small, pilot studies[45] and a lack of rigor may have contributed to inconsistent findings. No large trials have tested physical activity together with a dietary pattern (e.g., the DASH diet) shown to decrease cardiovascular disease and its antecedent risk factors that commonly develops in these patients. The AUA acknowledges the ADT-induced adverse effects but there are no proactive prevention guidelines and early intervention is not part of standard of care clinical protocols for patients on ADT.[46] This represents an important gap that we will address first in this pilot followed by a fully powered RCT in an R01.

The study has the following primary **specific aims**:

1. Examine intervention effects on ADT-induced insulin resistance measured by HOMA-IR;
2. Examine intervention effects on ADT-induced changes in anthropometry (weight and waist circumference) and body composition (fat and lean mass).

**Exploratory aims:**

1. To explore intervention effects on blood lipids (total, HDL- and LDL-cholesterol) and HbA1c;
2. To explore intervention effects on patient reported outcomes;
3. To explore intervention effects on gut microbiome.

## 2. STUDY DESIGN

### 2.1 Overview

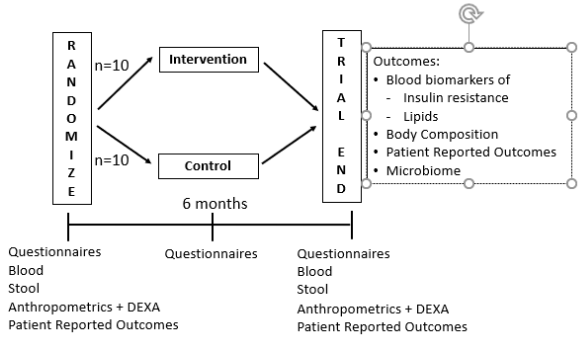
This is a pilot randomized controlled trial to investigate the effects of a 6-month nutrition and physical activity intervention on blood measures of lipids and insulin resistance, and anthropometry, body composition, and patient reported outcomes in n=20 newly diagnosed intermediate and high-risk prostate cancer patients

undergoing RT+ADT. Patients will be randomized to either:

1. Diet and physical activity intervention (modified DASH diet and aerobic activity and resistance training), or
2. Control (oral and written information based on general U.S. dietary and physical activity guidelines).

We will recruit and enroll patients from the VAPSHCS and UW prostate cancer clinics. The study design is a six-month single blind, parallel-arm, randomized clinical trial with equal numbers in the intervention (n=10) and control (n=10) arms (**Figure 1**). Study activities in **Figure 1** take place at both the Fred Hutch Prevention Center and at the VAPSHCS. The intervention will be delivered by 10 in-person or virtual sessions with a Registered Dietitian, and on the same day, individual sessions with an Exercise Physiologist plus optional drop-in exercise sessions. We have already established procedures for safe participant contact and procedures during COVID-19. Data collection includes self-reported lifestyle habits (diet, physical activity), objective measures of anthropometry/body composition (height, weight, waist circumference, dual x-ray absorptiometry (DXA)), biologic (blood biomarkers) and Patient Reported Outcomes (Health-Related Quality of Life and fatigue).

Figure 1. Study Design




## 3. ELIGIBILITY CRITERIA

Subjects with a diagnosis of intermediate or high risk localized prostate cancer who meet all of the inclusion and none of the exclusion criteria will be eligible for participation in this study. All races/ethnicities are eligible to participate.

### 3.1 Inclusion Criteria

1. Age ≥ 40 years;
2. Histologically confirmed adenocarcinoma of the prostate, (D'Amico risk category intermediate or high risk, localized or locoregional);
3. Primary treatment is RT + ADT [Zoladex, Lupron, Degarelix, and other luteinizing hormone-releasing hormone (LHRH)-directed therapies] with standard RT dose and fractionation (anti-androgen monotherapy will not be allowed);
4. Physically able to undertake an exercise program

### 3.2 Exclusion Criteria

1. Advanced, metastatic disease;
2. Planning to join a commercial/structured diet change or fitness program;
3. Have significant pre-existing T2D (poor glycemic control while on medication, defined as Hemoglobin A1c of ≥ 10 within the prior 12 months) or significant pre-existing CVD (myocardial infarction or stroke within prior six months);
4. Physician confirmed cognitive impairment or alcohol/narcotic abuse;

## 4. STUDY PROCEDURES

### 4.1 Recruitment

**UW:** Clinic study staff will identify potential eligible participants from the UW urology clinic. Clinic study staff will pre-screen men to determine medical eligibility as listed in section 3. Recruitment efforts will be targeted towards medically eligible men living in the greater Seattle area. All of our recruitment messages and brochures will outline the parameters of the project and will stress the time commitment necessary in order to participate. Clinic study staff will approach eligible prospective participants during a clinic visit to tell them

about the study. Interested men will be asked to sign consent (Triple-A Consent for Contact UW_V5b) to allow their contact information to be sent to Fred Hutch for final eligibility screening and scheduling. Fred Hutch study staff will contact potential participants by phone to provide additional information about the study, answer question and confirm eligibility (Triple-A ScreeningScript_V1). Interested participants will be scheduled for Clinic Visit 1 and asked to provide verbal consent to complete pre-visit 1 study activities (Triple-A_VerbalConsentScriptPreStudy_V1). Clinic Visit 1 will be scheduled to occur at Fred Hutch approximately 4 weeks of the first scheduled ADT dose. Once consented, participants will be mailed instructions to prepare for Clinic Visit 1 (Triple-A CV1 instructions, Triple-A Stool collection), a stool collection kit, Serving Size Booklet (Serving Size Booklet) and Food Record (Food Record) to complete prior to Clinic Visit 1.

**VAPSHCS:** Clinic study staff will identify potential eligible participants from the VA urology clinic. Clinic study staff will pre-screen men to determine medical eligibility as listed in section 3. Recruitment efforts will be targeted towards medically eligible men living in the greater Seattle area. Given the high proportion of minority patients at the VAPSHCS, we will make every effort to recruit eligible minority patients into the study. All of our recruitment messages and brochures will outline the parameters of the project and will stress the time commitment necessary in order to participate. Clinic study staff will approach eligible prospective participants either during a clinic visit or by phone to tell them about the study and confirm their eligibility. Interested men will be scheduled for Clinic visit 1 and study staff will ask potential participants to provide verbal consent to complete pre-visit 1 study activities. Clinic visit 1 will be scheduled to occur at the VA within approximately 4 weeks of the first scheduled ADT dose. Once consented, participants will be provided (or mailed) instructions to prepare for Clinic Visit 1, a stool collection kit, Serving Size Booklet and Food Record to complete prior to Clinic Visit 1.

### 4.2 Clinic Visit 1

**UW (at Fred Hutch):** Fred Hutch study staff will review study procedures and confirm interest in participating in the study. Participant will be given the opportunity to ask questions and interested participants will sign the UW study consent and HIPAA(Triple-A UW consent; Triple-A HIPAA). Study staff will collect the participants' completed 4-day food record and stool sample (completed at home in preparation for Clinic Visit 1), measure height, weight and waist circumference, and collect fasting blood. In addition, participants will complete questionnaires on demographics/lifestyle characteristics (Triple-A demographic questionnaire), physical activity (Triple-A PA questionnaire) and quality of life/fatigue (Triple-A QOL questionnaire). Clinic staff will conduct a DXA scan and participants will be randomly assigned (via computerized program located within the Triple-A REDCap database) to either the intervention or control arm. After Clinic Visit 1 procedures are complete, participants randomized to the control arm will receive general healthy lifestyle instruction (Triple-A Control lifestyle instruction), while participants assigned to the intervention arm will receive an overview of the intervention goals (Triple-A Nutrition Intervention overview) and be scheduled for the first intervention session.

**VAPSHCS (at VAPSHCS):** VA study staff will review study procedures and confirm interest in participating in the study. Participant will be given the opportunity to ask questions and interested participants will sign the VA study consent and HIPAA. Study staff will collect the participants' completed 4-day food record and stool sample (completed at home in preparation for Clinic Visit 1), measure height, weight and waist circumference, and collect fasting blood. In addition, participants will complete questionnaires on demographics/lifestyle characteristics, physical activity and quality of life/fatigue. Clinic staff will conduct a DXA scan and participants will be randomly assigned (via a computerized program) to either the intervention or control arm. To randomize participants, study staff will use a computerized program located within the Triple-A REDCap database.

After Clinic Visit 1 procedures are complete, participants randomized to the control arm will receive general healthy lifestyle instruction. This instruction will be provided via teleconference by the Fred Hutch study nutritionist. Participants assigned to the intervention arm will receive an overview of the intervention goals (Triple-A Nutrition Intervention_Orientation) and be scheduled for the first intervention session (which will occur at Fred Hutch). If requested, a participant may receive a copy of their DEXA scan results.

### 4.3 Mid-Study Questionnaire (both sites)

At the mid-point of study (month 3), participants will be asked to complete the quality of life/fatigue questionnaire (Triple A QOL questionnaire). This questionnaire can be completed remotely via a web-survey link, on paper (via mail) or in person (if the study mid-point coincides with the participants' second treatment visit or a nutrition intervention visit)..

### 4.4 Clinic Visit 2

**UW (at Fred Hutch):** Clinic Visit 2 will occur at the end of the study, 6 months after Clinic Visit 1. In preparation for Clinic Visit 2, participants will be mailed (or given) the end of study Food Record (Food Record, Serving size booklet), stool collection kit, and instructions (Triple-A CV2 instructions, Triple-A Stool collection) to prepare for the visit. Participants will be asked to complete the Food Record and collect a small amount of stool, and bring both to Clinic Visit 2. At Clinic Visit 2, study staff will measure weight and waist circumference, conduct a DXA scan and collect fasting blood. Participants will complete the final questionnaires on physical activity and quality of life (Triple-A QOL questionnaire, Triple-A PA questionnaire), and will complete an End of Study questionnaire (Triple-A Exit Survey). Participants assigned to the control arm will also be given a copy all of the intervention materials and the study dietitian will review the materials.

**VAPSHCS (at VAPSHCS):** Clinic Visit 2 will occur at the end of the study, 6 months after Clinic Visit 1. In preparation for Clinic Visit 2, participants will be mailed (or given) the end of study Food Record, stool collection kit, and instructions to prepare for the visit. Participants will be asked to complete the Food Record and bring it to Clinic Visit 2. At Clinic Visit 2, study staff will measure weight and waist circumference, conduct a DXA scan and collect fasting blood. Participants will complete the final questionnaires on physical activity and quality of life (Triple-A QOL questionnaire, Triple-A PA questionnaire). Finally, participants assigned to the control arm will be given a copy all of the intervention materials and the study dietitian will be scheduled for a brief teleconference with the study dietitian to review the materials.

If requested, a participant may receive a copy of their DEXA scan results.

### 4.5 Consents

Waiver of HIPAA authorization. A waiver of HIPAA authorization will be obtained to allow the UW urology clinic study staff to pre-screen patients for eligibility. A waiver of HIPAA authorization will also be obtained from the VAPSHCS obtained to allow the VA urology clinic study staff to pre-screen patients for eligibility.

**Triple-A Consent for contact UW**. Potential participants recruited from the UW will be asked to sign a consent for contact to allow their contact information to allow their personal contact information to be sent to the Fred Hutch for recruitment into this study. [No comparable consent is needed for VA participants, since the clinic visits occur at the VA].

**Triple-A_VerbalConsentScriptPreStudy:** Prior to the first study clinic visit, participants will be asked to provide verbal consent to complete pre-visit 1 study activities.

**Triple-A UW Consent**. At Clinic Visit 1,potential participants recruited from UW will be asked to sign the main study consent to participate in the intervention trial.
A comparable consent will be created for VA patients, which will cover the study activities that take place at the VA. VA participants who are assigned to the diet and exercise intervention will complete those study activities at Fred Hutch, and will be asked to sign a separate consent (see below) to cover these activities.

**Triple-A VA_Intervention Consent.** VA participants assigned to the intervention arm will complete an additional consent to participate in the intervention (diet and exercise instruction) activities that occur at Fred Hutch.

### 4.6 Intervention

Intervention arm participants will attend 10 sessions with a registered dietitian over six-months to receive instruction on a modified-Dietary Approaches to Stop Hypertension (DASH) diet. In addition, participants will attend two one-on-one sessions with an exercise physiologist to receive instruction on aerobic physical activity and strength/resistance training. Participants will also be offered the opportunity to complete up to 21 additional supervised exercise sessions at either the Fred Hutch Prevention Center (PC) or VA Clinical Research Unit (CRU). The following materials will be used to provide Intervention instruction to participants in the Intervention arm: Triple-A Nutrition Intervention; Triple-A PA Intervention; Triple-A Supplemental Nutrition_V1; Triple-A Supplemental PA_V1.

Diet.
One-on-one diet instruction will be provided by the Fred Hutch study dietitian. This instruction will occur either in person at the Fred Hutch PC or, if necessary, via teleconference. The dietary goals are to adopt and maintain a modified DASH eating pattern. The DASH feeding trial was designed to test whether the provided diet would lower blood pressure and serum lipids.[47] The trial diet was high in fruits and vegetables, whole grains, and low in sodium.[47] The preponderance of evidence supports that a DASH eating pattern or a modified-DASH, lowers inflammation, promotes healthy weight and body composition,[48] and reduces T2D and CVD- both common complications that accompany ADT use.[48,49]

The Triple A Pilot intervention has modified DASH to: 1) limit saturated fat to 7% of total energy. This will be accomplished via substitution with PUFA-rich plant oils; 2) restrict added sugars as DASH made no specific recommendation about added sugars (only sweetened beverages were reduced in DASH); 3) specify that > 75% of grains should be whole grain and 4) advise lean protein with plentiful essential amino acids (especially branched chain amino acids, BCAAs) and to spread the protein intake throughout the day.[50] The protein component is based on BCAAs' well-known role in muscle protein synthesis and to help alleviate the muscle loss that accompanies ADT use. Additionally, skeletal muscle synthesis is more efficient when amino acid intake is spread throughout the day, particularly in older individuals.[50] Sample menus will be provided across a range of estimated daily kcal (e.g., 2000, 2200). Information on the participant's body weight, age and usual physical activity level will be used to calculate an individualized caloric need for weight maintenance for each. This calorie level will be explained to each participant as incorporated into the DASH curriculum and will be updated to accommodate changes to the participant activity level and/or weight as the study progresses. The modified-DASH diet can be adapted to participant food preferences, dietary restrictions, cultural values (e.g. Kosher, Halal) and cost.[51]

Physical Activity. The physical activity goals are to increase daily moderate to vigorous aerobic activity to at least 150 minutes/week; and to engage in strength/resistance training at least three times per week. One-on-one physical activity instruction will be provided by an exercise physiologist at the Fred Hutch PC. In-person training is critical to properly demonstrate safe resistance training and to receive an aerobic prescription suitable for each participant. Learning specific aerobic and resistance exercises will be coupled with behavioral skills instruction in setting and adhering to goals, making active choices, introducing variety and tools for motivation. Study staff have experience working with cancer patients in active treatment. If at any time, participants experience undue fatigue or other treatment-related symptoms, the exercise regimen will be altered as needed. In addition, participants may complete up to 21 supervised (but not one-on-one) exercise sessions at the Fred Hutch PC. Alternatively, the supervised exercise sessions can be completed at the VA Clinical Research Unit (CRU), which is a comparable exercise facility. At each exercise session, study staff will weigh the participant, and participants will record their activities completed (Exercise Training Record within the Triple-A Supplemental PA)

### 4.7 Controls.

Written information (Triple-A Controls) on standard healthy lifestyle recommendations will be provided along with a 20-30 minutes individual session with a dietitian including 1) US Dietary Guidelines (www.dietaryguidelines.gov); 2) Activity goal of 30 minutes of physical activity 5 days/week; and 3) Discussion of the health benefits of weight maintenance.

### 4.8 Compliance.

Compliance to dietary and physical activity goals will be evaluated by weight, which will be measured at each session, check-ins with the study dietitian and exercise physiologist, and self-monitoring through diet (Triple-A diet daily log within the Triple-A Nutrition Intervention) and physical activity tracking (Triple-A PA daily log within the Triple-A PA Intervention). Formal compliance will be assessed by the 4-day food record (Food Record) and exercise questionnaire (Triple-A PA questionnaire).

## 5. DATA COLLECTION

This study involves a total of two participant visits.Study visits will occur at baseline and at the end of study (6-months), where participants will undergo assessments of anthropometrics, collection of fasting blood and completion of study questionnaires. At the mid-study timepoint (month 3) participants will complete questionnaires remotely.

Twelve-hour fasting blood. Fasting blood samples will be collected at baseline and 6 months at the Fred Hutch. Vacutainers will be labeled with participants' study ID and date, processed within 1 hour of collection and stored at -80ºC.

Stool sample. Stool samples will be collected by participants at home prior to the clinic visits at baseline and 6 months. Vacutainers will be labeled with participants' study ID and date, stored within 1 hour of receipt at -80ºC.

Questionnaires:

Food Record. All participants will complete a 4-day food record at baseline and 6 months.

Triple-A PA questionnaire. Physical activity will be assessed at baseline and 6 months with a self-administered administered physical activity questionnaire, the Community Healthy Activities Model Program for Seniors Physical Activity Questionnaire for Older Adults (CHAMPS),[52] which assesses a variety of physical activities that are meaningful and appropriate for older adults. For participants assigned to the intervention arm, resistance and aerobic activities will also be documented during supervised exercise sessions.

Triple-A lifestyle questionnaire. Race/ethnicity, education, smoking, alcohol use and family history of prostate cancer will be assessed at baseline only.

Triple-A Exit survey. Participants will be asked about their experience in the study, and for participants in the intervention arm – challenges they experienced with the intervention.

### 5.1 Outcomes

#### 5.1.1 Blood Biomarkers

Blood markers of glucose, insulin, hemoglobin A1c, triglycerides and total, LDL- and HLD-cholesterol will be analyzed by the University of Minnesota Advanced Research and Diagnostics Laboratory. Homeostatic model assessment of insulin resistance (HOMA-IR) will be computed from glucose and insulin concentrations.

#### 5.1.2 Body Composition and Anthropometrics

Height will be measured at baseline only, and weight and waist (1" above umbilicus) circumferences will be measured at baseline and 6 months. Dual x-ray absorptiometry (DXA) using a GE Lunar DXA will be obtained to measure body fat and lean mass at baseline and 6 months.

#### 5.1.3 Patient Reported Outcomes.

Triple-A QOL questionnaire. Patient reported outcomes including quality of life and fatigue will be measured at

baseline, month 3 (mid-study) and at 6 months (end of study). This questionnaire will be based on the Expanded Prostate Cancer Index Composite (EPIC)-26 Short Form, including prostate and ADT-specific questions[53] and the Functional Assessment of Chronic Illness Therapy (FACIT) fatigue scale, measuring fatigue.[54]

### 5.1.4 Microbiome

Stool DNA will be extracted from the stool samples. The gut microbial community will be characterized by sequencing the 16SRNA and comparing the readouts between the intervention and comparison groups.

## 6. PARTICIPANT RISKS AND BENEFITS

### 6.1 Potential Risks

1. Participants may experience a little discomfort or have a temporary bruise from having blood drawn. Occasionally a participant may feel lightheaded or feel faint when having blood drawn.
2. Participants in the intervention arm may experience fatigue, muscle soreness, and possible joint or skeletal injury, injury from exercise (such as a fall) or a medical event during exercise at home or in the VA Clinical Research Unit or the Fred Hutch Prevention Center.
3. Participants in the intervention arm may experience fatigue, muscle soreness, and possible joint or skeletal injury or other unspecified medical events.
4. Some participants may feel that coming to clinic visits (including the nutrition and physical activity curriculum training sessions) may be inconvenient and/or burdensome.
5. Other potential risks are associated with the collection of personally identifiable and health information from the subjects, and the potential for financial and/or employment risk, as a breach of confidential information could make it harder for the subject to find health insurance, life insurance, or employment.

### 6.2 Protection Against Risks

In the event that this research activity results in an injury, medical treatment will be available, including first aid, emergency treatment and follow up care, as needed. All procedures involving blood collection, DXA and anthropometry will be done at the Fred Hutch Prevention Center Clinic. Trained staff will be available to assist should a medical emergency occur. An MD licensed in Washington State is the Prevention Center Director. Participants will be informed in the written consent form that payment for any such treatment must be provided by the individual and/or the individual's insurance company.

1. Blood draws are associated with certain physical risks such as bruising, fainting, or phlebitis. We will minimize these risks by making sure that all blood draws will be conducted by well-trained phlebotomists at the Fred Hutch Prevention Center. Subjects will be asked before the blood draw if they have experienced problems with blood draws in the past and will be offered an opportunity to lie down during the procedure if they wish. In our experience, blood draws performed in this manner are well tolerated, and any side effects are minimal. Participants should be able to tolerate the loss of 10-20 cc of blood without negative health consequences.

2. We will screen participants so that persons with significant cardiovascular disease that would preclude exercise, will be excluded from participation in this study. The risks associated with the exercise intervention will be reduced by proper warm-up/cool-down periods, instruction from a trained exercise specialist at a slow-paced progression which will be determined by the participants' current fitness level and careful monitoring by an exercise specialist. The exercise specialists will teach participants techniques to minimize joint or muscle injury.

   In the extremely rare and unexpected event of an emergency while participants are attending to the Fred Hutch Prevention Center, a staff member and study staff will be on hand at all times throughout the visit to call for help as needed, and a physician will be on call. For complications arising among subjects that have left clinical facilities, participants will be provided with the telephone numbers of the study PIs and

the study coordinator and will be encouraged to call with any problems at any time. Participants will be encouraged to call 911 in case a life-threatening emergency occurs; such an event is unlikely, and it would be extremely unlikely to be related to the study procedures.

3. We will make every effort to schedule participants to come to the FHCRC at times that are convenient for them. This includes all sessions with the study dietitian and exercise specialist.

4. To minimize the risk of breach of confidentiality, we will make sure that all health information and records are labeled with a study identification number only. Personally identifiable information will be kept physically separate from any health information, and only one computer file will link the study identification number to the personally identifiable information such as name, address, telephone.

### 6.3 Benefits

The data generated from this proposed research study will provide the data necessary to inform the final design, power, sample size and endpoints for a fully powered randomized controlled trial in newly diagnosed prostate cancer patients receiving RT + ADT.

Our long-term research and clinical goals are to reduce the morbidity and mortality from prostate cancer. This pilot will provide much needed preliminary data to support an R01. We expect that the future R01 RCT results could lead to practice changing paradigms for newly diagnosed prostate cancer patients receiving radiation + ADT as primary curative-intent treatment. Demonstration that the intervention intercepts the abrupt metabolic and physiologic changes could be widely disseminated to allow more men to receive the most effective cancer therapy without compromising their overall health.

### 6.4 Compensation

Participants will be paid $100 total (25$ at the baseline visit, and 75$ at the 6-month visit) to help compensate for time and travel.

### 6.5 Alternatives

Alternatives to participating in this research study include not participating

## 7. DATA ANALYSIS PLAN

This pilot trial tests whether a nutrition and physical activity intervention initiated concurrently with RT+ADT will intercept ADT-induced metabolic and physiologic abnormalities compared to control. We expect clinically meaningful changes in the control arm and minimal to no changes in the intervention arm, as the primary intervention goal is prevention. To test the intervention effects for our aims, we will use this difference in differences approach, which accounts for expected temporal changes in the biomarkers and body composition measures in the control arm.[55]

1. The effects of the intervention on ADT-induced changes in HOMA-IR will be evaluated using linear regression models with adjustment for the baseline biomarker.
2. The effects of the intervention on ADT-induced changes in body weight and composition will be evaluated using linear regression models. Separate models will be fit for each measure, with an indicator variable for study arm (intervention/control) and adjustment for the respective body composition measure.

As exploratory aims, we will explore intervention effects on blood lipids HbA1c, patient reported outcomes and gut microbiome will be evaluated using linear regression models. Separate models will be fit for each biomarker, with an indicator variable for study arm (intervention/control) and adjustment for the respective baseline biomarker. Further adjustment for biomarkers that may have shared biology (i.e. total and LDL cholesterol) and for medication use that could affect biomarker concentrations will be considered.

We expect most potential confounding variables will be evenly distributed between arms at randomization, but

this assumption will be checked prior to analysis. Analyses will follow an intent-to-treat approach, tests will be 2-sided and statistical significance will be set at $P<0.05$.

### 7.1 Sample Size

For this pilot trial with a fixed sample size of 20 participants total (10 per arm), we estimate that we will have 80% power to detect a minimum detectable difference in differences in HOMA-IR (intervention effect) between intervention and control participants of 2.6 (HOMA-IR is unitless). Power calculations used R (package::function) stats::power.t.test for t-tests and assumed a standard deviation of 1.4, pre-post correlation of 0.5 and 2-sided α=5%.

## 8. DATA SAFETY MONITORING PLAN

Oversight for this study will be provided by the Principal Investigators, Drs. Marian Neuhouser and Jonathan Wright, with delegation of responsibilities to designated study personnel. Study PIs will ensue all entry criteria are met prior to the initiation of the protocol, and all study procedures and reporting of adverse events are performed according to the IRB-approved protocol.

Institutional support of trial monitoring will be in accordance with the Fred Hutch/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, Fred Hutch Clinical Research Support coordinates data and compliance monitoring conducted by consultants, contract research organizations, or Fred Hutch employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP. Study participants are prostate cancer patients undergoing ADT + RT, in whom the study intervention is non-therapeutic. The study is low risk, per the Consortium DSMP guidelines.

### 8.1 Adverse Event Reporting

All adverse events related to the study procedures will be fully documented on the appropriate case report form(s) and entered in a study database. For each adverse event, the investigator will provide the onset, duration, intensity, treatment required, and outcome, including documentation of need for premature termination of any study procedures. Anticipated adverse events for this study are expected to be very minimal since the diet and physical activity intervention activities have been safely used in many previous intervention studies without incident. Despite the low risk for adverse events, all study staff and investigators will carefully monitor and document any adverse events, which could include the following: bruising or fainting during the blood draws, injury from using the exercise equipment in the PHS Exercise Laboratory, injury from exercise at home (such as a fall) or a medical event during exercise in the PHS exercise Laboratory. Serious Adverse Events will be reported within to the Principal Investigator within 24 hours. Adverse event reporting to the IRO will occur within the required period of time depending on the nature and severity of the event.

### 8.2 Plan for safety review

The PIs will perform a cumulative review of all adverse events and premature terminations review every 6 months after study initiation.

### 8.3 Plan for annual reporting

A summary of the investigation including all adverse events and how they were handled, enrollment, drop-outs and reason for discontinuation and any protocol modifications will be provided to the IRB on an annual basis. Annual Reports will contain:

a. The number of adverse events and an explanation of how each event was handled
b. The number of complaints and how each complaint was handled
c. The number of subject withdrawals and an explanation of why the subject withdrew or was withdrawn
d. The number of protocol deviations and how each was handled

### 8.4 Monitoring for data integrity and safety

Monitoring for data integrity and safety will be the responsibility of the investigators. Investigators will include the following in routine monitoring review: A) Validity and integrity of data: Data are checked for missing, unusual, or impossible values when they are entered into the study's computer database. B) Enrollment rate relative to expectation: Early lags in recruitment will be rectified with increased recruitment efforts so that recruitment will be completed on time. The investigators will monitor this closely to ensure full enrollment of appropriate participants. C) Retention of participants and adherence to protocol: The investigators will monitor retention and adherence to study protocol. Adherence to the intervention will be monitored via participant weight, nutrition and physical activity visits.

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