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Personalized Risk Estimator for Rheumatoid Arthritis (PRE-RA) Family Study: Rationale and design for a randomized controlled trial evaluating rheumatoid arthritis risk education to first-degree relatives

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ABSTRACT

We present the rationale, design features, and protocol of the Personalized Risk Estimator for Rheumatoid Arthritis (PRE-RA) Family Study (ClinicalTrials.gov NCT02046005). The PRE-RA Family Study is an NIH-funded prospective, randomized controlled trial designed to compare the willingness to change behaviors in first-degree relatives of rheumatoid arthritis (RA) patients without RA after exposure to RA risk educational programs. Consented subjects are randomized to receive education concerning their personalized RA risk based on demographics, RA-associated behaviors, genetics, and biomarkers or to receive standard RA information. Four behavioral factors associated with RA risk were identified from prior studies for inclusion in the risk estimate: cigarette smoking, excess body weight, poor oral health, and low fish intake. Personalized RA risk information is presented through an online tool that collects data on an individual's specific age, gender, family history, and risk-related behaviors; presents genetic and biomarker results; displays relative and absolute risk of RA; and provides personalized feedback and education. The trial outcomes will be changes in willingness to alter behaviors from baseline to 6 weeks, 6 months, and 12 months in the three intervention groups. The design and the execution of this trial that targets a special population at risk for RA, while incorporating varied risk factors into a single risk tool, offer distinct challenges. We provide the theoretical rationale for the PRE-RA Family Study and highlight particular design features of this trial that utilize personalized risk education as an intervention.

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1. Introduction

Rheumatoid arthritis (RA) is an autoimmune polyarthritis affecting about 1% of the population, which often leads to significant pain and disability [1]. While the etiology of RA is unknown, many epidemiologic factors have been associated with the development of RA. Having a first-degree relative with RA is associated with about a four-fold increased personal risk of RA [2,3]. This increased RA risk in first-degree relatives may be due to shared genetic or environmental factors. Many genetic factors have been associated with RA; however, the presence of the "shared epitope" alleles at *HLA-DRB1* most potently increases RA risk [4,5]. Environmental factors such as cigarette smoking, excess body weight, periodontitis, and low fish intake are associated with increased risk of RA [6–10]. Individuals with RA-related auto-antibodies, rheumatoid factor (RF), and anti-cyclic citrullinated peptide (anti-CCP), detectable in the serum prior to symptom onset, are at especially elevated risk of RA [11].

Prior studies suggest that modifiable behaviors may account for a substantial proportion of RA risk. About 25% of RA risk may be due to cigarette smoking alone, while a combination of risk factors (smoking, alcohol intake, obesity, and reproductive factors) may account for up to 41% of RA risk [12,13]. Genetic risk is estimated to account for 50% of RA risk based on twin studies [14]. RA prediction models composed of genetic and environmental factors can accurately distinguish RA cases from controls when performed among RA first-degree relatives, suggesting these factors are useful in RA prediction among this population [15]. Personalized risk education may be an important method to encourage those at increased RA risk to change behaviors to potentially modify their risk. Family history of a disease, in the context of personalized risk education, may be an important motivating factor for encouraging individuals to adopt positive health behavior changes [16].

The Personalized Risk Estimator for Rheumatoid Arthritis (PRE-RA) Family Study aims to assess whether first-degree relatives (FDRs) of RA patients are willing to change RA-related behaviors based on their personalized RA risk. Our goal is to evaluate educational interventions that use personalized RA risk education based on demographics, behaviors, genetics, and autoantibodies among FDRs. We ascertain RA knowledge, risk attitudes, and behaviors of RA FDRs. We describe the development of a personalized RA risk tool and study measures for use in this randomized controlled trial. This study is important for providing a rationale for RA prevention efforts and incorporating many epidemiologic risk factors for a complex disease in a prospective, clinical trial.

2. Design and methods

2.1. Aim and design

The PRE-RA Family Study will evaluate whether RA risk education will affect willingness to change RA-associated behaviors using a randomized controlled trial. The study consists of three arms of RA education interventions (see Fig. 1). All aspects of the study were approved by the Partners Healthcare Institutional Review Board.

2.2. RA-associated risk factors

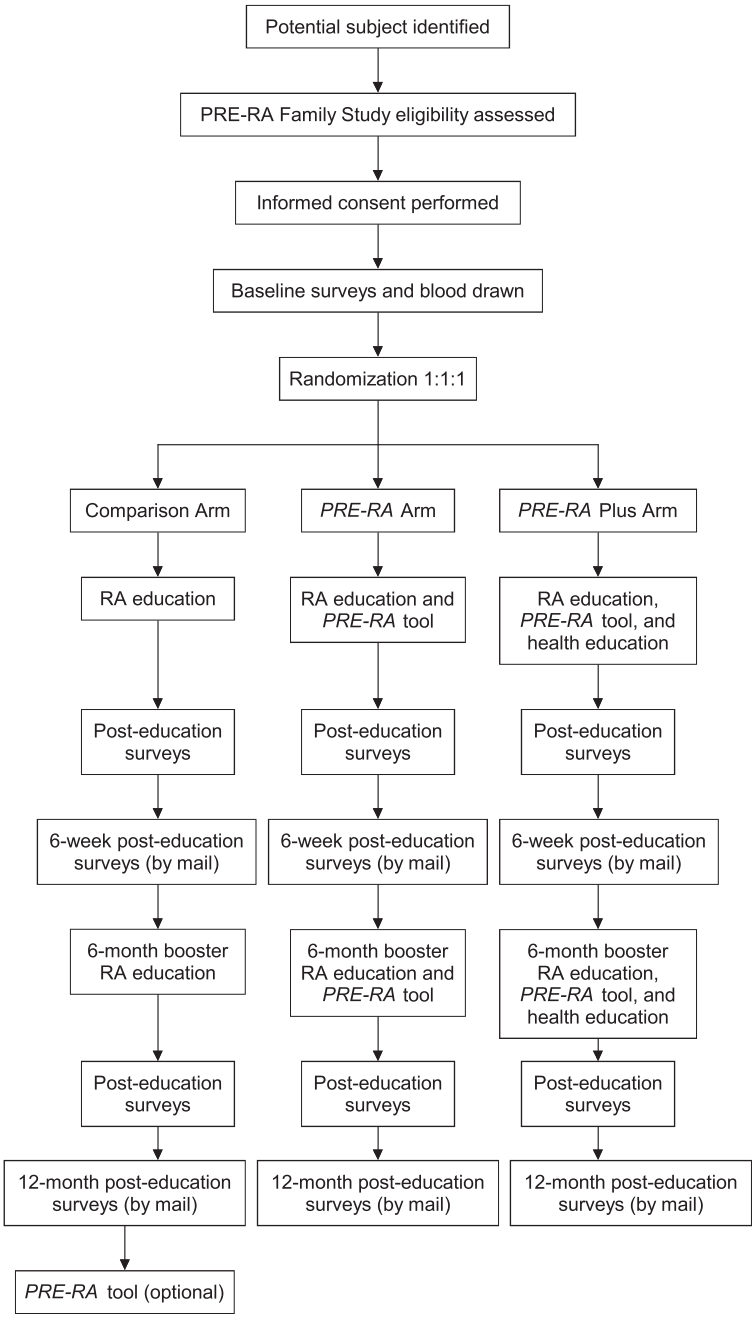
Table 1 summarizes the background and rationale of RA-associated risk factors utilized in the PRE-RA Family Study.

RA is about twice as prevalent in females than in men, perhaps due to hormonal and reproductive factors [1]. RA also becomes more common with increasing age, with peak incidence in the fifth decade [17]. Having an FDR with RA increases the personal risk of RA by about 4-fold compared to those without an affected FDR [3,13].

Genetic variants in the major histocompatibility complex (MHC) region on chromosome 6 are associated with RA susceptibility and are referred to as the "shared epitope" [37]. MHC polymorphisms in *HLA-DRB1*, in particular, are highly associated with RA [5]. Large genetic consortia have identified 101 other single nucleotide polymorphisms (SNPs) that are associated with RA [4]. However, most of these SNPs are only modestly associated with RA and offer little clinical ability to predict RA compared to the shared epitope. For this reason, we operationally defined high-risk RA genetics as the presence of any shared epitope allele [5]. Previous studies exploring genetic risk disclosure did not show any short-term increase in psychological distress after disclosing to individuals their high genetic risk status for Alzheimer disease [38].

RA patients typically present clinically once symptoms of arthritis develop. However, immune dysregulation, as measured by the presence of the RA-related autoantibodies, rheumatoid factor (RF), and anti-cyclic citrullinated peptide antibody (anti-CCP), occurs about 3–14 years prior to the onset of joint symptoms and clinically apparent RA [19,20]. Patients with arthralgias, but not synovitis, and detectable anti-CCP are six-fold more likely to develop RA after 2 years of follow-up [39]. The presence of RA-related autoantibodies, especially anti-CCP, is highly associated with the future development of RA [11,19,21].

Four lifestyle behaviors associated with RA are included in this trial: cigarette smoking, excess body weight, low fish intake, and poor oral health. Cigarette smoking has the strongest evidence to support an increased risk for developing RA [6]. Smoking has a dose- and duration-dependent response for RA risk, with heavy smokers at the highest risk [22]. Smoking may contribute up to 25% of the population attributable risk for RA [12]. After about 20 years of smoking cessation, RA risk returns to the risk of a non-smoker, suggesting modifiability [6,22,23]. Obesity, inflammation, and RA have been linked by a variety of mechanisms, including adipokines and chemokines [24–28]. Being overweight or obese is associated with the development of RA [7,27,28]. Consumption of fish may improve RA symptoms and delay RA progression [40–42]. Oily fish intake may provide RA protection, perhaps due to the anti-inflammatory effects of omega-3 polyunsaturated fatty acids [9,10,29,30]. RA-related autoimmunity has been associated with tissue inflammation and injury at sites other than the joints. There is a consistent association between periodontal disease and RA [8,31–33]. *Porphyromonas gingivalis*, a bacterium that causes periodontitis, may mediate citrullination of peptides and lead to the development of RA-related autoimmunity [34–36].



PRE-RA, Personalized Risk Estimator for Rheumatoid Arthritis; RA, rheumatoid arthritis.

Fig. 1. Study scheme for the PRE-RA Family Study.

2.3. Theoretical basis of behavioral change

Health promotion interventions grounded in social and behavioral science theory are superior in changing target behaviors compared to those lacking a theoretical base [43–45]. The Theory of Reasoned Action and the Theory of Planned Behavior hold that the most proximal predictor of behavior is behavioral intention [46,47]. Behavioral intention is predicted by attitudes toward the behavior (affective and instrumental evaluations of performing the behavior), subjective norms (perceived social pressure on whether to perform the behavior), and perceived behavioral control (perceived ease or difficulty of performing the behavior). These theories were combined with the Trans-Theoretical Model to understand levels of motivation for behavioral change [48,49]. The Trans-Theoretical Model describes five discrete "stages of change": pre-contemplation, contemplation, preparation, action, and maintenance. The order in which internal factors are addressed has implications for the likelihood of sustaining change. Individuals in a higher stage of change for one behavior are likely to be in a higher stage for other

Table 1
RA risk factors and rationale for inclusion in the PRE-RA Family Study.

Risk factor	Background and rationale
Demographics	
Age	Risk of RA increases with increasing age [17].
Gender	RA is twice as common in females than in males [1].
Family history of RA	RA risk is about 4-fold higher with an RA-affected first-degree relative compared to no affected relatives [3].
Biomarkers	
Genetics (*HLA-DRB1*)	Major histocompatibility complex polymorphisms on chromosome 6 at *HLA-DRB1* (the shared epitope) are highly associated with RA [5]. The shared epitope explains 12% of the genetic risk for RA, compared to only 4% from all other known RA genetic loci [18].
Rheumatoid factor (RF)	RA-related autoantibodies, RF and anti-CCP, can predict the onset of joint symptoms and clinically apparent RA [19,20].
Anti-cyclic citrullinated peptide (Anti-CCP)	Presence of anti-CCP while asymptomatic increases the risk of developing RA by about 16-fold [11,19,21].
Modifiable	
Cigarette smoking	Strong evidence supports an association of smoking with RA development [6]. After 20 years of smoking cessation, RA risk returns to the risk of a non-smoker, suggesting modifiability [6,22,23].
Overweight/obesity	Increased body mass index, inflammation, and RA are linked by a variety of mechanisms, including adipokines and chemokines [24–28]. Several studies associate overweight and obesity with RA development [7,27,28].
Low fish intake	Oily fish intake has a protective effect for RA, perhaps due to omega-3 polyunsaturated fatty acids [9,10,29,30].
Periodontitis	Periodontal disease has been consistently associated with RA [31–33]. *Porphyromonas gingivalis*, a bacterium that causes periodontitis, may mediate citrullination of peptides that leads to the development of RA-related autoimmunity [34–36].

Anti-CCP, anti-cyclic citrullinated peptide; RA, rheumatoid arthritis; RF, rheumatoid factor.

types of behaviors, supporting studies that aim to address multiple behaviors with a single intervention [50].

2.4. Setting and study sample

The PRE-RA Family Study is a single center study at Brigham and Women's Hospital (BWH) in Boston, Massachusetts. Potential subjects are targeted by identifying RA patients at BWH, a large academic rheumatology center in Boston, Massachusetts, and recruiting their FDRs. Rheumatologists see patients at the Robert Breck Brigham Arthritis Center at BWH and affiliated rheumatology clinics: the Arthritis and Orthopedic Center at Brigham and Women's Faulkner Hospital, the 850 Boylston Arthritis Center, the Fish Center for Women's Health at 850 Boylston, and the BWH Arthritis Center at Braintree.

2.5. Study eligibility

We focus the PRE-RA Family Study on FDRs of RA patients for several reasons: (1) increased risk of RA in FDRs and motivation to participate in prevention trials, (2) FDRs are intimately familiar with RA due to interaction with their RA-affected relatives, and (3) FDRs are likely to be motivated to change behaviors after education about RA associations. Eligible subjects for the PRE-RA Family Study must be a blood-related FDR of an RA patient and be 18–70 years of age. We limited participation to these ages since RA is an adult disease and lifetime risk of RA is less applicable once age is advanced (see Table 2 for full eligibility requirements). More than one FDR with the same affected RA family member can enroll in the PRE-RA Family Study.

Our materials and intervention were developed in English, so non-English-speaking individuals are not eligible. All potential subjects are screened for RA using the modified Connective Tissue Disease Screening Questionnaire (CSQ) [51]. Those who screen positive on the modified CSQ are assessed by a study rheumatologist (JAS or EWK) and, if there is suspicion for RA or other systemic rheumatic disease, are formally referred to a rheumatologist and deemed ineligible for the study. Those already diagnosed with a systemic rheumatic disease that might cause inflammatory arthritis are not eligible for the study (FDRs with other diseases not listed in Table 2 may be deemed ineligible at the study physicians' discretion). RA and these diseases have similar signs, symptoms, and treatment, so FDRs would be unlikely to benefit from RA prevention efforts.

2.6. Randomization

Study staff determines whether a subject meets eligibility criteria and subjects provide informed consent (Table 2). The randomization of subjects to arm assignment occurs after the baseline visit is completed (see Fig. 1 for study schematic). We use permuted block randomization in SAS version 9.2 for Windows (Cary, North Carolina, USA). If two or more subjects participate from the same family, study staff instructs these subjects not to discuss content of their education or results with their family members. At this writing, the PRE-RA Family Study is currently enrolling subjects for the trial.

2.7. Interventions and study arms

2.7.1. Development of PRE-RA tool

The PRE-RA tool was adapted from Your Disease Risk (http://www.yourdiseaserisk.wustl.edu), a website that provides personalized risk estimates for twelve different types of cancer, heart disease, type 2 diabetes mellitus, stroke, chronic bronchitis/emphysema, and osteoporosis based on demographics, anthropometrics, family history, and behaviors [52,53]. We customized the Your Disease Risk framework for the PRE-RA Family Study by adding biomarkers, new result pages, and interactive RA educational

Table 2
Inclusion and exclusion criteria for the PRE-RA Family Study.

Inclusion criteria	Rationale
First-degree blood relative with RA	Population at increased RA risk, familiar with RA, motivated to participate
Age between 18 and 70 years	RA is an adult disease, future risk of RA not applicable to population advanced in age
Exclusion criteria	**Rationale**
Non-English speaking	Interventions only available in English
Signs/symptoms compatible with RA*	Evaluation for RA by rheumatologist more appropriate than RA prevention efforts
Systemic rheumatic disease (including but not limited to RA, systemic lupus erythematosus, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, mixed connective tissue disease, scleroderma, reactive arthritis, adult-onset Still's disease, Sjögren's syndrome, dermatomyositis, polymyositis, polymyalgia rheumatica, ANCA-associated vasculitis, giant cell arteritis, polyarteritis nodosa, Behçet's disease, relapsing polychondritis)	Similar diseases to RA, subjects unlikely to benefit from RA prevention efforts

ANCA, anti-neutrophil cytoplasmic antibody; RA, rheumatoid arthritis.
* Assessed by modified Connective Tissue Disease Screening Questionnaire (CSQ) [51] and determined by study physicians.

materials. Questions on the website ask about risk factors, and responses are linked to relative risks, each of which represents the strength of the association between a risk factor and the disease.

The formula used to calculate an individual's relative risk (RR) of RA compared to the reference population, as previously developed for Your Disease Risk, is [54]

$$RR = \frac{RR_{I1} \times RR_{I2} \times \ldots \times RR_{In}}{[(P_1 \times RR_{C1}) + (1-P_1) \times 1.0] \times [(P_2 \times RR_{C2}) + (1-P_2) \times 1.0] \times \ldots \times [(P_n \times RR_{Cn}) + (1-P_n) \times 1.0]}$$

where RR_{In} is the individual's (I) assigned relative risk for each risk factor (denoted as n and based on its presence or absence), RR_{Cn} corresponds to the consensus-based (C) relative risk for each risk factor based on literature review, and P_n represents the estimated prevalence of each risk factor (n) based on literature review. For our study, calculations are stratified based on the individual's age (in 10-year blocks by decade) and sex. See example calculation in the Supplemental material.

The result (RR) is a single value that compares the user's personal risk to that of the average person of the same age and sex. Levels of risk are depicted by colors and text (Fig. 2a). Education on the website is tailored based on the risk factor profile of the user.

The intervention developed for this study differs from the diseases previously included on Your Disease Risk. Our study sample is already at an increased risk of RA by having at least one FDR with RA, so comparing RA risk to the general population was not appropriate. Thus, for our main result page, we consider the reference group to be FDRs (Fig. 2a). After pilot testing and reviewing the literature for methods of genetic risk communication, we determined that a second result page was needed to maximize risk interpretation for those with varying levels of numeric literacy [55]. We therefore include a lifetime absolute risk of RA calculation. This is computed based on residual lifetime risk at the user's age and sex on a cumulative hazard scale multiplied by the previously calculated relative risk (see Supplemental material) [17]. To enhance interpretability, the page displays both a pictogram and the number out of 100 who would develop RA in their lifetime based on their demographics, family history, behaviors, genetics, and autoantibodies (Fig. 2b) [17]. Unlike other diseases on Your Disease Risk, the PRE-RA tool utilizes laboratory data (genetics and autoantibodies) in addition to demographics, family history, anthropometrics, and behaviors. To focus the existing result pages on the potential modifiability of RA risk from behaviors, we developed separate result pages for genetics and autoantibodies.

For each subject, the study staff input personalized results for genetics, RF, and anti-CCP into PRE-RA. The tool provides subjects with interactive educational text and graphics developed for the study pertaining to many aspects of RA: symptoms, prevalence, treatment, prevention, and screening. Subjects input information about age, sex, height, weight, and family history of RA and other autoimmune diseases associated with RA for each first-degree blood relative, including relatives without RA [2]. Subjects answer questions about physical activity based on the Nurses' Health Study Physical Activity Questionnaire [56]. Diet is assessed using an adapted version of the PrimeScreen questionnaire with more detailed questions on fish intake and supplements based on the Food Frequency Questionnaire [57,58]. Dental health questions are based on validated questionnaires on oral health behaviors and dental history as they pertain to the risk of periodontitis [59]. Questions concerning quantity and duration of cigarette and cigar smoking were developed by Your Disease Risk [60].

After completing all questions on the PRE-RA tool, subjects are guided to the personalized genetics result page based on positive (presence of any shared epitope allele) or negative shared epitope. Subjects are provided with education about genetics and how genetic markers may impact their RA risk. Subjects receive autoantibody results (positive RF/anti-CCP or both negative) on a separate personalized result page. All subjects are directed to the RA relative risk result page (Fig. 2a), which is customized based on all data previously entered. This page is designed to be interactive, so that clicking on risk behaviors ("Watch Your Risk Drop" check boxes) shows how much their risk might be reduced if the subject eliminated that behavior. Subjects can click on links to summary pages about how their personal RA risk was calculated and which behaviors contributed to this calculation (either increasing or decreasing risk). Subjects are offered tips on how to change or maintain behaviors. After this page, subjects are directed to the lifetime RA risk page (Fig. 2b), which

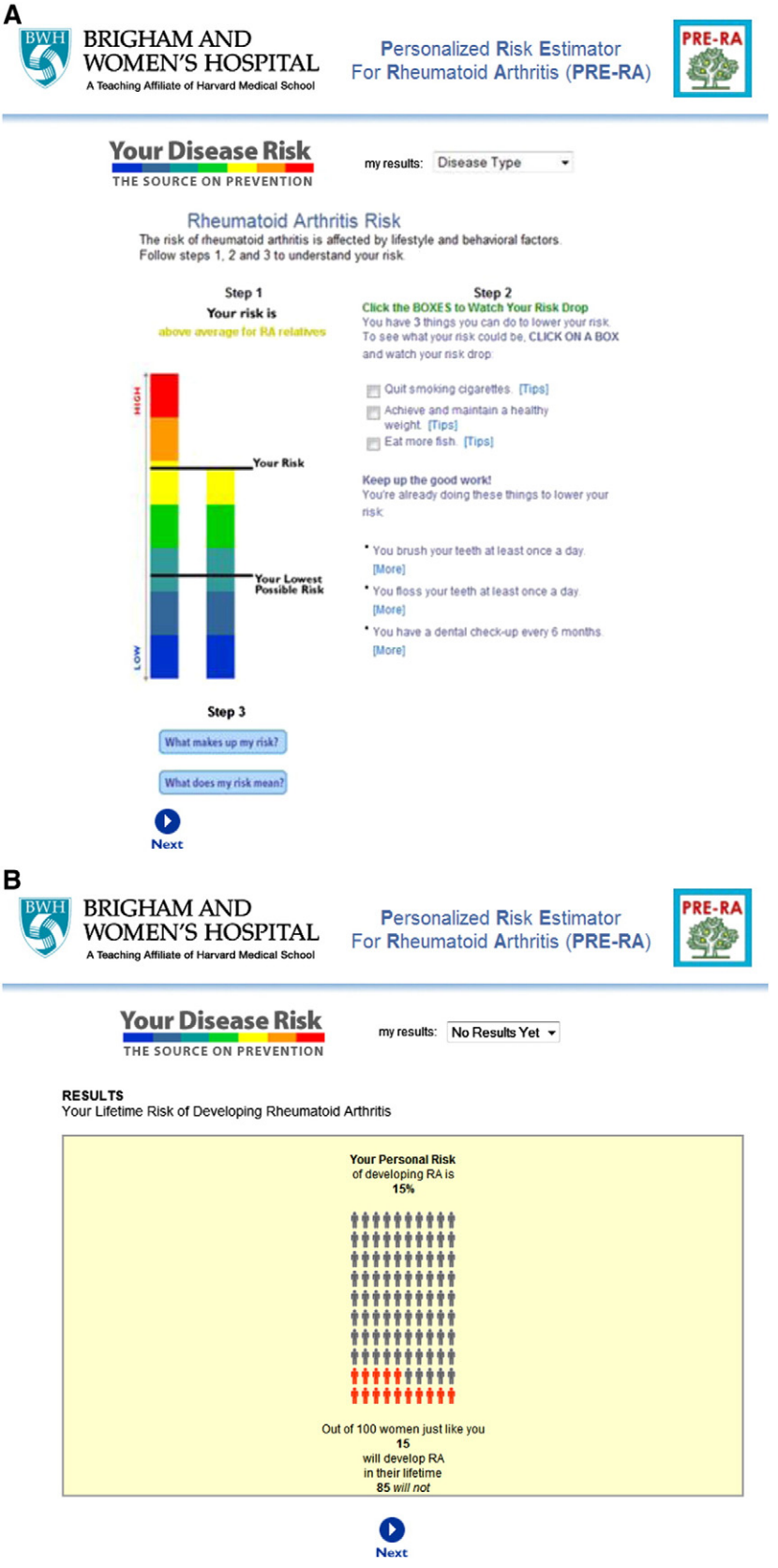


Fig. 2. Sample results pages of the PRE-RA tool showing relative risk of RA (A) and lifetime risk of RA (B).

provides a pictograph and a percentage estimate of RA risk based on their personalized risk factor profile. The last page of this series offers summary education about each behavior's association with RA and more tips for changing behaviors. All subjects that complete the PRE-RA tool are given their personalized RA relative risk and lifetime absolute risk results pages as well as genetic and autoantibody results pages, if positive.

2.7.2. Comparison Arm

Subjects randomized to the Comparison Arm serve as the comparison group for the PRE-RA Family Study. These subjects receive standard education about RA. To maintain consistency, we utilize RA educational material presented in the PRE-RA tool. This information is given as an oral presentation and in a pamphlet. RA oral education consists of signs and symptoms, treatment, screening, and prevalence. Specific information on RA behavioral risk factors, genetics, and autoantibodies are not presented, as is typical for standard practice. We decided to randomize subjects to arms after the baseline visit and blood draw and perform the same testing on all subjects to offset possible differential attrition due to lack of attention in the Comparison Arm. These subjects are given the option of completing the PRE-RA tool at the conclusion of their contribution to the study.

2.7.3. PRE-RA Arm

Subjects in the PRE-RA Arm of the study receive the PRE-RA tool as an intervention. After the PRE-RA tool is completed, these subjects receive a printed version of their PRE-RA tool result pages including relative and absolute risk figures as well as genetic and autoantibody results pages, if positive (Fig. 2).

2.7.4. PRE-RA Plus Arm

Subjects in the PRE-RA Plus Arm of the PRE-RA Family Study receive the most intensive educational intervention. This education consists of the PRE-RA tool and directed education from a health counselor (RMK). After the PRE-RA tool is complete, subjects undergo an interactive presentation personalized to their behaviors and the results attained from the PRE-RA tool. This education includes interpretation of genetic and autoantibody blood tests. Subjects are given the rationale of how behaviors might increase or decrease risk of RA as well as tips on changing and sustaining these behaviors. At the end of the educational session, subjects are given material to take home on each behavior and tips on changing or maintaining a healthy lifestyle as well as the results pages from the PRE-RA tool.

2.8. Measures

Table 3 details the administration schedule for all measures in the PRE-RA Family Study.

2.8.1. Development of measures and educational materials

The survey, website, and educational materials were developed using an iterative process. Materials were drafted using adult learning principles and cognitive interviewing among focus groups of pilot phase subjects [61–63]. A total of 39 subjects participated in the pilot testing. The study's behavioral scientist (MDI) developed an interview guide and structured training sessions for study team members using concurrent and retrospective recall methods. Study team members who provide the interventions were trained in cognitive interviewing through a series of sessions to refine the study materials and PRE-RA tool. For example, subjects were asked to read survey directions aloud and restate directions to each section in his/her own words. When answering the survey, the subject was instructed to read each item and to circle an item if he/she thought that the item was too difficult or had problems with item comprehension. During the interview, the study team member observed the subject's affective behavior and documented these behaviors. These data were used to implement specific retrospective probes for the subject. When the subject completed surveys, the interviewer discussed the subject's interpretation of the surveys, using general and specific verbal probes. For example, the interviewer requested the subject to rephrase questions, define meanings of words, and explain his/her responses to identify

Table 3
Assessment schedule for measures, interventions, and outcomes in all arms of the PRE-RA Family Study.

Measures	Time point				
	Baseline	Education/Disclosure[a]	6-week mailing	6-month visit	12-month mailing
Demographics	✓				
Modified CSQ	✓				
REALM-SF	✓				
Computer fluency	✓				
Blood draw	✓				
RA knowledge and attitudes	✓	✓	✓	✓	✓
Decisional balance	✓	✓	✓	✓	✓
RA risk concern		✓	✓	✓	✓
Lifestyle changes		✓	✓	✓	✓
Healthcare utilization			✓	✓	✓
RA education (intervention)[b]		✓		✓	
Contemplation ladders (outcomes)	✓	✓	✓	✓	✓

CSQ, Connective Tissue Disease Screening Questionnaire; PRE-RA, Personalized Risk Estimator for Rheumatoid Arthritis; RA, rheumatoid arthritis. REALM-SF, Rapid Estimate of Adult Literacy in Medicine-Short Form.

[a] Subsequent mailings and visit are based on the date of education/disclosure.

[b] Subjects are randomized to either general RA education, PRE-RA, or PRE-RA Plus.

difficulties in understanding, interpretation or completing the surveys [61].

Study team members observed and recorded pilot subjects' affective behaviors while navigating the PRE-RA tool web pages and embedded educational materials to ascertain whether any features of the site were difficult to use or comprehend [64,65]. Staff prompted subjects to share their thoughts as they moved through the site and express to staff how they understood the information communicated to them through the thermometer and pictographs. From these qualitative data, the team discovered that subjects were skipping some interactive portions of the tool, thus missing critical opportunities for behavior change motivation. The results pages were refined to guide subjects to participate in interactive portions of the PRE-RA tool.

2.8.2. Blood collection and laboratory measurements

Once consented, all subjects have blood drawn to test for genetics and RA-related autoantibodies. DNA is extracted and allele level *HLA-DRB1* genotyping is performed by the American Red Cross East Division HLA laboratory using a combination of sequencing based typing (SBT) and sequence-specific oligonucleotide probes hybridization (PCR-SSOP) for HLA alleles associated with RA: *DRB*04:01*, *DRB*04:04*, *DRB*04:05*, *DRB*04:08*, *DRB*01:01*, *DRB*01:02*, *DRB*10:01*, *DRB*14:02*, and *DRB*09* [5]. We define a positive genetic test as the presence of at least one of these alleles.

RF testing is performed at the BWH Clinical Immunology Laboratory by nephelometry and reported in units per milliliter(U/mL). Positive RF is considered as >15 U/mL, the clinical cutoff at BWH. Anti-CCP testing is performed at the BWH Clinical Immunology Laboratory using second generation DIASTAT™ enzyme-linked immunosorbent assay [Axis-Shield Diagnostics Limited, Dundee, UK]. Study sample anti-CCP levels are reported in U/mL. We consider positive anti-CCP as >7 U/mL, the clinical cutoff at BWH.

2.8.3. Contemplation Ladders (outcome measure)

The Contemplation Ladder is a simple visual analog tool based on the Trans-Theoretical Model (see Fig. 3 for cigarette smoking example) [66]. The tool consists of "rungs" representing the stages of behavior change readiness as a progression through pre-contemplation, contemplation, preparation, action, and maintenance phases [49]. A higher score indicates a greater intention to change behavior. This tool demonstrates convergent, concurrent, and predictive validity with stated intentions to quit cigarette smoking and later smoking behaviors [66]. Strong intercorrelations have been reported between the Ladder and a 32-item Stage of Change tool [67]. Validity has been demonstrated with adaptations of the Ladder for alcohol use and substance abuse and with low literacy groups [68–70]. The Contemplation Ladder is specifically tailored to assess health behavior change.

In the PRE-RA Family Study, separate Contemplation Ladders are included for cigarette smoking (Fig. 3), diet, exercise, dental care, health screening for RA, and caffeine (Supplemental material). Only those who smoke or use caffeine are instructed to answer these Ladders. We include caffeine reduction, despite null association with RA, as a control behavior to evaluate whether subjects might be willing to change other behaviors despite not receiving directed education about them [71]. We include RA health screening to gauge willingness of subjects in possible RA prevention studies.

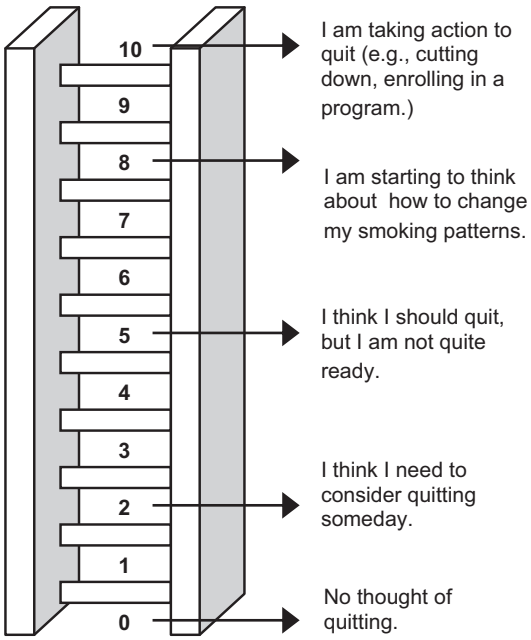


Fig. 3. Contemplation Ladder for cigarette smoking, the outcome measure in the PRE-RA Family Study. Separate Contemplation Ladders for diet, exercise, dental care, health screening for ra, and caffeine are also included in the study (see Supplemental material).

2.8.4. Modified CSQ

The validated CSQ was modified to include only questions pertinent to RA since our study is specific for RA [52,72]. The modified CSQ consists of questions about joint symptoms, morning stiffness, and nodules and includes a homunculus to quantify number and location of painful/swollen joints. If a participant answers affirmatively to any question, a study physician (JAS or EWK) evaluates whether a participant is eligible for the study or should be referred for formal rheumatology consultation. Potential subjects with arthralgias and other musculoskeletal symptoms in the absence of synovitis are considered eligible for the study as long as no other signs or symptoms of RA are present as determined by the study physicians.

2.8.5. Other measures assessed at baseline visit

After all subjects are consented, the Rapid Estimate of Adult Literacy in Medicine-Short Form (REALM-SF) assesses English literacy and reading grade level [73]. Since the PRE-RA tool is web-based, all subjects answer a validated survey about computer, e-mail, and Internet fluency [74].

2.8.6. RA knowledge and attitudes

To assess knowledge of RA, subjects answer questionnaires designed to assess their perception of RA risk for the general population, for an RA FDR, and their individual risk. Attitudes about lifetime risk of other chronic diseases (cancer, diabetes, and heart disease) are also assessed using measures modified for this study [38]. Subjects provide their opinions about causes of RA from a variety of different mechanisms in a validated survey, the Revised Illness Perception Questionnaire, and details of RA in their affected relative and perception of their RA relative's functionality using the modified Health Assessment Questionnaire [75,76]. Concern about subjects' own RA risk and a numerical estimation of RA lifetime risk are obtained. The questionnaire gathers information on subjects' beliefs about the relative contributions of genetics, autoantibodies, and behaviors to RA risk. Finally, the Risk Propensity Scale measures subjects' tolerance of and inclination toward risk scenarios [77].

2.8.7. Decisional balance

Decisional balance consists of eight domains of decision making: gains or losses for self, gains or losses for significant others, self-approval or self-disapproval, and approval or disapproval of others [78]. These domains are measured with five-point Likert scales ranging from not important (1) to extremely important (5) for reasons to change the behavior (pros) and reasons to not change the behavior (cons). Decisional balance is associated with behavioral Stages of Change and is a sensitive marker of movement through stages [49,79]. More cons are reported among subjects in pre-contemplation, but more pros of changing the problem behavior are reported among subjects in contemplation. This suggests that a systematic approach for changing the pros and cons can enable progression from pre-contemplation to action [49]. Decisional balance measures have been used to study the decision-making process for smoking cessation, drug rehabilitation, and breast cancer screening [48,80].

In the PRE-RA Family Study, decisional balance is used to measure barriers and motivating forces for subjects. We utilize decisional balance for the following behaviors: flossing teeth every day, exercising regularly, taking medications to prevent RA, eating fish or taking omega-3 supplements, eating healthily, quitting cigarette smoking, and reducing caffeine intake. Examples of decisional balance for flossing are: may prevent RA, will improve dental hygiene, mouth feels cleaner, and prevents bad breath (pros); takes time/inconvenient, don't like to use dental floss, and no floss available (cons).

2.8.8. Other measures assessed after baseline visit

After the intervention, subjects' RA Risk Concern is measured to determine how they interpret and process their own risk. On follow-up surveys, healthcare utilization evaluates whether subjects might see healthcare providers more often for musculoskeletal complaints following the intervention. While the PRE-RA Family Study is not powered to detect sustainable lifestyle changes, we ask subjects about lifestyle changes that occurred after intervention.

2.9. Recruitment

We identify RA patients through electronic queries who have an upcoming rheumatology clinic appointment at BWH or BWH-affiliated satellite clinics. After attaining physician approval to approach the RA patient, we mail the RA patient study materials to share with family members. Study staff personally meets with the RA patient in clinic to provide further study information. Interested patients and FDRs can also call, e-mail, or mail an intent card that is included with mailed materials. Since our interventions must be performed in person and over multiple study visits, participation is limited to those who are inclined to participate and live in the Boston area or travel to Boston regularly.

While this method efficiently identifies patients with physician-diagnosed RA, it offers other challenges to recruitment. We are unable to directly contact potentially interested family members. Instead, the RA patient must give materials to his or her interested family members. To enhance recruitment, we recruit at BWH-affiliated satellite clinics to increase the number and scope of patients approached, promote the study at officially sanctioned rheumatology foundation events, and use social media (Facebook: https://www.facebook.com/PreRAFamilyStudy) to broaden study accessibility and disseminate study information. We offer remuneration to subjects (for completing each study visit and returned questionnaires as well as parking vouchers for study visits) to increase recruitment, encourage retention, and acknowledge subjects' time and effort.

2.10. Sample size and power calculations

The power analysis is based on the primary outcome, change in Contemplation Ladder scores toward behavior change for any of four behaviors (smoking, dental care, diet, or exercise). The primary outcome is binary, expressed as positive if the subject has a change of at least one point in the positive direction (toward behavior change) in the Contemplation Ladder scores for at least one behavior compared to baseline.

For our primary analysis, we will compare the personalized education arms (PRE-RA and PRE-RA Plus arms) collectively to the Comparison Arm. A previous study evaluating passive

smoking Trans-Theoretical Model stages of behavior change among pregnant women found that 25.4% improved their stage of behavior change after intensive education, compared to 12.8% of the comparison group who received standard education, which is similar to our Comparison Arm [81]. We therefore assume the proportion of subjects with a positive outcome may range from 5% to 20% in the Comparison Arm. We will use generalized estimating equations to account for intra-subject correlation of four repeated measures (post-education, 6 weeks, 6 months, and 12 months). We reasonably assume the correlation between observations on the same subject is 0.50 with two-sided alpha of 0.05 [82]. A sample size of 148 in the PRE-RA and PRE-RA Plus arms and 74 in the Comparison Arm provides >80% power to detect a difference ranging from 8 to 14% between the two groups for a range of 5 to 20% positive outcomes in the Comparison Arm. For example, we have 83% power to detect a difference between the PRE-RA arms with 20% positive outcomes compared to 10% in the Comparison Arm. We have 80% power to detect a difference between PRE-RA arms with 27% positive outcomes compared to 15% in the Comparison Arm.

2.10. Analytic approach

We will conduct an intention-to-treat analysis for change in Contemplation Ladder scores on any of the four behaviors (smoking, dental care, diet, and exercise) by at least one point at follow-up compared to baseline as our primary analysis. The primary analysis will compare the personalized education arms (PRE-RA and PRE-RA Plus arms) collectively to the Comparison Arm. The primary intention-to-treat analysis will examine change in Ladder score comparing the PRE-RA and PRE-RA Plus arms collectively compared to the Comparison Arm. We hypothesize that a greater proportion of subjects in the PRE-RA and PRE-RA Plus arms will demonstrate a one point change in any of the Ladder Scores than in the Comparison Arm. We will use generalized estimating equations to compare the repeated measures (baseline, immediate post-education, 6 weeks, 6 months, and 12 months) in the groups and account for intra-subject correlation. We will assess baseline covariates to determine if there is balance across treatment arms. Covariates that are unbalanced at baseline will be adjusted for in regression models. We will perform exploratory analyses to examine the nature of missing data and whether subjects lost to follow-up were likely to be missing at random or whether systematic trends were present. After we understand the patterns of missing data, we will adjust analyses accordingly. In a conservative set of analyses, we will assume that all patients lost to follow-up did not achieve any changes in Ladder score. Based on pilot phase data and the breadth of lifestyle risk factors, we assume that most subjects will engage in at least one lifestyle risk factor related to RA (since all pilot subjects had at least one RA-related behavior that increased risk). We will perform secondary analyses comparing specific follow-up time points to baseline. Secondary analyses will also compare the three arms to each other (PRE-RA Plus Arm vs. Comparison Arm, PRE-RA Arm vs. Comparison Arm, and PRE-RA Plus Arm vs. PRE-RA Arm). Subgroup analyses will examine subjects with high-risk genetics, positive auto-antibodies, and those at elevated risk according to the PRE-RA tool.

2.11. Lessons learned

The design and execution of the PRE-RA Family Study present distinct challenges (see Table 4). The study intervention needs to serve multiple functions, all in an easily interpretable, quick, and interactive format. The PRE-RA tool provides education, collects data, calculates personalized risk, and displays results. This multi-functionality required extensive pilot testing and tool refinement. We further developed the educational component by limiting text and adding graphics and using bullet points. We included a limited set of measures in the PRE-RA tool to maximize subjects' attention and minimize the time needed to complete it. We refined calculations based on all available literature to provide the most precise personalized risk estimate possible. We added a lifetime risk of RA result page to reinforce the personalized risk message and better quantify results for subjects with high numeric literacy. We discovered that pilot subjects were not using interactive portions of the tool, so we redesigned the layout of results pages to guide use. Finally, we found that pilot subjects desired to know genetic and autoantibody results in addition to their risk estimates, so separate result pages were developed. These modifications improved the functionality of the PRE-RA tool significantly but required time and intense resource utilization.

While we were designing and refining the PRE-RA tool, we also developed the Comparison Arm. We utilized the educa-

Table 4
Challenges in the design and recruitment for the PRE-RA Family Study.

Challenges	Modifications
Display and interpretation of results pages on the PRE-RA tool	1) Emphasized potential modifiability of RA risk in results pages 2) Added lifetime RA risk result page for subjects with high numeric literacy 3) Added steps to guide subjects on relative risk results page 4) Developed separate genetic and autoantibody results pages
Comparison Arm design and possible differential attrition	1) Utilized education developed for the PRE-RA tool and similar presentation format to maintain consistency and minimize attention differential 2) Randomization occurs after baseline visit 3) Option for Comparison Arm subjects to receive PRE-RA intervention after study conclusion
Low recruitment rate and inability to directly recruit RA first-degree relatives	1) Mailed RA patients study information for relatives prior to recruitment in clinic 2) Added off-campus rheumatology clinics to maximize number of RA patients approached 3) Promoted study with rheumatology foundations 4) Used social media to broaden study accessibility 5) Offered remuneration for subjects

PRE-RA, Personalized Risk Estimator for Rheumatoid Arthritis; RA, rheumatoid arthritis.

tional material about RA signs, symptoms, and risk factors developed for the PRE-RA tool to maintain consistency and allow for comparison between study arms. We initially planned to only collect blood on subjects randomized to the PRE-RA Arm and PRE-RA Plus Arm. Interviews from pilot phase subjects suggested that receiving blood results was an important motivating factor to participate in the study. Since differential attrition in the Comparison Arm could compromise the analysis and interpretation of the study, we decided to collect and test all subjects' blood and to perform randomization after the baseline visit in order to minimize any differential attention between study arms. Subjects in the Comparison Arm have the option to receive results at the study's conclusion. Therefore, disclosure of lab results is delayed for 1 year after blood testing in this arm.

Finally, recruitment for the PRE-RA Family Study is challenging. We are able to identify RA patients who are seen at BWH and satellite clinics, but cannot directly identify or recruit their FDRs. In advance of clinic appointments, we mail study materials to all RA patients whose physicians provide approval. However, clinic visits are often cancelled or rescheduled in the interim. This method has limited success due to: complicated family dynamics; perception of FDRs by RA relatives to be too busy to participate; and FDRs not living locally. We discovered that RA patients at the main BWH campus are approached by other study teams. We decided to concentrate recruitment on BWH satellite clinics where RA patients are not typically approached for research studies. We also participated in rheumatology-specific foundation events to promote the study and personally meet RA patients and their FDRs. We gave scientific presentations at local division conferences and international symposia to familiarize physicians and researchers with the study. We used social media to engage FDRs and RA patients directly. Finally, we offered remuneration to subjects to encourage participation and acknowledge their time and sacrifice. Recruitment of unaffected FDRs is challenging, requiring a constant re-evaluation of tactics.

3. Summary

The PRE-RA Family Study provides personalized risk education composed of multiple validated RA risk factors encompassing four behaviors, genetics, and biomarkers to a group at increased RA risk. We created a novel online intervention called the PRE-RA tool that collects data on demographics, family history, and behaviors and provides tailored education on RA risk. The process of designing and implementing the PRE-RA Family Study presents many challenges, summarized in Table 4. The trial outcomes will include longitudinal patterns in willingness to change RA risk behaviors among three randomized groups. Results from this study will be important for RA and other complex diseases to clarify how best to incorporate many behavioral factors into a simple and understandable metric that will promote public health. The PRE-RA tool can be modified to include other lifestyle, behavior, biomarker and genetic associations or adapted for other diseases or conditions. Thus, these methods and results may be widely applicable. Utilizing personalized medicine to promote positive health behaviors in a population at high risk and who are motivated to change behaviors has the potential to guide prevention strategies. We acknowledge that our personalized risk tool provides only an estimate of RA risk and that measuring willingness to change behaviors may not directly translate into sustained behavior change. However, the PRE-RA Family Study will improve the understanding of pre-clinical RA and provide important evidence basis for the feasibility of RA prevention trials among those with a family history of RA.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.cct.2014.08.007.

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