Contemporary Clinical Trials 47 (2016) 101–108

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Determining the effects and challenges of incorporating genetic testing into primary care management of hypertensive patients with African ancestry

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ARTICLE INFO

Article history:
Received 2 November 2015
Received in revised form 21 December 2015
Accepted 28 December 2015
Available online 30 December 2015

Keywords:
Genetics
Chronic kidney disease
Disparities
African ancestry
Race
Community-based research

ABSTRACT

People of African ancestry (Blacks) have increased risk of kidney failure due to numerous socioeconomic, environmental, and clinical factors. Two variants in the *APOL1* gene are now thought to account for much of the racial disparity associated with hypertensive kidney failure in Blacks. However, this knowledge has not been translated into clinical care to help improve patient outcomes and address disparities. GUARDD is a randomized trial to evaluate the effects and challenges of incorporating genetic risk information into primary care. Hypertensive, non-diabetic, adults with self-reported African ancestry, without kidney dysfunction, are recruited from diverse clinical settings and randomized to undergo *APOL1* genetic testing at baseline (intervention) or at one year (waitlist control). Providers are educated about genomics and *APOL1*. Guided by a genetic counselor, trained staff return *APOL1* results to patients and provide low-literacy educational materials. Real-time clinical decision support tools alert clinicians of their patients' *APOL1* results and associated risk status at the point of care. Our academic–community–clinical partnership designed a study to generate information about the impact of genetic risk information on patient care (blood pressure and renal surveillance) and on patient and provider knowledge, attitudes, beliefs, and behaviors. GUARDD will help establish the effective implementation of *APOL1* risk-informed management of hypertensive patients at high risk of CKD, and will provide a robust framework for future endeavors to implement genomic medicine in diverse clinical practices. It will also add to the important dialog about factors that contribute to and may help eliminate racial disparities in kidney disease.

1. Introduction

While a growing number of initiatives integrate genetic testing into clinical care, few focus on genetic risk factors for common chronic diseases, in part because there are few identified genetic variants that increase the risk of such illnesses. New knowledge of genetic variants that confer an increased risk of chronic kidney disease (CKD) has not been translated to clinical care. We describe the design and implementation of a randomized trial exploring the impact on patients, clinicians and clinical care, of incorporating genetic risk information for CKD into the treatment of hypertensive adults of African ancestry (Blacks) in diverse primary care settings. To our knowledge, this is the first genomic medicine program to integrate genetic risk for a common chronic disease into primary care.

CKD is commonly associated with hypertension (28%) and affects 26 million adults in the US. Blacks with hypertension have a 5-fold increased risk of end stage renal disease (ESRD) compared to Whites. Previous studies have implicated the *APOL1* gene in increasing the risk for CKD and ESRD [1]. This increased risk is conferred by two variants (G1

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http://dx.doi.org/10.1016/j.cct.2015.12.020
1551-7144/

and G2) in the last exon of *APOL1* [2,3]. The presence of two *APOL1* risk variants confers a 5-fold increased risk for hypertensive CKD and a 7-fold increased risk for hypertension-attributed ESRD [1–4]. The added risk is lower among adults who also have diabetes [5,6]. While one in seven Black adults carry two *APOL1* risk variants [5,6], these variants are nearly absent in other populations. This is likely because the G1 and G2 variants protect against infection with African trypanosomiasis (sleeping sickness) that is transmitted by tsetse flies in sub-Saharan Africa. As the disease is endemic to Africa, these variants are almost exclusively present in Blacks, in a manner similar to the high prevalence of sickle cell trait in regions exposed to malaria [7].

While it remains critical to recognize the contribution of multiple factors, particularly social determinants, to chronic disease disparities [8–15], genomic contributors also warrant careful evaluation [16]. High-risk *APOL1* variants are thought to explain approximately 70% of the excess prevalence of CKD in Blacks [4]. As patients are not routinely screened for their *APOL1* status, it is unknown whether patient or clinician knowledge of this genetic risk for CKD impacts patient care (i.e., renal surveillance, antihypertensive medication intensification), patient affect or behaviors such as anxiety and medication adherence, or patient outcomes such as blood pressure control and CKD.

GUARDD (Genetic testing to Understand and Address Renal Disease Disparities) is a randomized trial designed to determine the effects and challenges of incorporating *APOL1* information into primary care management of Black adults with hypertension. Led by an academic–community–clinical partnership, GUARDD was designed to assess primary outcomes, including blood pressure reduction and renal surveillance, secondary psycho-behavioral outcomes, and best processes to improve adoption of genomic medicine.

2. Methods

2.1. Study overview

As shown in Fig. 1, at participating clinical sites, study coordinators enroll eligible, interested, consented patients, collect a baseline survey and clinical measures, and randomize patients to immediate (intervention group) or delayed (control group) *APOL1* testing. Patients in the intervention group receive their results from study coordinators, and the results are then sent to their primary care clinicians via an electronic health record (EHR) best practice alert. All patients are scheduled to return for 3 and 12-month follow up visits and control patients receive *APOL1* testing at 12 months. The study received Institutional Review Board approval at all sites.

The study has two primary endpoints, comparing patients who are *APOL1* positive (high risk) and *APOL1* negative at three months after enrollment. The primary aim is a renal care endpoint, the correct utilization, by clinicians, of serum creatinine and/or urine albumin tests. The primary sub-aim is reduction of systolic blood pressure. Secondary outcomes include impact on primary outcomes at 12 months, psycho-behavioral differences of patients between groups and over time, clinician knowledge, attitudes and beliefs at baseline and 12 months, and differences in outcomes between those tested and not tested. We will also conduct focus groups with study participants after study completion to investigate their experiences in more depth.

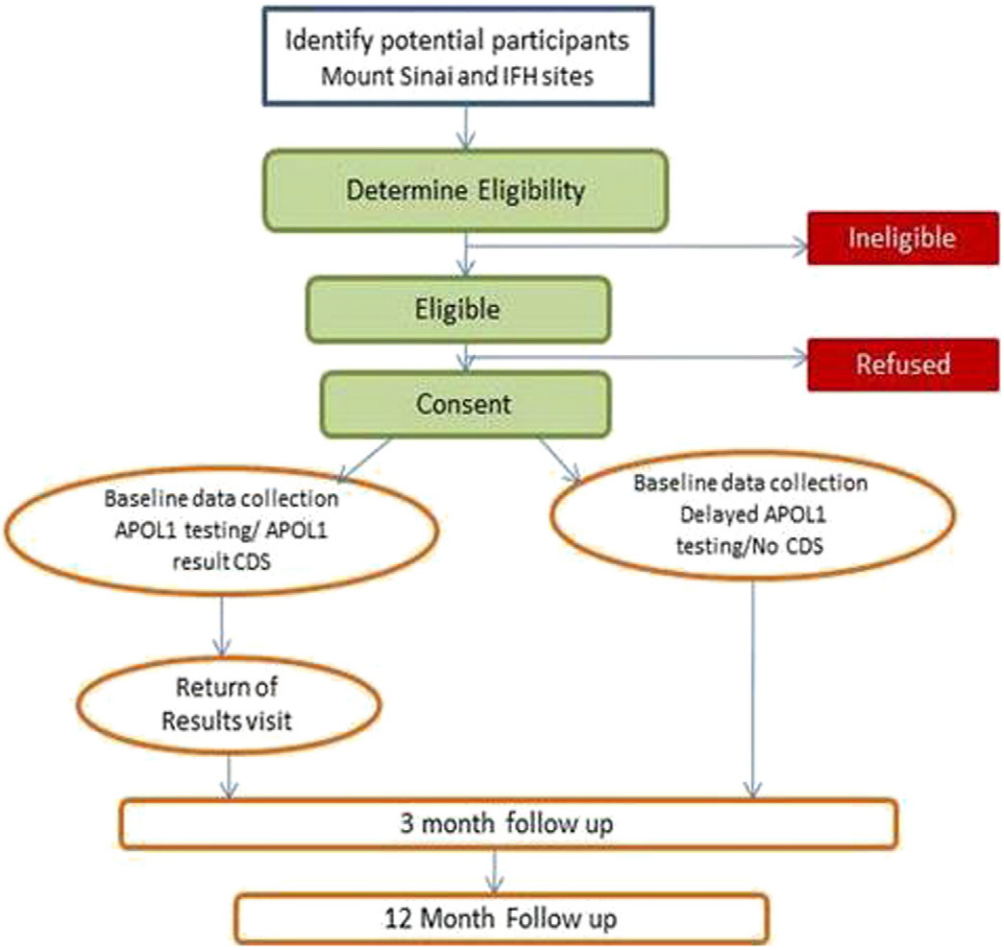

Fig. 1. Study flow.