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ARTICLE

Establishing the value of genomics in medicine: the IGNITE Pragmatic Trials Network

Geoffrey S. Ginsburg[1]✉, Larisa H. Cavallari[2], Hrishikesh Chakraborty[3], Rhonda M. Cooper-DeHoff[2], Paul R. Dexter[4], Michael T. Eadon[5], Bart S. Ferket[6], Carol R. Horowitz[6], Julie A. Johnson[2], Joseph Kannry[6], Natalie Kucher[7], Ebony B. Madden[7], Lori A. Orlando[1], Wanda Parker[3], Josh Peterson[8], Victoria M. Pratt[9], Tejinder K. Rakhra-Burris[1], Michelle A. Ramos[6], Todd C. Skaar[5], Nina Sperber[1,10], Kady-Ann Steen-Burrell[3], Sara L. Van Driest[11], Deepak Voora[1], Kristin Wiisanen[2], Almut G. Winterstein[12], Simona Volpi[7], the IGNITE PTN*

PURPOSE: A critical gap in the adoption of genomic medicine into medical practice is the need for the rigorous evaluation of the utility of genomic medicine interventions.

METHODS: The Implementing Genomics in Practice Pragmatic Trials Network (IGNITE PTN) was formed in 2018 to measure the clinical utility and cost-effectiveness of genomic medicine interventions, to assess approaches for real-world application of genomic medicine in diverse clinical settings, and to produce generalizable knowledge on clinical trials using genomic interventions. Five clinical sites and a coordinating center evaluated trial proposals and developed working groups to enable their implementation.

RESULTS: Two pragmatic clinical trials (PCTs) have been initiated, one evaluating genetic risk *APOL1* variants in African Americans in the management of their hypertension, and the other to evaluate the use of pharmacogenetic testing for medications to manage acute and chronic pain as well as depression.

CONCLUSION: IGNITE PTN is a network that carries out PCTs in genomic medicine; it is focused on diversity and inclusion of underrepresented minority trial participants; it uses electronic health records and clinical decision support to deliver the interventions. IGNITE PTN will develop the evidence to support (or oppose) the adoption of genomic medicine interventions by patients, providers, and payers.

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INTRODUCTION

The National Human Genome Research Institute's (NHGRI's) genomic medicine research programs have explored and tested appropriate uses of genomic information in clinical care through collaborative networks that evaluate electronic health record (EHR)–driven phenotyping and return of genomic results,[1] newborn and clinical genome sequencing,[2] variant curation,[3] and dissemination of genomic medicine approaches to diverse clinical settings outside specialized centers.[4,5] It has become clear that a major barrier to large-scale genomic medicine implementation is the lack of convincing clinical evidence that would compel clinicians to adopt promising strategies and payers to pay for them. This gap in evidence stems from (1) that many genomic tests are laboratory developed tests and thus are subject to enforcement discretion by the Food and Drug Administration; as a result, few if any are used as the intervention in clinical trials, and (2) studies conducted to validate the tests, that is to demonstrate that the report on the phenotype of interest, are not sufficient to show clinical utility—that the test result changes provider and/or patient behaviors and clinical and/or economic outcomes as a result. Clinical trials are the usual strategy to develop evidence of clinical utility and owing to their expense, low margin testing firms have seldom, if ever, conducted these studies.

The Implementing Genomics in Practice (IGNITE) Network was created in 2013 to enhance the use of genomic medicine by supporting the development of methods to incorporate genomic information into clinical care and explore the methods for their effective implementation.

A 2017 National Academy of Medicine report highlighted the need for rigorous evaluation of the validity and utility of genomic medicine interventions and the best approaches for incorporating them in medical practice.[6] Although randomized clinical trials (RCTs) have been regarded traditionally as the gold standard for determining clinical utility, pragmatic clinical trials (PCTs) have been promoted as a means of addressing the weaknesses in RCTs.[6] Genomic interventions are particularly well suited for PCTs to determine the impact of the intervention on the full spectrum of populations and clinical settings in which and to which the intervention will eventually be applied. RCTs are constrained by inclusion and exclusion criteria and often by additional training and feasibility assessment for the sites involved in these studies.

[1]Duke Center for Applied Genomics & Precision Medicine, Duke University, Durham, NC, USA. [2]Department of Pharmacotherapy and Translational Research, College of Pharmacy, University of Florida, Gainesville, FL, USA. [3]Duke Clinical Research Institute, Duke University, Durham, NC, USA. [4]School of Medicine, Indiana University, Indianapolis, IN, USA. [5]Division of Clinical Pharmacology, Indiana University, Indianapolis, IN, USA. [6]Department of Population Health Science and Policy, Mount Sinai, New York, NY, USA. [7]Division of Genomic Medicine, National Human Genome Research Institute, NIH, Bethesda, MD, USA. [8]Department of Biomedical Informatics, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA. [9]Department of Medical and Molecular Genetics, Indiana University, Indianapolis, IN, USA. [10]Department of Population Health Sciences, Duke Margolis Center for Health Policy, Durham VA Health Services Research & Development Service, Duke Center for Applied Genomics & Precision Medicine, Durham, NC, USA. [11]Department of Pediatrics, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA. [12]Department of Pharmaceutical Outcomes and Policy, Center for Drug Evaluation and Safety, University of Florida, Gainesville, FL, USA. *A full list of members and affiliations is present at the end of the paper. ✉email: Geoffrey.ginsburg@duke.edu

The IGNITE Pragmatic Trials Network (PTN) (https://gmkb.org/) will support multisite clinical groups in diverse settings and populations to conduct PCTs of genomic medicine interventions.

MATERIALS AND METHODS

The IGNITE PTN Network

IGNITE PTN, initiated in July 2018, will conduct PCTs of genomic medicine interventions. Each applicant proposed one trial to test a genomic medicine intervention that:

1. has evidence of feasibility from prior studies,
2. addresses clinically important outcomes achievable within one year of randomization,
3. is adaptable to a wide range of clinical settings.

Suitable topics included prescribing pharmacogenomics-based drugs, reducing risk in genetically defined high-risk individuals, and making early genomic-based diagnoses in critically ill newborns. Proposed trials included assessing approaches for real-world applications and providing generalizable knowledge about using PCTs in genomic medicine. Applicants were asked to include a plan to compare results of each trial to those from existing noninterventional studies to identify potential biases affecting the generalization of observational data to clinical practice.

The goals for recruitment were to include at least 50% of patients from diverse clinical settings such as community hospitals, family medicine or primary care practices, and at least 35% from underrepresented populations, underserved populations, or populations who experience poorer medical outcomes. A second RFA solicited clinical groups with at least 75% enrollment from underrepresented populations, underserved populations, or populations who experience poorer medical outcomes. The criteria the network chose to capture date relevant to these goals were self-reported nonwhite non-Hispanic race/ethnicity, Health Resources Services Administration–defined medically underserved areas, and Medicaid insurance. Of note, the race and ethnicity data were captured to assure compliance with the criteria for the RFAs as set by NHGRI to engage underrepresented populations but will not be used in the primary analyses for the trials.

PCT selection

Five groups were selected for funding along with a coordination center. Funding criteria included the capabilities of each site to carry out genomic medicine clinical trials across a range of possible testing interventions and their abilities to recruit participants meeting the diversity criteria for the Request For Applications (RFA) they responded to. Each group proposed a PCT that could be carried out by the network. An independent protocol review committee (PRC) evaluated and ranked the five proposals based on criteria, defined by NHGRI, in Supplementary Table 1.

Structure of the network

NHGRI, PRC, DSMB. The structure of the network is shown in Fig. 1. NHGRI established an independent PRC of 11 scientists—with expertise in design and analysis of RCTs; multicenter clinical trials; human, cardiovascular, and

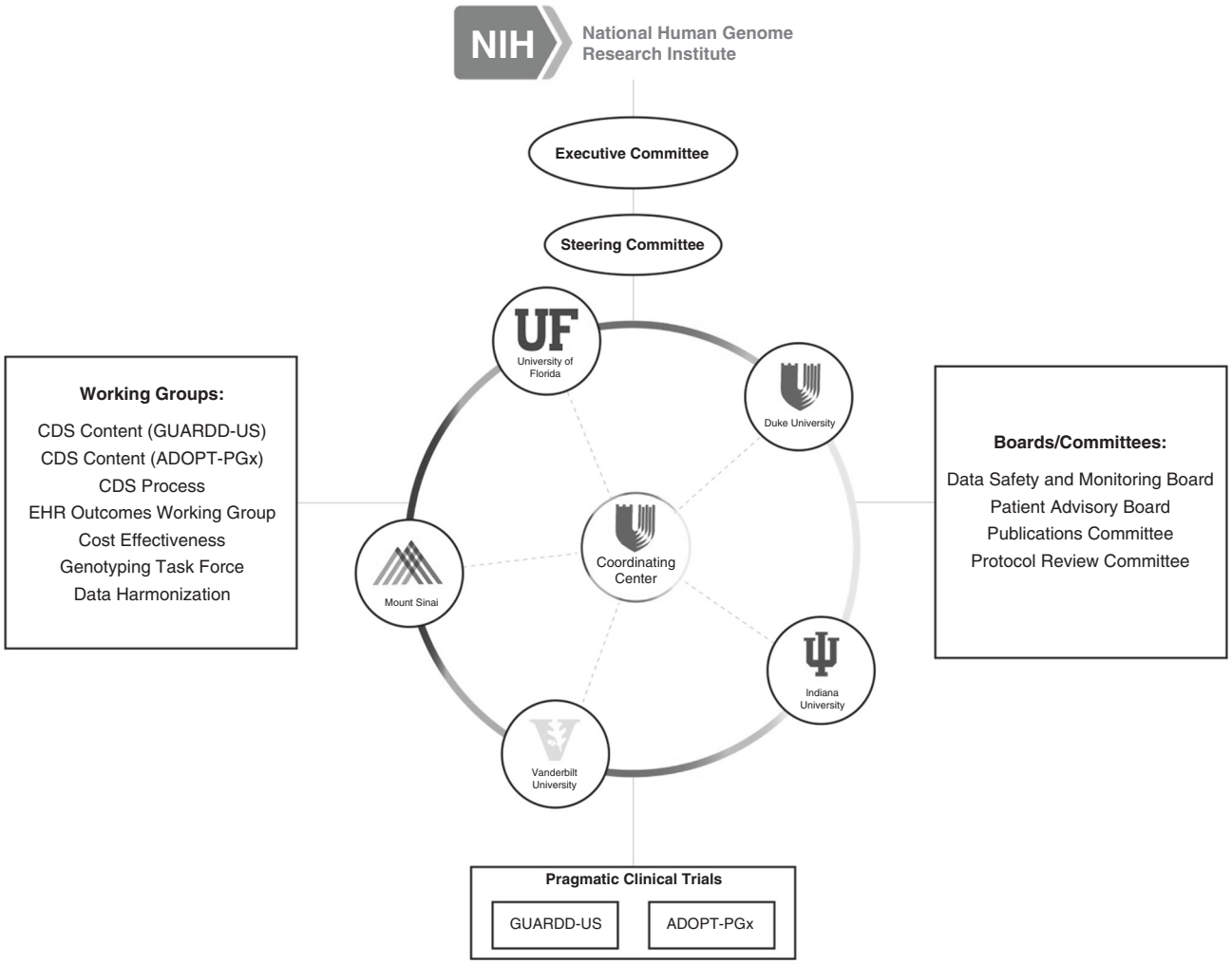

Fig. 1 Structure of the IGNITE PTN. Five clinical groups (Duke University, Indiana University, Mount Sinai, University of Florida, and Vanderbilt) are represented in the surrounding circle. The relationship to the National Institutes of Health (NIH) is at the top. The coordinating center (Duke University) is at the center. On the left are the network working groups that may change over time. On the right are major standing committees and boards. The two pragmatic clinical trials (PCTs) are at the bottom.

statistical genetics; pharmacogenomic testing; ethics; and recruitment of diverse populations—to review the five PCT protocols.

NHGRI also established an independent Data and Safety Monitoring Board (DSMB) consisting of seven scientists with expertise in human and statistical genetics, pharmacogenomic testing, design and analysis of multicenter clinical trials, hypertension, and psychiatry, to monitor protocol development, trial data, patient safety, and overall progress of the PCTs.

Executive and steering committees. The IGNITE PTN Executive Committee (EC) comprises the Steering Committee (SC) Chair and Co-chair, the NHGRI Program Officers, and the Principal Investigators of the Coordinating Center. The EC plans Network strategies and is a forum for decision-making for SC and PCT activities that need guidance or arbitration. The SC comprises the Principal Investigators of each clinical group, the Coordinating Center, and the NHGRI Program Officers and constitutes the main governing body of the IGNITE Network. The SC's responsibility is to ensure agreement on all major scientific decisions; finalize clinical protocols, facilitate the conduct and monitoring of the trials, report trial results in a timely manner, and work with the NHGRI Program Office to disseminate the findings.

Protocol and Implementation Teams. Each trial has a Protocol and Implementation Team (PIT) that is responsible for preparing the master protocol for institutional review board (IRB) submission and for preparing the case report forms and manual of operations. They also identify the data elements for the database, required training, and any additional materials for trial startup. Each PIT has lead principal investigators with appropriate expertise. The membership consists of representatives from NHGRI, the Coordinating Center, clinical groups, and enrolling sites.

The Coordinating Center. The IGNITE PTN Coordinating Center at Duke University is a partnership between the Duke University Center for Applied Genomics and Precision Medicine (https://precisionmedicine.duke.edu/) and the Duke Clinical Research Institute (https://dcri.org/). It provides a central resource for coordination, cost-effective PCT design, adaptation, oversight, and integration for the network, organized in four core areas (Fig. 2) of activities and expertise. Duke University is also a clinical group in the network (see below).

The Network Administration & Coordination Core oversees day-to-day operations, setting agendas and capturing minutes for the Executive and Steering Committees, working groups, and publications subcommittee. The PCT Implementation and Standardization Core coordinates clinical activities at the sites (e.g., development of the Investigators Brochure and Manual of Operations) required for implementation of the PCTs. It manages the Participant Advisory Board and the network's presentations and responses to the DSMB. The Data Management, Analysis, and Effectiveness Core ensures efficient and standardized data capture for analyses, sample size calculations, and has established a common data management system through REDCap.[7,8] At the conclusion of the trials, this Core will conduct primary analyses. The Dissemination Core publishes a bimonthly newsletter and captures best practices for implementation and evidence generation through the website and its toolbox. It will be creating and maintaining a "living" repository of information as the Genomic Medicine Knowledge Base (GMKB).

Clinical groups. The clinical groups are responsible for conducting the PCTs and for recruiting subjects, implementing all study procedures within their practice environments, and working to monitor recruitment goals and adjust recruitment and retention strategies as needed.

The clinical groups comprise different clinics and practice environments chosen to demonstrate how the genomic medicine pragmatic trials could be implemented in diverse settings:

- Duke University comprises the Duke Health System (academic and community-based clinics), Baylor Scott & White (urban, underserved), University Medical Center New Orleans (academic, urban, underserved), and Southeastern Healthcare (rural, underserved).
- Mount Sinai comprises the Mount Sinai Health System (academic with community-based primary care practices) and the Institute for Family Health (network of Federally Qualified Health Centers).
- Vanderbilt includes Vanderbilt University Medical Center tertiary care centers (academic); Meharry/Nashville General Hospital, which is described as a Safety Net Medical Center (urban, underserved); and Sanford Health (rural).
- Indiana University Clinical Group includes IU Health tertiary care centers (academic and rural) and Eskenazi Health, a safety net health system (urban, underserved).
- University of Florida Health Clinical Group includes the campuses of UF Gainesville (academic), UF Jacksonville (academic, both urban and rural clinics), and Nemours (pediatric).

Special features of the IGNITE PTN

RCTs vs. PCTs. RCTs have classically been the primary methodology used to answer clinical questions. The design of RCTs includes a high degree of

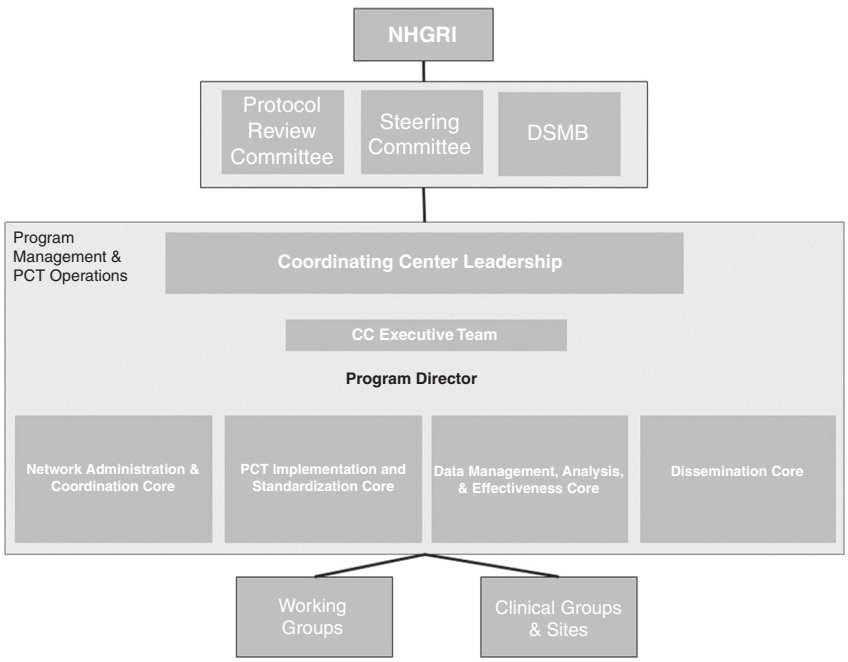

Fig. 2 Organization of the Coordinating Center (CC). The CC cores are in the main box; the CC's relationship to the National Institutes of Health (NIH) is above, and to the working groups and clinical groups is below. DSMB Data and Safety Monitoring Board, NHGRI National Human Genome Research Institute, PCT pragmatic clinical trials.

control to isolate a treatment effect. The strictness of RCTs is ideal for testing whether a new investigational treatment has the intended effect. However, this strict control means that the environment of an RCT is divorced from actual clinical care.

PCTs are designed from the start with input from health-care providers, participants, and systems to produce practical evidence on improving outcomes of greatest value to these stakeholders. PCTs are designed to improve practice and policy, and unlike most traditional RCTs, take place in settings where routine care occurs, such as community clinics, primary care practices, hospitals, and pharmacies. They allow the inclusion of diverse, representative populations in multiple, heterogeneous clinical care settings and compare selected interventions to real-world alternatives rather than to placebo or no intervention. The IGNITE PTN is taking advantage of the following pragmatic features of PCTs:

1. The trials are conducted in real-life settings encompassing the full spectrum of the population to which an intervention will be applied.
2. There are minimal inclusion or exclusion criteria.
3. Practitioners are not constrained by guidelines on how apply the experimental intervention. Practitioner guidance is facilitated through clinical decision support in the electronic health record.
4. The best alternative treatments are used for comparison with no restrictions on their application, covering the full spectrum of clinical settings.
5. The primary outcome is a clinically meaningful one that does not require extensive training to assess.
6. There are no plans to improve or alter compliance and no special strategy to motivate practitioners' adherence to the trial's protocol.

PCTs for IGNITE PTN were selected to emphasize assessment of effectiveness (in routine settings) rather than efficacy (in ideal settings) and to produce results that will directly inform decision-making of health-care providers, patients, administrators, and policymakers. The clinical questions of the IGNITE PTN make are a natural fit for PCTs and focus on how the knowledge of genetic status affects the behavior and/or treatment of participants as well as behavior of providers.

Use of electronic health records and clinical decision support. To support the generalizability and reproducibility of IGNITE PTN interventions, the Network specified that all trials would return genomic results to the EHR with clinical decision support (CDS) informing and guiding care providers. The CDS includes an interpretation of the results (a.k.a. "passive CDS") and recommended specific clinical actions (e.g., a change in dosing, drug selection, monitoring laboratory test).

Generating evidence. A unique feature of the IGNITE PTN is its focus on generating evidence that will address real-world questions while at the same time amassing a data resource that can be leveraged to answer other related questions. Given the prior success of IGNITE,[5] processes to support data harmonization, clinical outcomes, and economic outcomes were established a priori as part of IGNITE PTN.

RESULTS

The PRC selected two trials based on its review.

GUARDD-US

Genetic testing to Understand Renal Disease Disparities across the United States (GUARDD-US) is a prospective, multicenter, unblinded, two-arm, randomized pragmatic clinical trial expanding on a previous study.[5] Participants are randomized in a 1:1 ratio to receive immediate *APOL1* risk genotype results and or delayed *APOL1* testing 6 months after enrollment (control arm). The hypothesis for GUARDD-US is that immediate knowledge of genotype in *APOL1* high-risk patients (with two *APOL1* risk alleles) will result in better blood pressure control compared with high-risk controls who are delayed in receiving this information.

The primary endpoint is the change in systolic blood pressure from enrollment to three months postenrollment between the high-risk control and intervention subjects. Secondary outcomes include urine microalbumin or proteinuria testing and an appropriate diagnosis of chronic kidney disease in the EHR. To achieve adequate power, the study will enroll 5,435 total individuals to recruit over 500 individuals with high-risk genotypes in each arm. The high-risk genotype frequency in the general African ancestry population is 14%, but up to 29% in populations with existing cardiovascular and kidney disease.[9] Genotype frequency was considered in recruitment targets and power calculations, balancing expected enrollment of subjects with and without existing kidney disease.

GUARDD-US also includes a substudy that randomizes low-risk participants in the intervention arm who test negative for *APOL1* to a pharmacogenomic (PGx) intervention, specifically, immediate PGx return of results versus delayed PGx return of results in a 1:1 ratio. The genes that are tested are *NAT2* (hydralazine), and *YEATS4* (thiazides) for guiding antihypertensive therapy. The major endpoint is the change in systolic blood pressure from enrollment to three months postenrollment between the immediate and delayed return of results groups.

ADOPT-PGx

A Depression and Opioid Pragmatic Trial in Pharmacogenetics (ADOPT-PGx) is a set of pragmatic, multicenter, prospective, randomized, controlled clinical trials to test the efficacy of genotype-guided therapies to treat depression and pain. The Network will conduct three individually powered trials targeting three prescribing scenarios: control of postoperative acute pain, control of chronic pain, and relief from depressive symptoms. Each trial will be randomized to receive immediate (on enrollment) or delayed (at 6 months after enrollment) pharmacogenetics testing. The primary intervention genes include *CYP2D6* for all three trials and additionally *CYP2C19* for the participants enrolled for the depression treatment. *CYP2D6* is known to activate opioids (tramadol, codeine, and hydrocodone), and variability in the *CYP2D6* gene contributes to efficacy and toxicity of these opioids. For antidepressants, *CYP2D6* also metabolizes, but inactivates, fluvoxamine and paroxetine, while *CYP2C19* metabolizes and inactivates citalopram, escitalopram, and sertraline.

The hypothesis for ADOPT-PGx is that genotype-guided interventions will improve pain control and depressive symptoms. All endpoints are patient-reported through Patient-Reported Outcomes Measurement Information System (PROMIS) based surveys administered at baseline and at various times up to six months. Trial-specific outcomes will be compared between participants in the intervention arm (immediate genotyping) and control arm (delayed genotyping) who have an actionable *CYP2D6* or *CYP2C19* predicted phenotypes. Phenotypes for *CYP2C19* will be based on genetic test results alone, whereas *CYP2D6* phenotypes will also incorporate phenoconversion resulting from drug interactions. Both opioid and antidepressant prescriptions will generally be guided by recommendations published in the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines.

Working groups and their products

CDS content (GUARDD-US). To support the pragmatic GUARDD-US study, a robust CDS system is required. Given the lack of consensus nor society guidelines surrounding *APOL1*, GUARDD-US CDS content development working group focused on crafting CDS to attain current blood pressure targets rather than create new thresholds based on *APOL1* genotyping.[10–14] All subjects regardless of genotype receive advice on blood pressure control and education on the relationship between high blood pressure, cardiovascular disease, and chronic kidney disease. The CDS system is designed to alert providers to elevated blood pressures in individuals with high-risk *APOL1* genotypes and facilitate expeditious blood pressure control and chronic kidney disease screening.

The five institutions participating in this PCT vary in their current utilization of clinical risk criteria to define blood pressure targets. Some sites plan to enroll participants with lower cardiovascular risk and almost universally preferred to target a <140/90 mm Hg

threshold. Other sites plan to enroll patients across the spectrum of cardiovascular risk, already integrating clinical risk factors into routine blood pressure care algorithms. Since target blood pressure guidelines vary across clinical societies, the GUARDD-US CDS system emphasized a threshold of <140/90 mm Hg for most individuals in the CDS, but allowed flexibility for stricter control at sites considering cardiovascular disease risk factors. Given a lack of evidence, one clear decision by the investigators was to *not* consider the *APOL1* high-risk genotype alone as a cardiovascular risk factor equivalent. Instead, the CDS recommends screening for chronic kidney disease with a urine microalbumin test in individuals who have not been screened in the previous six months. Chronic kidney disease is already a cardiovascular disease risk factor. If practitioners are made aware of the presence of chronic kidney disease, they can elect to target a stricter threshold of <130/80 mm Hg based on current guidelines. Individuals randomized to immediate genotyping but not found to possess two *APOL1* risk alleles are re-randomized to a substudy of immediate or delayed pharmacogenotyping for two antihypertensive gene–drug pairs. The first drug–gene pair links genotype for an expression quantitative trait locus in *YEATS4* to thiazide diuretic response.[15] The second drug–gene pair uses N-acetyltransferase 2 (*NAT2*) genotype to guide dosing of hydralazine.[16] Neither drug–gene pair possesses dosing recommendations from CPIC; thus, CDS algorithms were created based on current pharmacokinetic and pharmacodynamic evidence. Blood pressure targets were set analogously to the GUARDD-US study.

CDS content (ADOPT-PGx). The CDS content development process for ADOPT-PGx focused on creating standardized, evidence-based, genotype-informed drug therapy recommendations that incorporated effects of drug–drug–gene interactions, when applicable.

The working group relied primarily on CPIC guidelines for selective serotonin reuptake inhibitors and codeine. Since publication of the CPIC guidelines, members of the IGNITE PCT network had completed clinical trials of genotype-informed opioid therapy in acute and chronic pain.[17] These additional data were used to further inform recommendations for opioids with lower levels of evidence in the CPIC guideline, including tramadol and hydrocodone. The working group also identified clinical areas of uncertainty with the use of genotype information in practice, such as genotype-guided dosing recommendations for CYP2D6 intermediate metabolizers and ranged phenotypes (*CYP2D6* NM-UM) in patients taking codeine, tramadol, or hydrocodone. In these cases, the group conducted additional review of the literature and iterative discussions to reach consensus on clinical recommendations.

Given the pragmatic nature of the ADOPT-PGx clinical trial, it was necessary to develop consistent clinical recommendations and/or interventions that could be implemented among diverse clinical settings with variability in EHRs, health informatics capabilities, degree of experience with implementing pharmacogenomics in clinical practice, and population age ranges (e.g., adult versus pediatrics). The working group created templates for synchronous CDS that could interrupt providers during the prescribing process as well as asynchronous clinical notes that could be returned to providers electronically. This approach allowed for maximal flexibility: some sites used existing CDS as available, while other sites built CDS de novo as part of the trial. It also allowed for each site to choose which CDS to employ while ensuring the core components of the intervention were preserved across the network. Examples of CDS alerts developed are in Supplementary Figs. 1 and 2.

Part of the intervention in ADOPT-PGx relies on clinical decisions that incorporate the effects of CYP2D6 phenoconversion, or the combinatorial impact of concomitant medications with the patient's genetic profile to provide a more precise prediction of the patient's CYP2D6 enzyme function. While the concept of this approach is not new, to our knowledge, there were no standardized algorithms for clinical application. Through an exhaustive literature review, the working group arrived at a consensus algorithm to guide clinical interpretation of possible *CYP2D6* genotypes when patients were taking concomitant enzyme inhibitors, including accounting for copy-number variation. Each site will apply this algorithm either electronically or manually as part of the intervention and make recommendations concordant with the patient's predicted clinical phenotype.

CDS process. A CDS Process Working Group was established to develop laboratory result reporting and CDS for each pragmatic trial; one subgroup was devoted to ADOPT-PGx trial and another to GUARDD-US. As trial sites within IGNITE PTN use a variety of EHR vendors, the working group established knowledgebases and design guidelines to standardize the presentation of genomic risk to clinicians at the point of care. Through this workgroup, sites shared methods for developing alerts, screenshots of in-progress and developed CDS, and criteria for timing the genomic risk message and the scope of the recipients.

Genotyping. The goal of the Genotyping Working Group was to harmonize genes and variants for the studies and assignments of phenotypes based on genetic test results. The group initially discussed harmonizing to a common platform but ultimately decided against a common platform as there would be a significant cost in equipment and/or resources for each site to obtain and validate a common platform. Part of genotyping group discussion and decision-making was impacted by the safety communication from the FDA.[18] The working group decided only the genotype and phenotype would be reported. No other interpretive language would be provided by the clinical laboratory report as these were covered by the CDS Working Group. The working group also discussed preferred and alternative specimen types for clinical testing. Since both ADOPT-PGx and GUARDD-US are PCTs, it was decided that the validated specimens did not need to be harmonized. Of note, most laboratories preferred whole blood collected in ethylenediaminetetraacetic acid (EDTA) for clinical testing. Other noninvasive acceptable specimens were either buccal swabs or saliva samples.

Data harmonization. The Data Harmonization Working Group was convened to facilitate cross-network analyses by aligning data elements across Network-wide clinical trials where possible. Because the Network clinical trials each have specific aims and populations, the working group adopted a "flexible" approach to data harmonization.[19] Appropriate for a collaborative environment, a flexible approach does not require that each clinical trial capture data using identical tools or measures. Rather, researchers from the different clinical trials agree on a core set of variables with flexibility regarding how those variables will be collected or measured. However, because the working group was formed as the Network began, it has been possible to prospectively define a minimum core set of common data elements across the clinical trials[20,21] that will allow for rapid dissemination of cross-network patient characteristics. The working group finalized this core set of data elements iteratively, through multiple rounds of discussion during the protocol and database development phases.[22]

Cost-effectiveness. One crucial goal of studies addressing the value and process of implementation is long-term sustainability, and an essential component of sustainability is an understanding of costs as compared with the clinical effectiveness of the intervention. To this end, the Network established a working group that consists of decision and economic modelers, genomics experts, clinical specialists, and epidemiologists to assess healthcare utilization and evaluate the cost-effectiveness of the two trials. Novel to evaluating the impact of genomic interventions on

health-care utilization and cost will be the use of claims records for a subgroup of the trial samples with coverage by Medicare or Medicaid that will be linked to trial data. Claims records will enhance patient report and EHR-based capture of health-care utilization and allow direct extraction of reimbursed charges (i.e., cost to the payer). Cost-effectiveness analyses will assume the perspective of the payer to inform reimbursement decisions of genomic and pharmacogenetic testing.

Conclusions

IGNITE PTN is applying the rigor of PCTs to develop the evidence base that, if positive, will be used to support the widespread adoption of a suite of genomic medicine interventions by patients, providers, and payers. Whether or not the trials show a benefit to genetic testing, IGNITE PTN will have defined the standards and processes required to carry out genomic guided rigorous PCTs to determine clinical utility of these tests, filling an important gap in strategies to assess the value of genomic medicine.

IGNITE PTN expands the reach of the Network to a wider range of socioeconomic demographics and populations as well as health-care delivery settings. Importantly, it will explore genomic testing and return of results among underrepresented populations with an expectation that the research program will capture diverse populations of patients, complementing efforts underway in other federally funded programs to do so (e.g., in the All of Us Research Program and in eMERGE).

IGNITE PTN will foster the exchange of genomic testing implementation protocols within and outside the Network. The evidence generated will support implementing genomic medicine broadly and will build on the initial findings from IGNITE to expand collaborations with external groups and expert organizations (such as CMS, FDA) to define what additional evidence is needed to move genomic testing from the realm of research to become the standard of care.

DATA AVAILABILITY

While this paper does not contain any primary research data, the IGNITE PTN will provide materials the Network has developed upon request. The PTN is particularly interested in supporting those interested in carrying out PCTs with genomic interventions. A goal of the PTN is to always make protocols, consents, clinical decision support rules, and code (where appropriate) available publicly.

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AUTHOR CONTRIBUTIONS

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COMPETING INTERESTS

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Correspondence and requests for materials should be addressed to G.S.G.

THE IGNITE PTN

Aisha Montgomery[13], Heather Kitzman[13], Azita Sadeghpour[14], Deepak Voora[14], Geoffrey S. Ginsburg[14], Hrishikesh Chakraborty[14], Kady-Ann Steen-Burrell[14], Lori A. Orlando[14], Nancy Garrett-Mead[14], Nina Sperber[14], R. Ryanne Wu[14], Tejinder Rakhra-Burris[14], Wanda Parker[14], Michael T. Eadon[15], Paul Dexter[15], Sheryl Lynch[15], Todd Skaar[15], Victoria Pratt[15], Beth Nauman[16], Erica Johnson[16], Bart Ferket[17], Carol R. Horowitz[17], Diane Hauser[17], Joseph Kannry[17], Michelle Ramos[17], Mart Ferket[17], Nandini Shroff[17], Neil Calman[17], Sabrina Clermont[17], Saskia Shuman[17], Rajbir Singh[18], Ebony Madden[19], Natalie Kucher[19], Simona Volpi[19], Kathryn Blake[20], Benjamin Quang Duong[21], Colette Free[22], Lindsay Hines[22], Joseph Roberts[23], Almut G. Winterstein[24], Amanda Elsey[24], Erica Elwood[24], Julie Johnson[24], Kristin Wiisanen[24], Larisa Cavallari[24], Rhonda Cooper-DeHoff[24], Alex Parker[25], Kim Vigal[25], Jyotsna Fuloria[26], Asa Revels[23,27], Cherry Beasley[27], Henry Ong[28], Josh Peterson[28], Kerri Cavanaugh[28] and Sara Van Driest[28]

[13]Baylor, Scott & White Health, Dallas, TX, USA. [14]Duke Center for Applied Genomics & Precision Medicine, Duke University, Durham, NC, USA. [15]Indiana University School of Medicine, Eskenazi Health, Indiana University, Indianapolis, IN, USA. [16]Louisiana Public Health Institute, New Orleans, LA, USA. [17]Mount Sinai Clinical Group, New York, NY, USA. [18]Meharry Medical College/Nashville General, Nashville, TN, USA. [19]National Human Genome Research Institute, Bethesda, MD, USA. [20]Nemours Children's Specialty Care, Jacksonville, Jacksonville, FL, USA. [21]Nemours/Alfred I. Du Pont Hospital for Children, Wilmington, DE, USA. [22]Sanford Health, Fargo, ND, USA. [23]University of North Carolina Health-Southeastern, Lumberton, NC, USA. [24]Department of Pharamcology and Translational Research, College of Pharmacy, University of Florida, Gainesville, FL, USA. [25]Nemours Children's Health System, University of Florida-Jacksonville, Jacksonville, FL, USA. [26]University Medical Center–New Orleans, New Orleans, LA, USA. [27]Department of Nursing, University of North Carolina-Pembroke, Pembroke, NC, USA. [28]Vanderbilt University Medical Center, Nashville, TN, USA.