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Pharmacogenomics in Cardiovascular Diseases

Caitrin W. McDonough, PhD, MS[1,2]

[1]Department of Pharmacotherapy and Translational Research, College of Pharmacy, University of Florida, Gainesville, Florida

Abstract

Cardiovascular pharmacogenomics is the study and identification of genomic markers that are associated with variability in cardiovascular drug response, cardiovascular drug related outcomes, or cardiovascular drug related adverse events. This overview presents an introduction and historical background to cardiovascular pharmacogenomics, and a protocol for designing a cardiovascular pharmacogenomics study. Important considerations are also included for constructing a cardiovascular pharmacogenomics phenotype, designing the replication or validation strategy, common statistical approaches, and how to put the results in context with the cardiovascular drug or cardiovascular disease under investigation.

Basic Protocol 1: Designing a Cardiovascular Pharmacogenomics Study

Keywords

Pharmacogenomics; Cardiovascular; Complex diseases; Antiplatelet therapy; Antihypertensive therapy

INTRODUCTION:

Pharmacogenomics (PGx) aims to identify genomic markers, most commonly single nucleotide polymorphisms (SNPs), that are associated with variability in drug response, drug related outcomes, or adverse events (Meyer 2004, Wang, et al. 2011). Cardiovascular disease has been one therapeutic area that has seen many high impact PGx associations (Gage, et al. 2008, Mega, et al. 2010, Shuldiner, et al. 2009, Turner, et al. 2013a, Wilke, et al. 2012). However, the translation of these findings into clinical practice has not been straightforward (Cavallari, et al. 2017, Luzum, et al. 2017, Manolio, et al. 2015, Roden, et al. 2018). The purpose of this article is to give a general overview and methodology for designing a cardiovascular PGx study.

The first studies in cardiovascular PGx were focused on candidate genes known to be involved in the pharmacokinetics (PK) and pharmacodynamics (PD) of the drug. PK is often referred to as the study of what the body does to the drug, and in terms of PGx, relates to studying the variation in genes that encode drug metabolism enzymes, or cytochrome P450 enzymes (CYP enzymes), that metabolize the drug being studied (Meyer 2004). PD is often

[2] Corresponding author: cmcdonough@cop.ufl.edu.

referred to as the study of what the drug does to the body, and in terms of PGx, focuses on studying variation in genes that encode drug targets (Meyer 2004). Finally, the study of variation in genes that encode drug transporters can impact both PK and PD. Taken together, genetic variability in the genes that code for drug metabolizing enzymes, drug transporters, and drug targets can impact the variability in the PK and PD of a drug, which impacts variability in the efficacy (response) and toxicity (adverse outcomes) of a drug.

While some candidate gene studies were successful in cardiovascular PGx (Rettie, et al. 1994, Rieder, et al. 2005), there were also candidate genes that failed to replicate (Arnett, et al. 2005, Maitland-van der Zee, et al. 2011, Schelleman, et al. 2008), and additional unexplained variability in cardiovascular drug response. Through genome-wide association studies (GWAS), cardiovascular PGx candidate genes were confirmed (Cooper, et al. 2008, Takeuchi, et al. 2009), and novel associations were identified (Link, et al. 2008, Shuldiner, et al. 2009). Currently, the landscape in cardiovascular PGx stretches from candidate gene studies to GWAS to GWAS meta-analyses to studies utilizing other ‘omic technologies (e.g., RNAseq, proteomics, metabolomics) to implementation. While there are some cardiovascular drug-gene pairs being implemented clinically (Cavallari, et al. 2017, Luzum, et al. 2017, Weitzel, et al. 2016), there still remains much additional discovery work to be done.

A detailed protocol for designing a cardiovascular PGx study is described below. The factors to consider during the study design process are also provided. Additional information on example cardiovascular PGx applications, and common analysis methods are also given below.

STRATEGIC PLANNING

Designing a cardiovascular PGx study is a multi-stage process. While considering the many different steps, and the pros and cons in study design, the two most important factors to consider are the trait or disease state, and the drug response. Prior to designing the entire cardiovascular PGx study, additional time and planning should be spent on the phenotyping methods that will be used to determine these two factors.

1. *The Trait or Disease State*. The definition of the trait or disease state is one half of the cardiovascular PGx phenotype. When determining what the overall cardiovascular PGx phenotype will be, there are considerations that should be taken for the trait or disease state. Some common questions to ask include:
    a. How will the disease be reported (e.g., patient reported versus clinically confirmed)?
    b. Are there ways to clinically confirm the disease or trait under study (e.g., vitals, laboratory tests, clinical procedures, diagnoses, physician examination)?
    c. Is the drug currently, or has it been previously, approved for multiple indications or used off-label (e.g., the use of clopidogrel post stroke versus post percutaneous coronary intervention)?

d. What stage of the disease state would be most informative to study (e.g., mild to moderate hypertension versus severe hypertension)?

e. Do patients need to be newly diagnosed? Is the trait something that is measured routinely in healthy patients?

f. Can patients have other comorbidities? What are the influences on the disease or trait by age, sex, and ancestry?

g. Are there environmental influences on the disease or trait that need to be considered?

If the investigator designing the cardiovascular PGx study is not an expert in the trait or disease state being considered, it is recommended they identify a collaborator with this expertise.

2. *The Drug Response*. The definition of the drug response is the other half of the cardiovascular PGx phenotype. The most common drug responses are either an efficacy outcome or a safety outcome. When investigating these outcomes, some common questions to consider are:

a. Does a patient need to be drug naïve or washed-out from drug before treatment?

b. How is the drug response calculated (e.g., blood pressure response = blood pressure post-treatment – blood pressure pre-treatment)?

c. How many response phenotypes need to be studied (e.g., systolic blood pressure and diastolic blood pressure)?

d. Does medication dose information need to be collected?

e. Does the drug need to be titrated for maximum efficacy?

f. What is the half-life of the drug?

g. Are there known drug-drug interactions with the drug under study?

h. Are there known environmental-drug interactions with the drug under study?

i. Can patients be treated with other drugs during the study?

j. How are cardiovascular outcomes reported?

k. How are cardiovascular outcomes adjudicated?

l. Do laboratory values need to be collected?

m. Do patients need to be fasting when laboratory values are collected?

BASIC PROTOCOL 1

DESIGNING A CARDIOVASCULAR PHARMACOGENOMICS STUDY—Selecting the cardiovascular PGx phenotype to be studied is the main factor in designing a cardiovascular PGx study. However, there are many additional considerations, and factors

that may influence how the cardiovascular PGx phenotype is determined. This protocol describes the procedures for designing a cardiovascular PGx study. A summary of the elements to consider during the study design process is provided in Table 1.

Materials

- Cardiovascular Pharmacogenomic Phenotype.
  - The phenotype determination is the first step of the protocol; however, it helps to have an idea of some possible phenotypes before designing the study. Examples of cardiovascular PGx phenotypes are shown in Table 2.
- Existing SNP or GWAS data OR a DNA collection and genotyping plan.
  - To conduct a cardiovascular PGx study, there must be genetic data of some kind.
- Demographics and Characteristics of the Study Population.
  - This may be existing data or data that needs to be collected.
- Software for a Power Calculation

  Note: Examples of programs that can be used are listed in Table 3.
- Software for Analyses.

  Note: Examples of common programs are listed in Table 3.
- Databases used:
  - *For published literature:* PubMed (https://pubmed.ncbi.nlm.nih.gov/)
  - *For pharmacogenomic knowledge*: PharmGKB (https://www.pharmgkb.org/)
  - *For clinical pharmacogenomic guidelines*: CPIC (https://cpicpgx.org/)
  - *For drugs with biomarker information in the label (FDA)*: FDA Biomarker List (https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling)

Protocols steps and annotations

1. Select the cardiovascular pharmacogenomic phenotype.

A cardiovascular PGx phenotype includes a cardiovascular trait or disease, a cardiovascular drug, and a drug response. The phenotype can be dichotomous or continuous, where the coded phenotype is often the drug response. The PGx element of the phenotype can also be incorporated through an interaction analysis, by adding a SNPxDrug interaction term to the regression model. Examples of cardiovascular PGx phenotypes are shown in Table 2.

a. Clearly define the cardiovascular trait or disease state by diagnosis codes, prescription medications, or laboratory values. Construct a list of inclusion criteria and exclusion criteria for how the trait or disease state will be defined.

b. Determine what cardiovascular drug will be studied. Determine if an entire drug class will be included, or if a specific drug is being studied. Determine if a specific formulation is required, or all brand name and generics will be included.

c. Define how the drug response will be measured or collected. Determine when the drug response will be measured or collected. Determine if the study participants need to be drug naïve or washed out from the drug before the study.

2. Determine the type of study design.

There are factors in the study design that determine how data will be collected, how study participants will be recruited, and the number of SNPs or genes being studied.

a. Determine if the study will use existing data or is a new study. There are many cardiovascular PGx studies that are sub-studies of larger cardiovascular randomized controlled trials (RCTs) or other cardiovascular clinical trials. These studies have taken advantage of the larger design of the clinical trial, while also collecting DNA and any additional measures to construct the cardiovascular PGx phenotype under investigation. Other prior studies in cardiovascular PGx have been smaller, specifically designed PGx clinical trials, or prospective, observational studies. Additionally, prior cardiovascular PGx studies have been designed using longitudinal cohort studies, and biobanks that have collected DNA. By using an existing data source, often all data elements have already been collected, and DNA has also been collected. However, the phenotype needs to be designed considering what variables were collected and at what time points. By designing a new study, there is more flexibility in what variables will be collected and when they will be collected, but there is much more time and money needed for the overall study.

b. Determine the timeframe of the study. Will the study be retrospective, taking a timepoint to select study participants and looking back into time? Or will the study be prospective, recruiting study participants and then moving forward into time? Additionally, the study could be cross-sectional with information just at a single timepoint. However, often cardiovascular PGx are more difficult to design in a cross-sectional manner, as it is much harder to construct a drug-response phenotype from data from a single timepoint.

c. Determine if the study will be observational or a clinical trial. Do study participants need to be randomized to drug, or receive a specific intervention? Or can data be collected on drug response by observing study participants who are already, or were already, prescribed the drug being studied?

d. Determine the number of SNPs or genes that will be studied. PGx candidate gene or candidate SNP studies are based on prior knowledge or the PK and PD of the drug. Whereas a GWAS interrogates SNPs across the genome based off of a genome-wide SNP panel.

3. Determine how DNA will be collected, or if DNA has already been collected.

In study designs that are using existing data or retrospective, often DNA has already been collected, and in many studies, DNA has already been isolated and GWAS data may already exist. In study designs that are prospective or new studies, the collection of DNA must be included in the study design.

4. Consider the study population.

The study population often includes study participants from different race and ancestry backgrounds, study participants with other comorbidities, and study participants with other exposures.

a. Establish how race and ancestry will be determined and accounted for in the study. While many of the well validated PGx variants are important in all race and ancestry backgrounds, during the discovery phase it is important to conduct analyses separately in each race and ancestry group due to the differences in linkage disequilibrium across the genome.

b. Collect information on any additional comorbidities, traits, demographics, or vitals that may influence the cardiovascular PGx phenotype. These variables could be included as covariates in the statistical model(s). Additionally, these variables could be used for sensitivity analyses or sub-group analyses.

c. Determine if there are other exposures that may influence the cardiovascular PGx phenotype. Is the drug under study metabolized by a *CYP* enzyme that has known inducers or inhibitors? Can smoking or caffeine influence the metabolism of the drug being studied? These additional variables should also be collected.

5. Conduct a power calculation.

A power calculation is necessary when using an existing dataset to determine what effect size can be detected at different minor allele frequencies. A power calculation will also determine the ideal sample size for a new study.

a. Determine the sample size. If the study is using existing data, then the sample size is known. If the study is a new study, then use a power calculation to determine the sample size.

b. Determine the effect size. The effect size can be measured as an Odds Ratio in a case-control study design, or as a β-coefficient if the study is examining a continuous PGx phenotypes. Use prior validated or replicated associations in the literature to gauge what effect size is reasonable to detect. It has been shown that PGx variants have larger effect sizes when compared to other complex traits (Maranville and Cox 2016).

c. Select the minor allele frequency. If the study is a candidate gene or candidate SNP study, then the minor allele frequencies of the SNPs is known. If the study is a GWAS, then examine power across minor allele frequencies from 5% to 45%.

6. Determine a replication plan.

Replication can be more difficult in PGx studies. It is often difficult to find a study with the exact same study design and phenotyping. In cardiovascular PGx studies, there are often four types of replications or validations that are used.

a. Directly replicate the top SNPs examining the same PGx phenotype with the same drug in the same population.

b. Validate the top SNPs in a similar drug or a drug in the same drug class, with the same PGx phenotype and the same population.

c. Validate the top SNPs in a similar disease state, or related PGx phenotype, with the same drug and in the same population.

d. Validate the top SNPs in another race or ancestry group, with the same PGx phenotype and the same drug.

7. Determine the analysis plan.

The statistical analysis plan directly relates to the type of cardiovascular PGx phenotype, and the data sources for the study. Common analyses include logistic regression models in case-control based PGx studies, and linear regression models in continuous response or dose based PGx studies. Interaction analyses are also used to examine a phenotype or outcome by a certain drug treatment, adding a SNPxdrug interaction term into the regression model. Finally, there are both single study cardiovascular PGx designs, as well as meta-analysis cardiovascular PGx designs.

COMMENTARY

BACKGROUND INFORMATION

There have been many successful discoveries through cardiovascular PGx studies in multiple therapeutic areas. Several studies have further elucidated the PK/PD of the drug being investigated, by identifying significant associations with SNPs in and near genes that encode for drug metabolism enzymes, drug transporters, and drug targets. Further examination of these studies highlights important elements in cardiovascular PGx study design.

One of the first cardiovascular therapeutic areas that saw success through both candidate gene approaches and GWAS approaches was oral anticoagulants, specifically, the drug warfarin. Through multiple candidate gene studies SNPs in and near *CYP2C9* and *VKORC1* were associated with stable warfarin dose (D'Andrea, et al. 2005, Rettie, et al. 1994, Rieder, et al. 2005, Thijssen, et al. 2001). Next, the association between a SNP in *CYP4F2* and stable warfarin dose was identified using a drug metabolism and drug transporter SNP panel (Caldwell, et al. 2008). These associations were further confirmed through GWAS (Cooper, et al. 2008, Takeuchi, et al. 2009). In 2007, the Food and Drug Administration (FDA) added a genetic table to the warfarin label (Gage and Lesko 2008). Additionally, warfarin dosing algorithms have also been constructed to take both clinical and genetic information under consideration to calculate a starting warfarin dose for a patient (Finkelman, et al. 2011, Klein, et al. 2009). However, the translational of these results into the clinic has been difficult for multiple reasons including mixed results from randomized controlled clinical trials (Anderson, et al. 2012, Gage, et al. 2017, Kimmel, et al. 2013, Pirmohamed, et al.

2013), ancestry specific variants influencing stable warfarin dose (Asiimwe, et al. 2020, Daneshjou, et al. 2014, Scott, et al. 2009), and the use of direct oral anticoagulants or DOACs (Burn and Pirmohamed 2018). These studies highlight the importance of race, and ancestry specific variants that can impact drug response.

Clopidogrel, an oral antiplatelet medication, is cardiovascular drug with a significant association discovered through GWAS. The association between *CYP2C19**2 and diminished clopidogrel response was discovered through a GWAS for platelet activation in healthy individuals after taking clopidogrel for seven days (Shuldiner, et al. 2009). This finding was further validated through the association of *CYP2C19**2 and adverse cardiovascular events in clopidogrel treated patients undergoing percutaneous coronary intervention (PCI) (Mega, et al. 2009, Mega, et al. 2010, Simon, et al. 2009). This led to the FDA issuing a "Black Box" warning for the clopidogrel label in March 2010 (Ford and Taubert 2013), and the implementation of *CYP2C19* genotyping before prescribing antiplatelet treatment after PCI at some medical centers (Cavallari, et al. 2017, Empey, et al. 2018, Pulley, et al. 2012). In the setting of clopidogrel therapy after stroke, the association between *CYP2C19**2 and adverse cardiovascular outcomes has been mixed (Hoh, et al. 2016, Jia, et al. 2013, McDonough, et al. 2015). Additionally, while the results from real-world and pragmatic data support genotyping in the setting of PCI (Cavallari, et al. 2018), data from clinical trials are less clear (Claassens, et al. 2019, Pereira, et al. 2020). Further, with the introduction of newer antiplatelet agents, there have also been studies discussing using *CYP2C19* genotyping to de-escalate patients from a newer antiplatelet agent to clopidogrel (Angiolillo, et al. 2019, Cavallari and Lee 2019, Martin, et al. 2020, Sibbing, et al. 2017). Overall, the story of clopidogrel pharmacogenomics highlights the importance of therapeutic area, and the need to understand the changing use of the drug in the clinical setting.

Additional cardiovascular therapeutic areas that have seen various degrees of success in discovery PGx are hypercholesterolemia (statins) and hypertension (antihypertensives). In a GWAS of patients treated with high dose simvastatin (80 mg per day) of 85 cases of incident myopathy compared to 90 controls, a SNP in *SLCO1B1* was identified at the genome-wide significant level. The SNP is in linkage disequilibrium with rs4149056 (*5), a nonsynonymous SNP in *SLCO1B1*, which showed an ~5 times increased risk for statin-induced myopathy per C allele (Link, et al. 2008). Despite the small sample size, the association was replicated (Link, et al. 2008), and guidelines have been created for simvastatin dosing based on SLCO1B1 phenotype (Ramsey, et al. 2014). This illustrates that even with a small sample size, significant SNPs can still be identified in cardiovascular PGx studies if the effect size is large. While there are currently no clinical pharmacogenomic guidelines in hypertension, there have been significant SNPs identified and replicated with blood pressure response and adverse cardiovascular outcomes after treatment with antihypertensive drugs. SNPs in and near *NEDD4L*, *PRKCA*, and *YEATS4* have been significantly associated with blood pressure response to thiazide diuretics, and successfully replicated (Duarte, et al. 2012, McDonough, et al. 2013a, Turner, et al. 2013b). A meta-analysis of five randomized controlled trials identified a missense SNP in *BST1*, rs28404156, that was significantly associated with blood pressure response to β-blockers (Singh, et al. 2019). Additionally, SNPs in the following genes have been significantly

associated with adverse cardiovascular outcomes after treatment with antihypertensive drugs: *ADRB1* with β-blockers (Pacanowski, et al. 2008), *NEDD4L* with thiazide diuretics (McDonough, et al. 2013a, Svensson-Färbom, et al. 2011), *CACNA1C* and *CACNB2* with calcium channel blockers (Beitelshees, et al. 2009, Niu, et al. 2010), *FGB* with ACE-inhibitors (Lynch, et al. 2009), and *SIGLEC12*, *A1BG*, and *F5* with β-blockers and calcium channel blockers (McDonough, et al. 2013c). In hypertension, while there have been many studies there are few well replicated PGx SNPs. This illustrates the difficulty in replication, and the value in meta-analyses to increase sample size and power.

There is still great need for further study in each of these therapeutic areas to identify additional genetic variants that influence cardiovascular drug response. There is also great need to study the identified variants in other racial and ancestry groups, and to conduct additional studies in racial and ethnic minorities. Prior research has shown both the existence and importance of racial specific PGx variants (Asiimwe, et al. 2020, Cavallari and Perera 2012, Daneshjou, et al. 2014), and the need to include diverse populations in research so they may also benefit from any future implementation.

CRITICAL PARAMETERS AND TROUBLESHOOTING

One of the biggest issues in cardiovascular PGx is replication. Many cardiovascular PGx studies are sub-studies of larger, cardiovascular RCTs. While these studies are advantageous due to the higher quality of data and multiple time points for data collection, the exact same clinical trial will never be conducted twice, making replication harder. Other common data sources for cardiovascular PGx studies are longitudinal cohort studies with prescription drug information. However, this information is often patient reported and only recorded once a year, or once or twice over the study period. This methodology also makes it difficult to construct many cardiovascular PGx phenotypes. With these common themes in cardiovascular PGx studies, replication of top SNPs from one study in another study with the exact same PGx phenotype, drug, and population is very difficult.

Nevertheless, replication and validation in cardiovascular PGx studies is not impossible. The strategy for replication may require additional considerations. First, slight changes in the drug may be considered. Either a drug in the same class (e.g., the thiazide diuretic hydrochlorothiazide and the thiazide-like diuretic chlorthalidone), or a different dose of the same drug (e.g., 80 mg vs 40 mg of simvastatin). Second, the PGx phenotype maybe slightly different. A couple examples from prior cardiovascular PGx studies include a discovery GWAS of antiplatelet response to clopidogrel and a replication of adverse cardiovascular events after treatment with clopidogrel in patients undergoing PCI (Shuldiner, et al. 2009), and plasma renin activity in hypertension patients and validation with corresponding blood pressure response to antihypertensive therapy (McDonough, et al. 2018). Third, the study population may be different. There are multiple examples where a trans-ethnic or trans-racial validation strategy was used (Fontana, et al. 2014, Gong, et al. 2015, McDonough, et al. 2013b). Overall, considerations for a replication plan should occur early in the study design and should be flexible.

STATISTICAL ANALYSIS:

The most common statistical methods used for analysis of cardiovascular PGx studies are very similar to those used in other genetic studies and GWAS. If the cardiovascular PGx phenotype is continuous a linear regression model is often used, and if the cardiovascular PGx phenotype is binary a logistic regression model is often used. In consideration for additional comorbidities and exposures that could influence drug response, multiple covariates are often added to the regression model. Commonly these include age, sex, principal components for ancestry, other drug exposures, other comorbidities known to influence the drug response or outcome, and randomization arm if the data is originating from a RCT. Some cardiovascular PGx studies include a drug interaction term, investigating the interaction between SNP genotype and drug exposure. Many software programs that are used for GWAS analysis allow for the inclusion of an interaction term (e.g., SNPxdrug). A list of commonly used software programs in cardiovascular PGx studies is shown in Table 3.

For GWAS analysis, some of the common programs used in cardiovascular PGx include PLINK, ProbABEL, and EPACTS (Table 3). Additionally, there are also R packages that many investigators utilize for cardiovascular PGx GWAS analyses. For cardiovascular PGx meta-analysis studies, METAL is commonly used (Table 3). Another feature in cardiovascular PGx studies is interpreting the results of the top SNP(s) in context of the drug response, drug outcome, or drug interaction. In order to conduct analyses that are focused on the drug response or drug outcome, investigators may conduct genotypic means analyses for quantitative traits or look at the outcome by genotype and by drug for binary traits. Finally, in all cardiovascular PGx studies, it is important to conduct a power calculation (Table 3).

UNDERSTANDING RESULTS:

After completing the statistical analyses, the replication and validation plans, and compiling a list of top SNPs; the next step is to put them in context. During this phase, it is important to remember the PK and PD of the drug being studied, as well as the physiology of the disease process. There are many examples in prior cardiovascular PGx studies of associations with SNPs in and near genes that encode for drug metabolism enzymes or drug transporters. There are also examples of associations that connect back to the disease phenotype under study (e.g., adverse cardiovascular outcomes) and the findings suggest new mechanisms of action of how a drug may act to reduce risk for an outcome.

FUTURE DIRECTIONS

The field of cardiovascular PGx has seen many exciting discoveries emerge from candidate gene studies and GWAS. The PGx variants associated with warfarin, clopidogrel, and simvastatin have led to FDA label changes (Gage and Lesko 2008), clinical PGx implementation programs (Cavallari, et al. 2017, Empey, et al. 2018), and clinical PGx guidelines (Ramsey, et al. 2014, Relling and Klein 2011). As cardiovascular PGx expands, the use of other ‘omic technologies in discovery studies is also growing. Additionally, the results from cardiovascular PGx discovery GWAS and other –omic studies provide further insight into the pathways of these drugs, and targets for future drug discovery.

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SIGNIFICANCE STATEMENT:

Cardiovascular pharmacogenomics is the study and identification of genomic markers that are associated with variability in cardiovascular drug response, cardiovascular drug related outcomes, or cardiovascular drug related adverse events. This overview presents an introduction and historical background to cardiovascular pharmacogenomics, and a protocol for designing a cardiovascular pharmacogenomics study.

Table 1.

Elements to consider during the cardiovascular PGx study design process

Study Design Element	Consideration for PGx Study
Phenotype	1. Cardiovascular trait or disease 2. Cardiovascular drug 3. Drug response
Type of Study	1. Existing Data or New Study 2. Retrospective or Prospective 3. Observational or Clinical Trial 4. Candidate gene or GWAS
DNA	1. Existing DNA samples 2. Need to collect DNA samples
Study Population	1. Race and ancestry populations 2. Other comorbidities 3. Other exposures
Power	1. Sample size 2. Effect size 3. Minor allele frequency
Replication	1. Direct replication 2. Validation in similar drug 3. Validation in similar disease state 4. Validation in another race group
Statistical Analysis	1. Logistic regression 2. Linear regression 3. Interaction analysis 4. Single study or Meta-analysis

PGx: Pharmacogenomics

GWAS: Genome-wide association study

DNA: Deoxyribonucleic acid

Table 2.

Example cardiovascular PGx phenotypes

Cardiovascular PGx Phenotype	Trait or Disease State	Cardiovascular Drug	Drug Response
Blood Pressure Response to Thiazide Diuretics	Change in Blood Pressure in Hypertension patients	Thiazide Diuretic	Post-treatment Blood Pressure - Pre-Treatment Blood Pressure
Bleeding Outcomes after treatment with Warfarin	Atrial Fibrillation	Warfarin	Bleeding events after treatment with Warfarin
Myopathy after treatment with Simvastatin	Hypercholesterolemia	Simvastatin	Myopathy after treatment with Simvastatin
Cardiovascular Outcomes after treatment with Clopidogrel	Percutaneous Coronary Intervention	Clopidogrel	Cardiovascular Outcomes after treatment with Clopidogrel
Elevated Fasting Glucose after treatment with Thiazide Diuretics	Hypertension	Thiazide Diuretic	Post-treatment Fasting Glucose - Pre-treatment Fasting Glucose
Cardiovascular Outcomes after treatment with Calcium Channel Blockers	Hypertension	Calcium Channel Blocker	Difference in Cardiovascular Outcomes in patients treated with Calcium Channel Blockers compared to those not treated with Calcium Channel Blockers

PGx: Pharmacogenomics

Table 3.

Software used in Cardiovascular PGx Studies

Program	Input Data Type	Functions	Remarks	Website
PLINK	Directly Typed genotypes and Imputed genotypes	Linear Regression Logistic Regression Interaction Term	Allows for data management, Principal Component Analysis, Linkage Disequilibrium calculations, Genotypic means for quantitative traits	https://www.cog-genomics.org/plink/2.0/
ProbABEL	Imputed genotypes	Linear Regression Logistic Regression Interaction Term	Allows for Cox proportional hazards models	https://github.com/GenABEL-Project/ProbABEL
EPACTS	Sequence-based genotypes from sequencing or imputation	Linear Regression Logistic Regression EMMAX	Allows single variant and gene-wise or group-wise tests	https://genome.sph.umich.edu/wiki/EPACTS
METAL	Summary results from GWAS or top SNP signals	Meta-analysis	Allows for both inverse-variance weighting and weighting by sample size Includes options for genomic control correction	https://genome.sph.umich.edu/wiki/METAL_Documentation
SAS	Single SNP genotypes Demographics and Characteristics	Linear Regression Logistic Regression Interaction Term Descriptive Statistics	Used for PGx analyses by genotype or by drug for top SNPs	https://www.sas.com/en_us/home.html
R	Directly Typed genotypes and Imputed genotypes Single SNP genotypes Demographics and Characteristics	Linear Regression Logistic Regression Interaction Term Descriptive Statistics	Additional R Packages for GWAS analyses Used for PGx analyses by genotype or by drug for top SNPs	https://www.r-project.org/
Quanto	Study Characteristics	Power Calculation	Windows application	https://preventivemedicine.usc.edu/download-quanto/
G*Power	Study Characteristics	Power Calculation	Mac and Windows applications	https://stats.idre.ucla.edu/other/gpower/