2. CANDIDATE'S BACKGROUND

2.1 Commitment to Patient Oriented Research (POR): Dr. Limdi developed an interest in patient-oriented research in 1998, while working as a clinical pharmacist with the Stroke and Epilepsy services. Her initial research involved studying epilepsy and valproate in treating status epilepticus[1-6] and understanding factors contributing to the variability in warfarin response.[7] Reading the first report on the association of polymorphisms in the cytochrome P450 2C9 (*CYP2C9*) with warfarin dose and risk of bleeding,[8] was an "ah-ha" moment spawning her interest in understanding the genetic underpinnings of drug response (pharmacogenetics). As a pharmacist, she immediately recognized the promise of pharmacogenetics in elucidating reasons for variable drug response and its potential to improve efficacy and safety of drug therapy.

Not knowing where to start, in part due to a paucity of mentors, she attended the first Pharmacogenetic Research Network Conference in 2001 with the sole purpose of finding a mentor. She looked through the speaker biographies for the word "pharmacogenetics" and "the name of a drug (any drug)." Dr. David Flockhart (Tamoxifen; Pharmacogenetics) was her first mentor (Pharmacologist, Internist). In fact, the aims of her K23 award were drafted in the cafeteria adjoining the Natcher Conference Center at NIH. An epidemiologist at the conference introduced her to Dr. Ron Acton (Microbiologist, Immunogeneticist; Mentor #2). She came away with a plan to pursue patient-oriented research (POR) in cardiovascular pharmacogenetics.

Recognizing the need to develop crucial research skills she decided to pursue structured didactic training offered by the Masters in Public Health (Dr. David Allison; Mentor #3; Psychology, Statistical Genetics) during the K23 award (NS045598) period. She set ambitious goals and proceeded to exceed them building the largest pharmacogenetic cohort of chronic warfarin users. After consulting with her mentors and Program officer, she decided to pursue a PhD in Epidemiology (Dr. Donna Arnett; Mentor#4 Cardiovascular nurse, Epidemiologist, Genetic epidemiologist) writing her RO1 with Dr. Arnett's guidance. Her expertise in clinical pharmacy, pharmacology, biostatistics, clinical research and epidemiology has allowed her to leverage these skills to secure independent NIH funding (HL092173; 2008-2013; 2014 with extension) which was competitively renewed (2014-19). Her research portfolio has grown to encompass pharmacogenetics and pharmacoepidemiology of antithrombotic agents, with studies involving observational and clinical trial designs.

2.2 Evidence of Ability to Conduct High Quality Patient-Oriented Research: In a short time span she built the largest prospective warfarin cohort (n=1647, 43% African American) enabling the evaluation of multiple hypotheses. These factors have led to fruitful collaborations that have been at the forefront of warfarin pharmacogenetics; identifying novel polymorphisms in *CYP2C9*,[9-13] understanding the influence of *CYP2C9* and *VKORC1* on warfarin dose among Whites and Blacks,[10,11,14-26] conducting comprehensive *VKORC1* haplotype analysis[16] and genome-wide association analysis.[10,11,27] Moreover her focus on genetic influence on warfarin-related hemorrhage[21,28-30] is recognized as a significant contribution. She has expanded her efforts to include the influence of kidney function on warfarin dose and hemorrhagic complications[28-31] and genetic analysis methodology.[32-34] This expertise and experience has made her a valued contributor to the ongoing International Warfarin Pharmacogenetics Consortium (IWPC) effort [10,11,13,24,25,27,35-37]and as a site-principal-investigator for the recently completed NHLBI clinical trial "Clarification of Optimal Anticoagulation through Genetics (COAG)."[25] Of Dr. Limdi's 60 peer-reviewed publications, 30 led by mentees and junior faculty.[1,2,10-13,19,23,27,32,33,35,37-54] Dr. Limdi's interest in cardiovascular epidemiology and pharmacoepidemiology has also resulted in collaborative efforts to inform critical knowledge gaps in stroke and atrial fibrillation, target strategies to mitigate stroke severity, and assess the effects of antithrombotic and statin therapy (NS070307). Ongoing efforts with the CHARGE consortium (HL103612) aim to identify genetic susceptibility to adverse reactions of medications. Growing recognition of her expertise is attested by invited presentations to meetings (American Heart Association, National Kidney Foundation, Digestive Diseases Week, and International Thrombosis and Haemostasis and American Society of Hypertension).

Dr. Limdi serves as the Interim Director of UAB's Hugh Kaul Personalized Medicine Institute. The two principal strategic initiatives of the institute center on fueling discoveries through research and improving care through implementation of genotype-guided therapy. The implementation initiative aims to integrate precision medicine into routine clinical care, build a knowledge base that evolves as new knowledge is generated and provide clinical decision support at point-of-care using patient-specific clinical and genetic factors.

This unique career trajectory and seamless transition from K23 to RO1 and its competitive renewal was guided by a strong mentoring team. Her commitment to mentoring therefore reflects what she has learned from these role models regarding the skills needed to help potential investigators, appreciate their strengths, and the

wisdom needed to help them balance individual success with strong teamwork. Moreover ongoing collaborations with Drs. Veenstra (Economics, Pharmacogenomics) Prabhu, Brown, Brott (Cardiology), and Allon (Nephrology) have allowed her to broaden her skill set and develop a robust program in POR focusing on cardiovascular disease and its treatment. She has made specific choices in favor of research over clinical and administrative activities, and is now in a position to focus on mentoring others in this increasingly important area of research. The protected time afforded by this award will secure the time needed to devote to both the continuation of this highly productive career path and to mentoring the next generation of POR investigators in cardiovascular research and personalized medicine.

2.3 Mentoring Record: Dr. Limdi has mentored clinicians in POR since 2000 and has developed long-term mentor relationships with several investigators (Table 1). Drs. Irvin, Boehme and Albright successfully competed for AHA awards and Dr. Ather for the Walter B. Frommeyer, Jr., Fellowship in Investigative Medicine. Dr. Brown (KL2 awardee) is working in cardiometabolic syndrome and is now one of Dr. Limdi's collaborators. For her excellence in mentorship, Dr. Limdi was awarded the **2013 UAB Deans Mentorship award** (Appendix 1). In addition to the mentees, Dr. Limdi has served as a clinician mentor for post-doctoral T32 fellows in statistical genetics (Drs. Zhang, Cosgun and Yan).

Table 1: Investigators Mentored and mentorship role

Mentee; Dr. Limdi's Role	Present Position, research focus and funding
Sameer Ather, MD, PhD 2014-present: Co-mentor (with Dr. Prabhu)	• Assistant Professor, Division of Cardiovascular Disease • Cardiovascular pharmacogenetics; genetic predictors of Beta-blocker therapy in heart failure; anticoagulation response in heart failure. • Awarded Frommeyer Fellowship in Investigative Medicine. K23 planned for 2017 centered on Personalized Heart Failure therapy
Marguerite Irvin, PhD 2008-present: Co-Mentor (with Dr. Arnett)	• Assistant Professor, Epidemiology, School of Public Health, UAB. • Cardiovascular genomics and epigenomics: hyperlipidemia, hypertension, renal traits • Awarded Scientist Development Grant (AHA #15SDG25760021) K23 planned for 2018 in cardiovascular genomics and epigenomics
Karen Albright, DO, PhD Candidate Epidemiology 2010- present: Primary Mentor	• Fellow in Advanced Geriatrics at the Birmingham VA (July 1, 2014 to June 30 2016) • Awarded AHA Mentored Clinical and Population Research Award (#14CRP30380256; July 1 2014 to June 30, 2016). • Awarded: Post-doctoral fellow (T32 HS019463; July 1, 2012 to June 30, 2014) • K23 in preparation, planned for 2016: The influence of medication adherence on ischemic stroke: Racial disparities.
Amelia Boehme, PhD 2010- present: Primary mentor	• Awarded AHA fellowship (grant# 13PRE13830003; Jan 1, 2013 to Dec 1, 2014) • Predictors of thromboembolism and hemorrhage in patients on Ventricular Assist Devices; K23 in preparation; submission planned Oct 2016
Aditi Shendre MBBS, MPH Epidemiology PhD candidate Clinical Mentor	• Genomic and epigenomics and admixture mapping in cardiovascular traits • Genomic underpinnings of novel anticoagulant response K23 planned for 2018-2019.
Todd Brown, MD, MSPH 2010-2013: Co-mentor	• Assistant Professor, Cardiology; Division of Cardiovascular Disease, UAB. • Awarded Mentored Clinical Scientist Development Award (KL2RR025776): Variation in Cardiovascular Risk among Different Clinical Presentations of Metabolic Syndrome. • Currently Co-investigator (RO1HL092173; PI Limdi) and COAG trial (Site PI: Limdi)
Jonathan Thigpen, Pharm.D 2010-2013: Primary Mentor	• Assistant Professor, Notre Dame of Maryland University, Pharmacy • Antithrombotic pharmacoepidemiology, pharmacogenetics, acute coronary syndrome
Anderson, Aaron, MD 2010-2013: Primary Mentor	• Assistant Professor, Department of Neurology, Emory University • Influence of comorbidities on Stroke occurrence, severity and outcomes
Temeka Borden, Pharm.D 2010-2012: Co-mentor	• Drug Information Analyst at American Society of Health-System Pharmacists • Hypertension medication adherence in African Americans with diabetes (T32 Fellow)
Larry Ver Hoef MD 2000-2008: Co-mentor since residency, in decision making analysis in epilepsy surgery	• Associate Professor, Neurology, UAB. • Awarded Patient Oriented Career Development grant (NIBIB: K23EB008452**)** • Continuing to work in developing and integrating new neuroimaging tools and clinical decision-making in epilepsy surgery
Robert Knowlton MD, MSPH 2006-2012: Co-mentor	• Professor, Clinical Neurology. University of California San Francisco • Continued collaborations on pharmacogenomics (Epilepsy Phenome Genome Project) and race and gender differences in the epidemiology of adult onset epilepsy

3. CANDIDATES' CAREER GOALS AND OBJECTIVES

3.1. Dr. Limdi's short-term and long-term goals are to continue to build a patient-oriented cardiovascular research program bringing scientific rigor and innovation to the optimization of oral antithrombotic therapy. The maximum benefit of such a program can only be achieved if it also involves training and mentoring of the next generation of investigators. The work requires a thorough understanding of the principles and challenges of research using both observational and interventional approaches together with the ability to perform scientifically based and hypothesis-driven clinical research in complex and racially diverse population with multiple comorbidities (e.g. chronic kidney disease (CKD); heart failure (HF)) seen in routine clinical practice.

The long term goals are to incorporate genetic and clinical factors to **Personalized Antithrombotic Therapy** (PAT) including oral anticoagulants (warfarin; and the non-vitamin K antagonist oral anticoagulants (NoAC; dabigatran, rivaroxaban apixaban, and edoxaban) and antiplatelet (clopidogrel, ticagrelor and prasugrel) therapy; and also to develop and implement clinical prediction rules (CPRs) to personalize risk-benefit assessment and enable clinical decision making at point of care. To this end, more immediate-term goals are to leverage two resources and expand opportunities through three projects for MD, Pharm.D, and PhD trainees in POR to address key knowledge gaps. The resources and projects are detailed in the research strategy section. The IRB approvals are attached as Appendix 2.

a. **Resource I:** Genetic and Clinical Predictors of Response to Warfarin and Novel Anticoagulants (PI Limdi; R01HL092173; 2014-2019) has established a prospective inception cohort of patients on oral anticoagulants, including warfarin (warfarin pharmacogenomics cohort; goal=1800;1647 recruited) and dabigatran (DBG cohort; goal 500; 408 recruited).
   - **Project 1,** led by Dr. Ather, will focus on warfarin response in patients with heart failure.
   - **Project 2,** led by Dr. Shendre will focus on candidate gene analysis; elucidate predictors of DBG-related major hemorrhage and develop CPRs. We will specifically assess variants in ATP-binding cassette, sub-family B, member 1 (*ABCB1*) and carboxylesterase 1 (*CES1*).

b. **Resource II:** To facilitate delivery of precision medicine, the University of Alabama at Birmingham (UAB) is establishing infrastructure to integrate genomics into clinical care. As the interim director of the leadership in UAB's Personalized Medicine Institute, Dr. Limdi is currently leading the implementation of Cytochrome P40 2C19 (*CYP2C19*) genotype-guided antiplatelet therapy (GGAT) in patients with acute coronary syndrome (ACS) and those undergoing percutaneous coronary intervention (PCI). Antiplatelet therapy is personalized based on patient-specific clinical factors and *CYP2C19* genotype.
   - **Project 3**, led by Drs. Arora and Irvin, will determine racial differences in thromboembolic [major adverse cardiovascular events (MACE) and stent thrombosis] and hemorrhagic events [55-58] and assess clinical utility and economic value of GGAT.

These goals are a natural progression of Dr. Limdi's current research and will serve to develop a robust patient-oriented research program for complex patients to personalize antithrombotic therapy.

3.2. Evidence of Ongoing High-Quality Patient-Oriented Research- its Relationship to this Program: The research plan in this application builds on Dr. Limdi's work in warfarin pharmacogenomics, observational studies and clinical trials. It has the dual aim of building a comprehensive approach to assessing genetic contributions to anticoagulant response; and of extending these findings back to the clinical realm to demonstrate the benefit of integrating this information into current decision making tools for antithrombotic therapy initiation. These studies will provide the foundation to understand whether institution of PAT based on individual benefit vs. risk will improve patient outcomes (effectiveness) and if these improvements help realize tangible population benefit (clinical utility) and are of value (cost-effectiveness).[59-63] She will leverage her current research and her leadership in UAB's Personalized Medicine Institute to meet her long-term goals.

The research plan has been extended from her current RO1 on warfarin pharmacogenomics and incorporates dabigatran. Its success is particularly relevant to the overall mentoring goal of the K24 Award. It uses a variety of data sources and analytic approaches to articulate studies that integrate genetic information into the treatment paradigm, and outcomes research to evaluate the benefits of this approach. This interplay of research approaches can serve as a model for new investigators in POR.

3.3. Evidence of Monetary Support for Patient-Oriented Research is evident from the record of extramural funding (**Table 2**). The resources created by the ongoing research program will be harnessed by mentees to chart their research careers in POR and result in the development of new proposals well beyond the funding period of this K24.

Table 2: Extramural Research grants (current and completed within the last 5 years)	
2014-19	Genetic and Clinical Predictors of Response to Warfarin and Novel Anticoagulants (R01HL092173; PI Limdi)
2011-15	Prospective meta-analyses of drug-gene interactions: CHARGE GWAS consortium (R01HL103612; PI Psaty)
2012-16	Potential EEG biomarkers and antiepileptogenic strategies for epilepsy in TSC (1P20NS080199; PI Bebin)
2008-14	Genetic and Environmental Determinants of Warfarin Response (R01HL092173; PI Limdi)
2008-14	Prediction of Warfarin Dosing Using Clinical and Genetic Factors (R01HL066176; PI Kimmel)
2010-14	Effect of Statins and Modifiable Factors on Stroke Outcome in Atrial Fibrillation (R01NS070307; PI Hylek)
2011-14	Clarification of Optimal Anticoagulation through Genetics (COAG; NCT00839657; PI Kimmel)
2009-12	Personalization of Anticoagulation Reversal with vitamin K (PARK; R01HL092173-02S2; PI Limdi)
2009-10	Administrative Supplements for High School Summer Research Experience (R01HL092173-02S1; PI Limdi)
2003-09	Pharmacogenetic optimization of anticoagulation therapy (K23NS045598; PI Limdi)

3.4. Contribution of this Award to Attainment of Long-Term Career Objectives: Having started her career as a clinical pharmacist, Dr. Limdi recognizes the time-intensive nature of effective mentoring. In fact, she owes her success in patient-oriented research, in the field of pharmacogenomics and anticoagulation therapy, to the mentorship she received. To augment her capabilities and to broaden her work to include antiplatelet agents and to advance the implementation of personalized medicine, Dr. Limdi needs an intensive focus on research and in training the next generation of POR investigators.

Dr. Limdi currently serves as a mentor for Drs. Boehme and Albright and co-mentor for Dr. Irvin; each receiving AHA grants under her guidance. Given this success, she would like to refocus her efforts on mentoring patient-oriented researchers and help three to four trainees to submit K23 applications in the next 5 year period.

Table 3: Current and projected future distribution of effort		
Grants (start - end date)	**Current Effort**	**Effort projected**
	---	**25% With the K24 award**
R01HL092173 (2/1/2014 to 1/31/2019)	40%	40%
1P20NS080199-01 (9/1/2012 to 8/31/2016)	10%	0% (ends in 2016)
Departmental	20%	Reduce to 10%
SOM PMI	30%	25%

In addition to Drs. Boehme and Albright, Drs. Ather, Shendre, Irvin and Arora have demonstrated significant interest in antithrombotic therapy, pharmacogenomics and precision medicine research. Following her mentors advice,[64] Dr. Limdi has helped mentees articulate the research questions and develop the projects pursued herein. She has helped them understand their motivation, the novelty of the proposed research, its ability to provide a niche, its practicality and its conduct in a supportive environment. These issues hold the key to a quality research career, one that generates exciting, novel, and effective therapies that can change lives.

The K24 award will provide critical protection of Dr. Limdi's time to enable her to maintain focus on mentoring new promising mentees in POR while broadening her own skill set which will only further facilitate her capacity to train others. Dedicated time to foster the careers of the junior scientists listed in this application will be required to launch the next generation of patient-oriented researchers dedicated to personalized antithrombotic care. Dr. Limdi's track record demonstrates she is the ideal person for this important job.

Specifically, with the K24 award, Dr. Limdi will:

1. Commit 25% effort to augmenting her skills further facilitating her mentoring of Drs. Ather, Shendre, Arora and Irvin, engaging them to lead the research proposed herein and submit K23 grants (in 2017, 2018 and 2019). Dr. Limdi will serve as the primary mentor for Drs. Ather, Shendre, Arora and Irvin.
2. Dr. Limdi will reduce effort on required teaching and administrative activities to 10%. This will allow her to focus on mentoring junior clinical investigators and augment her capabilities in POR.

Dr. Limdi was recently promoted to professor (Oct 2014) from associate professor (Oct 2009 – Sept 2014; with award of tenure in Oct 2011). She continues to maintain her independent peer-reviewed research program and to provide mentorship in patient-oriented research.

Protected time is central to Dr. Limdi's' ability to capitalize on the past several successful years of clinical research. The K24 award will assure that Dr. Limdi is able to focus on a series of compelling scientific questions that arise from her current work. These questions will require focused and vigorous effort over the next several years and prepare junior clinician investigators in this emerging field.

4. CAREER DEVELOPMENT AND TRAINING ACTIVITIES DURING AWARD PERIOD

Dr. Limdi will commit 25% effort towards mentorship and further augmenting her POR skills.

4.1 Development as a mentor: Dr. Limdi's seamless transition from a clinician to a K23 awardee and finally to an independent researcher, was guided by a team of mentors with diverse expertise. These included Drs. Flockhart, Acton, Allison, and Arnett. Despite prior accomplishments, Dr. Limdi recognizes the need for continued mentoring. She has sought guidance from her mentors individually to discuss specific challenges in mentorship and developed strategies to address each challenge. These interactions have enabled her to develop effective skills which are reflected in the success of her mentees. She has:

- Encouraged junior faculty/ mentees to lead papers (30 published, 2 in press, 7 under review).[1,2,10-13,19,23,27,32,33,35,37-54]
- Successfully guided mentees to formulate hypotheses identify grant mechanisms for which they would be competitive and submit successful grant applications. In fact, in the last three years her mentees have secured AHA awards including Pre-doctoral fellowship (Boehme/ Limdi; grant# 13PRE13830003), Mentored Clinical and Population Research Award (Albright/ Limdi; grant #14CRP30380256) and Scientist Development Grant Award (Irvin/Arnett-Limdi #15SDG25760021).

Dr. Limdi has come to appreciate varying skill sets, strengths and weaknesses and has developed effective approaches to work with each individual. Her contribution in mentoring was recognized by UAB's 2013 Deans Mentorship award (Appendix 1). To continue to grow as a mentor and benefit from the interactions with senior faculty with extensive mentorship experience, Dr. Limdi has assembled a mentorship team (Drs. Saag, and Standaert). They will meet with Dr. Limdi (for 1.5 hours each time) quarterly to discuss specific challenges identified in Dr. Limdi's evaluations by mentees (discussed in section 6.3 of the mentoring plan).

In addition, Dr. Limdi will participate in a structured mentor training program "Mentor Training for Clinical and Translational Researchers" (http://www.uab.edu/ccts/TrainingAcademy/Pages/Mentoring.aspx) which focusses on six core competencies:

1. Maintaining effective communication (e.g., active listening, communication styles, constructive feedback, communication with diverse groups, strategies for improving communication).
2. Aligning expectations (establishing expectations, communicating expectations, aligning expectations of mentor and mentee, consideration of personal and professional differences).
3. Assessing understanding (understanding of core concepts and processes, identification of reasons for lack of understanding, strategies to enhance understanding across diverse perspectives).
4. Addressing equity and inclusion (expand understanding and influence of diversity, recognize impact of assumptions, and identify strategies for recognizing and addressing issues).
5. Fostering independence (define core elements of independence, strategies to build confidence and trust, identify benefits and challenges of fostering independence).
6. Promoting professional development (identify roles, develop strategies for guiding development, conversations about goals and objectives, open dialogue about competing demands).

4.2 Development of new skills: The most critical issue impeding improvements in cardiovascular health is the enormous gap between what we know can optimize health and what actually gets implemented in practice. This is widely recognized. Senator Lister Hill said "*We must develop a communication system so that the miraculous triumphs of modern science can be taken, from the laboratory and transmitted to all in need.*" We must go beyond *"Bench-to-Bedside"* and demonstrate benefit the individual patient, the population and the health care system……*"Patient-to-Policy Maker."*

To complement her expertise in clinical pharmacology, statistics and epidemiology and to instill skills necessary for implementation of personalized medicine, Dr. Limdi will undertake additional training in:

- Dissemination and Implementation Research: To gain a thorough grounding in conducting dissemination and implementation research and develop methods to ensure that evidence-based strategies to improve health and prevent disease are effectively delivered in clinical practice, Dr. Limdi will attend the NIH Training Institute for Dissemination and Implementation Research in Health (TIDIRH; https://www.regonline.com/Register/Checkin.aspx?EventID=1690463) in the summer of 2016.[65]
- Clinical Decision Making and Cost-Effectiveness Analysis: To evaluate the clinical utility and economic value of evidence-based interventions Dr. Limdi will undertake didactic training through doctoral level courses Clinical Decision Making (HCO721) and Cost-Effectiveness Analysis (HCO722) in year 2. She will work closely with Dr. Pisu to lead the economic analysis for Project 3 while training her mentees.

5. TRAINING AND INSTRUCTION IN THE RESPONSIBLE CONDUCT OF RESEARCH

Dr. Limdi has participated in training in the responsible conduct of research since 2000 both to meet IRB training requirements and to advance her knowledge on specific issues with regard to genetics research (Duke University Modules; self-study; July 2004). She also attended a formal 3-credit-hour course in fall of 2007 (approximately 40 hours for in-class instruction*; Principles of Scientific Integrity; GRD 717*). Dr. Limdi is a frequent discussion leader, working with the UAB IRB on issues of genomics, biobanking and data-sharing.

UAB offers a variety of resources for training in the responsible conduct of research, organized by the CCTS (http://www.ccts.uab.edu/pages/RCR.aspx). Specific requirements for K24 participants will include:

1. Agreement to the UAB Research Code of Conduct (http://main.uab.edu/show.asp?durki=114608)
2. Enrollment in "Principles of Scientific Integrity" (GRD 717; 3 credit hours) taught by Dr. Jeff Engler with guest faculty contributing to specific subject matter.
   - Format: GRD 717 is a three-credit hour course offered twice each year. It provides systematic instruction on ethical issues and principles in the practice of science through reading, case discussions and lecture.
   - The textbook is Introduction to the Responsible Conduct of Research by N H. Steneck, modified to reflect more recent changes in rules and regulations. The team based learning pedagogic approach is modeled after a course developed by Dr. McCormack at the University of Florida School of Medicine.
   - Course material is made available online approximately one week before the class meeting. In-class time is spent in teams of 6 to 7 students, taking quizzes to measure comprehension of the course materials, followed by discussion of case studies.
   - Subject Matter: Topics covered in GRD 717 include the nature, extent, and causes of fraud in science; UAB policies on fraud; ideals of good science; the responsibilities of authorship and peer review; potential problems raised by the commercialization of research; scientists as public policy advisors; and ethical issues involved in animal experimentation and in clinical trials, conflict of interest, issues in research, authorship, ownership and data sharing, etc.
   - Duration and Frequency of Instruction: Students will read the textbook, watch slide presentations and videos (when available) on the class web site, and attend all course meetings. The class meets weekly over the course of the semester for 2.5 hours at each class meeting (40 contact hours).
3. Training in human subject's research ethics, offered by the UAB IRB through the Collaborative Institutional Training Initiative (CITI) web course.
4. Dr. Limdi will provide each trainee a copy of the book "*On Being a Scientist"* published by the National Academy of Sciences.[66] During the orientation (July/ August) Dr. Limdi will lead a one hour of *face-to-face instruction* with mentees to discuss specific ethical issues as they relate to the project at hand.
5. Starting September each year, Dr. Limdi will also lead hour long monthly discussions on topics related to Responsible Conduct of Research using the training modules developed by UAB's Center for Ethics and Values in Sciences (http://www.uab.edu/ethicscenter/educational-materials/rcr-materials). Attendance will be mandatory for all mentees. The team will view the video followed by discussion on how the issues presented relate to ongoing research projects that the mentees are involved with. Topics include conflicts of interest, misconduct, data management, responsible authorship, collaborative science, intellectual property, genetics and race, misconduct and whistle blowing and modeling ethical behavior.
   - This will be supplemented with additional resources such as "**Ethics for Authors"** to help discussions on issues around authorship (http://www.uab.edu/ethicsforauthors/).
6. Dr. Limdi will develop a 4-hour interactive education session on the ethical, legal, and social issues (ELSI) of genomic research. This independent scholarly activity will enhance her understanding of evolving issues and will be used to develop IRB training modules for investigators pursuing genetic research.

To summarize, the format will incorporate written materials, classroom didactics, web based training, and video materials. The subject matter will cover ethics in both laboratory and clinical settings; faculty participation will include both classroom and individual interaction. The duration of instruction will encompass one semester of formal coursework and ongoing informal interaction; and the frequency of instruction will encompass both the didactic period of coursework as well as informal education throughout the period of support.

6. PLAN FOR MENTORING CLINICAL INVESTIGATORS IN PATIENT ORIENTED RESEARCH

6.1 Mentoring Philosophy and Commitment: The applicants' career has been profoundly influenced by role models in mentoring such as Drs. Arnett, Flockhart, Acton and Allison. Through the 5 year K23 award period her mentors' fostered independent thinking tempered with realism and sound methodology and guided the assimilation of a comprehensive skill set that allowed a seamless transition from clinical pharmacist to an independent patient oriented researcher**. Having walked the path from a clinical pharmacist with an idea, to a K23 awardee, and finally to an independent patient oriented researcher, makes her an outstanding candidate for this award.**

Given the collaborative nature of research, a mentee's career development often requires a team-based approach for success. As the primary mentor, Dr. Limdi has worked with each of her current mentees to define unique research questions, met with co-mentors to chart a training plan in POR that allows the mentees access to expertise in relevant fields. Moreover, while mentees work on individual career interests, they work with each other to learn to appreciate and work with different points of view. This multidisciplinary approach provides the "big-picture" and allows the mentee to develop a comprehensive view of the issues at hand and build collaborations see section 6.3 for a full description of the mentoring plan). The role of co-mentors (Drs. Prabhu, Brott, Pisu, Brown, and Beasley) is discussed in their letters of support and reflected in the personal statement of their biosketches.

Dr. Limdi has built a record of successful mentoring of clinician scientists and is deeply committed to furthering the careers of POR investigators. In fact, three of her mentees (Dr. Irvin 15SDG25760021, Dr. Boehme 13PRE13830003 and Dr. Albright 14CRP30380256; Table 1) for whom Dr. Limdi has served as the primary mentor, have successfully been awarded grants from the American Heart Association. Dr. Irvin was also awarded two pilot intramural grants from the Minority Health Research Center and the UAB Diabetes Research and Training Center.

The breadth of her expertise has allowed Dr. Limdi to mentor investigators in several disciplines as they build their own independent patient-oriented research through UAB's training programs (Table 4) which target MD's and PhD's. Mentees report that she conveys the excitement of the creative process as well as the need for rigorous standards. She has created an environment that will support the development of independence by allowing fellows to implement their own ideas by leveraging resources. Her contributions were acknowledged by UAB's 2013 Deans Mentorship award.

Dr. Limdi has sought opportunities to influence young people considering research at the earliest stages of education, incorporating high school, undergraduates and medical students into her research. She has encouraged mentees to develop an original hypothesis, plan and implement a study and present findings at national meetings and submit publications. Her diverse skill set and her ability to explain complex concepts are attested to by the varied audiences she engages (from high school to faculty) across disciplines (cardiology, epidemiology, biostatistics, and neurology). She has even sought opportunities to influence high school (and even obtained NIH funding R01HL092173-02S1) and undergraduate students considering research careers.

The students are supported through programs for high school students (CORD Summer Science Institute) and medical students (Medical scientist training program, Short-term training in health professional schools) and pre-doctoral and post-doctoral scholars (through institutional training grants T32 and K12; See **Table 4).**

Table 4: Mentoring activities in patient-oriented research

Pre-doctoral, Post-doctoral Mentorship
Short Term Training in Health Professional Schools NHLBI T35 HL007473 (PI: Lorenz; 05/1/1991 - 04/30/2018)
Mentee: Ramy Bolis: A predictive algorithm for citalopram efficacy (co-mentor with Dr. Shelton; 2015, current)
Mentee: Alana Pearson: Influence of Apolipoprotein E genotype on warfarin response (primary mentor 2009-2010)
Medical Scientist Training Program (MSTP) NIGMS T32 GM008361 (PI: Lorenz; 07/01/1992 - 06/30/2020)
Mentee: David Figge: Genetics of levodopa induced dyskinesia's (co-mentor with Dr. Standaert; 2014- current; F31 NS090641-0A1)
Statistical Genetics Post-doctoral Training Program 5T32HL072757-10 (PI: Tiwari; 04/15/2003 - 7/11/2018)
Mentee: Qi Yan: Application of statistical genetic methodology for continuous and dichotomous drug response traits (co-mentor with Dr. Liu; 2012-2014)
Mentee: Erdal Cosgun: Machine learning techniques to mine genomic data to predict of drug response (co-mentor with Dr. Duarte; 2012-2013)

Table 4: continued
Biostatistics Pre-doctoral Training Program T32 HL079888 (PI: Tiwari; 9/1/2005 - 8/31/2016)
Mentee: Allison Fialkowski, MS: Pathway analysis approaches to predicting response to antidepressant medications (co-mentor with Dr. Liu; 2015, current)
Interdisciplinary Training in Kidney Research T32 DK007545 (PI: Agarwal; 7/1/1987 to 3/31/2019)
Mentee: Megan Yanik, MD: Personalized Medicine in pediatric kidney transplant recipients (co-mentor with Dr. Feig; 2014-2016)
Health services, outcomes and effectiveness research training program (T32HS013852 Saag; 7/1/2003-6/30/2015)
Patient Centered Outcomes Research K12 HS0230091 (PI: Saag; 8/1/2014 to 7/31/2019)
Mentee: Karen Albright, DO, MPH: Causes and consequences of racial differences in adherence to stroke prevention therapies (primary mentor T32 form 2012-2015; currently AHA grant #14CRP30380256)
Mentee: Jonathan Thigpen, Pharm.D: Antithrombotic Pharmacoepidemiology, Pharmacogenetics, Acute coronary syndromes (primary mentor: T32 form 2011-2013)
Mentee: Temeka Borden, Pharm.D: Racial differences in non-adherence to antithrombotic medications (primary mentor; T32 form 2010-2011)
Undergraduate Mentorship
McNair Scholars Program (co-mentor with Dr. Acton)
Mentee: Kiera Walker, B.S: Racial differences in the prevalence *CYP2C9 *2* variant (summer 2005)
Mentee: Jansa Lassiter, B.S: Racial differences in the prevalence of Apolipoprotein E (summer 2006)
High School Summer Mentorship
Administrative Supplements for Summer Research Experience: Genetic and Environmental Determinants of Warfarin Response (PI: Limdi R01HL092173-02S1; 2009-2011)
Center for Community Outreach and Development – Summer Science Institute for High School students
Mentee: Priya Shah: Myths and facts surrounding obesity- a survey of high school students (summer 2012)
Mentee: Arina Ghosh: Effect of kidney function on Cytochrome P450 2C9 expression (summer 2010)
Mentee: Jessie Strickland: Effect of kidney function on VKORC1 expression (summer 2009)

6.2 Recruitment of Trainees: Trainees will be recruited from departmental fellowship programs (cardiology, neurology, nephrology, and epidemiology), and through our T32, KL1, K12 and the MSTP programs based on referrals by program directors, including former fellows of the program, and through the K programs. Criteria will include commitment to a career in translational POR; strong clinical training and evidence for critical and independent thinking; capacity for the teamwork required for POR; and secondarily, interest or experience with a focus on cardiovascular outcomes. The list of current trainees in Table 1, attests to the range and quality of available mentees for recruitment into careers in patient oriented research.

Dr. Limdi presents opportunities in POR to trainees in various UAB POR training programs (**Table 4**). Interested trainees in these programs will be encouraged to leverage these resources to propose K23 applications in POR. These presentations are important as they provide potential mentees a thorough understanding of the POR research. During the post-presentation question and answer sessions, trainees frequently come up with ideas for additional analysis and propose manuscripts. This is how the current mentees came up with hypotheses proposed herein. Dr. Limdi will mentor Drs. Ather, Shendre, Irvin and Arora in POR and in preparing and submitting their K23. In addition she will continue to co-mentor Dr. Albright in cardiovascular pharmacoepidemiology.

6.3 Mentoring Program: Dr. Limdi will work with each mentee to assemble a mentoring-team of clinician investigators and researchers to best guide them to develop their careers in POR.

6.3.a Mentorship plan and contract: Dr. Limdi will work with mentee to implement a systematic/formal prospective evaluation process including the following**:**

1. A baseline assessment of each mentees POR core competencies that will identify areas of strength and areas for improvement.
2. Development of a mentoring plan with accompanying project goals document. The mentoring plan/contract will be drafted collaboratively by the mentee and Dr. Limdi (Appendix 3).
3. Mentee evaluation: Each mentees' progress will be reviewed every six months by Dr. Limdi to ensure mentees are working towards their individual goals. If goals are not being met, Dr. Limdi will encourage (and help, if needed) the trainee to identify reasons for this and propose plans to address issues.

4. Mentor evaluation: Every 6-month, the mentee will evaluate Dr. Limdi. These evaluations will be provided to Drs. Saag and Standaert.
5. Both evaluations will be discussed with Dr. Limdi's mentoring team (Drs. Saag and Standaert) at their quarterly meetings to ensure progress, document milestones achieved and identify and address issues that arise (e.g. lack of mentee progress, conflicts with mentor/ co-mentors, etc.).

6.3.b Mentorship components: Although mentoring for each trainee will be individualized based on their prior experience, long-term goals, and individual abilities, a common basic approach (outlined below) will be followed. Mentoring will involve both formal and informal training, including one-on-one, working groups and didactics, taking advantage of the structure established as part of the T32, K12 and KL2 programs at UAB.

The core experience for trainees for who Dr. Limdi serves as the primary mentor will involve frequent (twice a week) contact for discussion of progress and problems; a more formal weekly session with each mentee to review progress and analyze primary data or prepare abstracts and manuscripts. Mentees for who Dr. Limdi serves as part of the mentoring team, monthly research meetings involving the mentoring team will be held to review progress. For all mentees, discussions every 3 months on career development and long-term planning will be scheduled. The overarching steps are presented below:

1. Mentoring begins with research presentations by Dr. Limdi, including principles of study design, biostatistics, clinical relevance, economic implications and focus on patient-centered outcomes. Mentees are challenged to think critically and creatively to design research projects.
   - *Example 1: During Warfarin Pharmacogenetics study meetings,* Dr. Ather, *a cardiologist by training, recognized that the patients with advanced heart failure require lower warfarin dose. We will formally test this hypothesis in the existing warfarin cohort in project 1.*
2. Mentees will typically choose or be assigned to *work on an existing project*. A beginning educational project, generally involving participation in ongoing efforts, will provide an introduction to the team and to research methods. A relatively straightforward independent study may also be performed by those with some prior training, providing early positive reinforcement. Guided by early progress and long-term goals, a more independent project will eventually be selected, building toward a research theme.
   - *Example 2: Dr. Irvin is working on Warfarin Pharmacogenetics dataset (along with Dr. Liu, co-investigator on RO1) to understand the influence of rare genetic variation in the existing UAB Warfarin Pharmacogenetics cohort (N~1200).*
     - She is conducting gene-based analysis wherein, rare variation (MAF<5%) within each gene is represented by a rare-variant-score (RVS).[67] For each gene, each common variant (MAF ≥ 5%) and the RVS are jointly modeled with adjustment for clinical and known genetic (*VKORC1*, *CYP2C9*) factors using R package v 2.14.2. Preliminary results indicate that rare variation in FVII (vitamin K dependent clotting factor; inhibited by warfarin) for Whites and 3 novel rare variants in *CYP2C9* may explain additional variation in dose among Blacks. We are collaborating with Dr. Kimmel (sub contract HL092173) to genotype an additional 643 samples as the genes show a trend toward significance ($P<3*10^{-4}$); with planned submission of our publication in spring 2016.
   - *Example 3: Dr. Shendre has been working with Dr. Limdi since 2013. She is now working to integrate genetic factors associated with warfarin-related hemorrhage into risk prediction rules; with planned submission of our publication in fall 2015. She will be using a similar approach for Project 2.*
     - *Trainee publication:* Shendre S, Beasley TM, Brown TM, Hill CE, Arnett DK, Limdi NA. Influence of physical activity on warfarin dose and risk of hemorrhagic complications. Pharmacotherapy. 2014; 34: 545-54. PMC4109410.
     - *Trainee publication: Influence of CYP4F2 on warfarin dose, anticoagulation control and risk of hemorrhage. Under review British Journal of Clinical Pharmacology*
3. Throughout the mentoring relationship, trainees are introduced to resources available for research, especially members of the research team who create a supportive environment. Working with a team helps trainees learn how to translate theoretical hypotheses into workable analyses.
   - *Example 4: Dr. Boehme has leveraged our institutions experience in patients with Ventricular Assist Devices (VAD) to identify predictors of thromboembolism and hemorrhage. As most of these patients are on warfarin and antiplatelet agents one of her aims is to understand the role of treatment in modifying the risk of thromboembolism and hemorrhage. This will have implications for her work in VAD*

patients as they are frequently admitted with hemorrhage and thromboembolism. She has published one paper, one is under review and two more are in draft.

- *Trainee publication: Boehme AK, Pamboukian SV, George JF, Dillon C, Levitan EB, Griffin G, Beasley TM, McGwin G, Limdi NA. Predictors of Thromboembolic Events in Ventricular Assist Device Patients. American Society of Artificial Internal Organs.2015, In Press*
- *Trainee publication: Improvement in Kidney Function after Ventricular Assist Device Implantation and Its Influence on Thromboembolism, Hemorrhage and Mortality. Under review American Journal of Kidney Disease.*

- *Example 5: To familiarize himself with warfarin, its monitoring requirements, drug interactions and reversal of oral anticoagulation – Dr. Arora is working with Drs. Limdi, (and Beasley, co-investigator on Dr. Limdi's RO1) on an analysis in the warfarin pharmacogenetics cohort. The main goal of this paper is to determine if genetic variation in genes affecting warfarin response influence INR reversal. Paper in draft (submit by October 2015).*

4. Mentees are exposed to the principles of *scientific manuscript writing* through CCTS and T32 seminars. They also learn by working with Dr. Limdi directly. We review one of several excellent references that provide principles of scientific writing, review existing literature critically, and then the mentees' own writing. We focus on logic and clarity, beginning with the aims, methods, results, implications and limitations.

5. Critical review of concepts and research takes place during our *weekly research conferences* for ongoing studies. At these weekly meetings, mentees discuss their progress with their analysis, interpretation and write-up of manuscripts/ abstracts. Mentees will be encouraged to attend and present their findings at national meetings focused on their area of POR. We have requested funds to support this. Additional practice meetings are scheduled in preparation for scientific meetings, which trainees are expected to attend to present their work (AHA, ASCPT, ACC, UAB venues).

6. As mentees advance toward independence, they are encouraged to *develop their own ideas and carry out studies to test their hypotheses*. With a firm grounding in the literature, we challenge ourselves to think independently, and trainees are strongly encouraged to pose questions to the mentor and the team, and vice versa. Our discussions include questions such as: *What are the knowledge gaps? What is the next step in this line of inquiry? What is the clinical or policy relevance of this line of inquiry?*
   - *Example 6: Dr. Albright is working with a large stroke cohort (REGARDS) to understand if racial differences in adherence to antihypertensive medications and statins explain the differences in ischemic and hemorrhagic stroke.*
     - *Trainee publication Albright KC, Boehme AK, Tanner RM, Blackburn J, Howard G, Howard VJ, Safford M, Beasley TM, Limdi NA. Addressing Stroke Risk Factors in Black and White Americans: Findings from the National Health and Nutrition Examination Survey, 2009-2010. Ethnicity and Disease (2015, In Press).*
   - *Example 7: The warfarin cohort has exome-chip data on 1200 warfarin cohort participants and information on antihypertensive treatment. This has enabled Dr. Irvin to generate some pilot data to support her hypothesis of genetic underpinnings of treatment resistant hypertension.*

7. Seminars and Didactic sessions**.** Many fellows pursue course work to gain core epidemiology and biostatistics (MSPH program) training, gaining in-depth skills for research.

   Dr. Limdi's mentoring opportunities and training possibilities are enhanced by the UAB Clinical and Translational Science Award (known as the UAB CCTS). Dr. Robert Kimberly, the Director and PI of the CCTS, will work closely with Dr. Limdi to integrate training of future researchers (letter attached). The UAB CCTS Research Education, Training and Career Development Component offers a range of degree and non-degree (certificate) programs for clinical and translational researchers and research team members. Currently, the predominant degree program is the *Master of Science in Public Health (MSPH) in Clinical and Translational Science* which provides strong training for professionals interested in careers in translational research. These options are available to all mentees.

   The Clinical and Translational Science (CTS) Training Program also identifies those motivated to further their clinical and translational research training. The CTS Training Program provides six months of research training, through 50 hours of lectures and interactive sessions. Didactic instruction includes lectures within: Clinical Trials, Epidemiology, Biostatistics, Ethics, Clinical Genetics Research, Behavioral Research, Outcomes Research, Dissemination of Results, and Grant Writing and Funding Opportunities.

- *Example 8: Dr. Ather will be participating in the 6-month CTS certificate program (applications are due Nov 12, 2015) that includes approximately 50 hours of didactic instruction and interactive experience. Classes will be held Wednesday mornings, 8-10 a.m., beginning January 2016. He will enroll in EPI 730 course (fall 2017) to develop his K23 proposal.*

8. Within the first year of working together, we begin to plan for the trainee's *research grant,* taking advantage of the seminars on this topic offered through the CCTS and the grant writing course (EPI 703). We emphasize developing the specific aims and hypotheses; selection of study design and methods, including power analysis and statistical analysis; emphasis on significance and relevance to clinical practice and policy; and logistical details.
    - *Example 9: Dr. Albright wrote her AHA grant during the EPI 730- grant writing course. This course provides a focused program to allow candidates to spend a semester writing a grant. The complete grants are reviewed by faculty at UAB who provide written critique formatted as NIH grant review.*
    - POR Mentees can also apply for funding through the CCTS *Mentored Career Development Program (KL2 Scholar)*, health services, outcomes and effectiveness research training program, and the patient centered outcomes research program. Each scholar receives research and career mentoring from two mentors with excellent training records committed to extend interactions with the scholar.
9. Dr. Limdi will also actively teach her mentees how to mentor, and will throughout the award period seek opportunities to continue to build her own mentoring skills. As mentees are promising candidates for independent research careers; therefore, they themselves will be in a mentoring position. As the mentee advances, these discussions transition to include planning the mentee's own mentoring activities.

    As mentees transition from K-type grants to RO1 they serve as peer mentors (e.g. Dr. Irvin is a peer mentor for Dr. Shendre). The peer mentoring model is less formal and less inhibiting than other mentoring models. Peers can share their experience, provide important advice and guidance. Peer-mentors will also participate in the structured mentor training program "Mentor Training for Clinical and Translational Researchers" (listed in section 4.1; http://www.uab.edu/ccts/TrainingAcademy/Pages/Mentoring.aspx).
10. As mentees transition from K-type grants to RO1, we will leverage the Biguan retreat which is designed for undisturbed grant writing support and is jointly sponsored by the UAB CCTS and the UAB School of Public Health's Office of Energetics (http://www.uab.edu/ccts/news/24-research-news/180-biguans-launch-for-undisturbed-grant-writing-support). The Chinese term "Biguan" loosely translates to a period of retreat to a quiet place for meditation. The cloistered sessions for grant application development and writing hosted receive heavy support from senior investigators and a grant consultant.
    - Each year 12-14 Biguan retreat sessions are offered with four investigators per Biguan
    - Once accepted, investigators are required to prepare a draft abstract or specific aims and have a phone consultation with senior investigator/grant consultant. This ensures that investigators start the Biguan with a working draft of the research aims.
    - This week long retreat begins with a Sunday evening dinner and ends on the following Friday. The participants can have no (i.e., zero) interruptions during the working day (roughly 9 to 5). By the end of the week, investigators break from the session with a near complete draft of their RO1 application.
11. Dr. Limdi has worked with each mentee to assemble a mentoring-team based on their research interests. In line with new research proposed, Drs. Brott, Brown, Prabhu (cardiology), Beasley (Biostatistics), and Pisu (Health economics) will serve as co-mentors. Their role and expertise contributed is defined and biosketches and letters of support (LOS).
12. Dr. Prabhu, recognizing the breadth and depth of opportunities this award will create for patient-oriented researchers in cardiovascular disease, has committed $15,000 over 5 years to support generation of pilot data by mentees as develop their K23 applications (see LOS).

In summary, Dr. Limdi will: 1) train patient oriented researchers to be rigorous and independent academic investigators able to use the range of approaches available in epidemiology to address research issues in cardiovascular diseases related to the treatment, clinical utility/ cost-effectiveness, implementation, medical decision making, and precision medicine; 2) provide closely mentored research experiences with expertise in clinical pharmacology, pharmacogenomics, epidemiology and precision cardiovascular medicine. Throughout, Dr. Limdi will model mentorship through demonstration of commitment, devotion of time, supportiveness and enthusiasm; and by providing mentees with a sense of positive accomplishment, encouraging their ability to accept suggestions, and fostering a sense of collaboration.

10. SPECIFIC AIMS

Dr. Limdi has built a successful research program in cardiovascular pharmacoepidemiology with a focus on anticoagulant pharmacogenomics (RO1HL092173; 2008-2019). She has harnessed the racial diversity of the patient population served at UAB and made seminal contributions to understanding the differential influence of genetic variants on warfarin response across race groups. Similarly, the rich clinical phenotyping has enabled her team to understand the influence of comorbidity on warfarin dose and hemorrhage risk.

Dr. Limdi has long recognized the promise of pharmacogenomics in elucidating variability in drug response and its potential personalize drug therapy. In addition to building her research program, since 2008, she has championed the precision medicine efforts at UAB. Harnessing scientific breakthroughs in genomics and informatics, precision medicine fosters a systematic approach to integrate genetic, clinical, and environmental factors a tailored treatment plan for the individual patient. She has les the creation of UAB's Personalized Medicine Institute and is now the institutional leader in the implementation of genotype-guided therapy at UAB. In this application, Dr. Limdi leverages her strengths and resources to create unique training opportunities through three well-defined projects in cardiovascular POR and precision medicine.

In **Project 1**, Dr. Ather will test whether heart failure (left ventricular ejection fraction; LVEF <40%) influences warfarin response.

1. Aim 1: Elucidate the influence of heart failure on therapeutic warfarin dose required.
2. Aim 2: Elucidate the influence of heart failure on anticoagulation control (measured as percent time in target range; PTTR) and risk of hemorrhage.

In **Project 2,** Dr. Shendre will test whether candidate genes influence DBG-related major hemorrhage.

3. Aim 3: Determine the influence of candidate genes, demographic (race, age) and clinical factors (antiplatelet therapy, kidney impairment and heart failure) on DBG-related-hemorrhage. We will specifically assess variants in *ABCB1* (rs4148738) and *CES1* (rs2244613, rs8192935).
4. Aim 4: Incorporate patient-specific genetic and clinical factors into clinical prediction rules (CPRs) to personalize the prediction of hemorrhage among DBG users.

Projects 1 and 2 will utilize the warfarin and dabigatran cohorts (Resource I) supported by Dr. Limdi's RO1 entitled "Genetic and Clinical Predictors Warfarin and Novel Anticoagulants Response (HL092173; 2014-19)."

In **Project 3,** Drs. Irvin and Arora will assess racial differences thromboembolic [major adverse cardiovascular events (MACE) and stent thrombosis] and hemorrhagic events and determine utility of genotype-guided antiplatelet therapy (GGAT) in ACS/ PCI patients.

5. Aim 5: Determine differences in thromboembolic and hemorrhagic outcomes among African Americans vs. European Americans and elucidate race-specific effects of *CYP2C19* and clinical factors.
6. Aim 6: Determine effectiveness (clinical utility) and economic value (cost-effectiveness) of GGAT.

Project 3 will utilize cohort of patients undergoing PCI (Resource II) supported by Dr. Limdi's intramural grant entitled "Pharmacogenomic Resource to Improve Medication Effectiveness (UAB-HSF; 2013-17)."

The mentorship aims of the current proposal centers on expanding the POR training opportunities for MD, Pharm.D, and PhD trainees. Mentees work with established resources to propose and test hypothesis, conduct analysis and publish original research and are actively engaged in POR including patient recruitment, documenting clinical phenotype and leading a specific part of the new research proposed with the opportunity to lead the analysis, presentation and publication of the new research and to submit NIH- K23 applications.

The K24 award would allow Dr. Limdi to assume primary mentorship responsibilities for Drs. Ather, Shendre, Arora and Irvin and guide their K23 award submissions (**Table 5**).

Table 5: Time line and deliverables during the K24 period

Task	Year 1	Year 2	Year 3	Year 4	Year 5
Analysis/ publications	x	x	x	x	x
Patient accrual, clinical phenotype	x	x	x	x	
K23 applications		Ather	Irvin, Arora	Shendre	

This application is being submitted at a key time point in the applicants' career at which it would be possible for her to either be drawn into a large number of administrative and supervisory responsibilities or for her to focus on clinical research productivity and mentoring. This award will ensure that the candidate maintains protected time to focus on enhancing her career in POR, a large part of which involves mentoring junior investigators to build their own careers in patient oriented research focused on personalized medicine.

11 RESEARCH STRATEGY

Dr. Limdi's long term goal is to integrate clinical and genetic knowledge with current approaches for prescribing antithrombotic therapy and developing patient-focused and population-based guidelines for "Personalized Antithrombotic Therapy" in patients with multiple comorbidities, reflecting the complexity of patients seen in routine clinical practice. The Research Plan describes rationale, current research, and new research (incorporating new oral anticoagulants and antiplatelet agents) that will be created by leveraging resources to enhance the candidates' research career and enable mentoring in POR.

11.1 Rationale for focus on antithrombotic agents: The aging population is driving an increasing need for chronic antithrombotic therapy. Consider, for example, the increasing prevalence of atrial fibrillation (AF); which with the aging population portends to be a worsening epidemic.[68-70] The morbidity and mortality related to AF are substantial: 5-fold increased risk of stroke, 3-fold increase in heart failure and 2-fold increase in overall mortality.[71-78] In patients with AF, the overall decision to institute antithrombotic therapy has been framed as a decision between "*antiplatelet (AP) versus anticoagulants (AC)"* as these constitute the mainstay of stroke prevention and treatment.[79-85] However, accumulating evidence suggests the superiority of oral anticoagulants over aspirin.[86-91] The introduction of NoACs (dabigatran, rivaroxaban apixaban, edoxaban)[92-107] adds another decision point for initiating anticoagulation "*warfarin vs. NoACs*." Compared to warfarin, the NoACs have superior or equal efficacy, a favorable bleeding risk profile, fewer drug interactions and lack of monitoring requirements. Anticoagulant and antiplatelet agents are "top-offenders;" accounting for 33.3% and 13.3% of all adverse-drug-related hospitalizations in the US. Hemorrhage was the main contributing cause for these hospitalizations; representing 63% of warfarin and 88% of antiplatelet related hospitalizations.[108-110]

11.2 Hemorrhage remains a recalcitrant problem. Patients requiring anticoagulation with comorbidities such as chronic kidney disease are often not well represented in clinical trials.[111-113] For example, with regard to the incidence of hemorrhage, **Table 6** illustrates two issues. First, the incidence of hemorrhage is higher in clinical practice compared to clinical trials (see warfarin data from our cohort vs. clinical trials). Second, in trials and practice, the incidence of hemorrhage is higher among patients with impaired kidney function.

Table 6: Rate of Hemorrhage (per 100 p-yrs) by kidney function (Creatinine Clearance ml/min)[92,101,104]

Creatinine	**Inception cohort**	**RELY trial**		**ROCKET AF**		**ARISTOTLE**	
Clearance	Warfarin (UAB)	Warfarin	**Dabigatran**	Warfarin	Rivaroxaban	Warfarin	Apixaban
≥80	6.7	2.3	**1.9**	3.17	3.2	1.8	1.5
50-79.9	6.5	3.6	**3.2**		3.3	3.2	2.5
30-49.9	11.1	5.3	**5.1**	4.7	8.0	6.4	3.3
<30	19.0	0.0	**13.6**				

Among the NoACs, from documents submitted for FDA review, DBG is associated with a higher risk of hemorrhage. Given the limited representation of patients with multiple comorbid conditions in clinical trials; cohorts representing the complexity of patients seen in clinical practice can help uncover such risks. In our warfarin cohort, 40% of patients have impaired kidney function, demonstrating that the kidney function-hemorrhage association is clinically relevant at the individual and population level.[17,114-117]

Dr. Limdi's research plans center on her successful program in Warfarin pharmacogenomics supported by the competitive renewal of her grant entitled "Genetic and Clinical Predictors of Response to Warfarin and Novel Anticoagulants" (RO1 HL092173; 2014-2019) and Genotype-Guided Antiplatelet Therapy (Funded by UAB Health Services Foundation; 2013-2017). Dr. Limdi uses this program to create mentorship opportunity and design patient oriented research projects to be led by trainees under her mentorship.

11.3 RESOURCE I: Warfarin and Dabigatran Cohort is supported by Dr. Limdi's RO1 entitled "Genetic and Clinical Predictors Warfarin and Novel Anticoagulants Response (HL092173; 2014-2019)" which aims to:

1. Identify rare and common variants influencing the risk of warfarin-related hemorrhage (in 700 cases vs. 700 controls) using genome wide analysis (GWA).
2. Elucidate the influence of race, kidney impairment and concurrent antiplatelet therapy on risk of warfarin-related hemorrhage among 1000 AF patients on warfarin. The genetic predictors from the GWA above will be replicated in this 1000 warfarin treated AF cohort.
3. Elucidate the influence of race, kidney impairment and concurrent antiplatelet therapy on risk of dabigatran related hemorrhage among 500 AF patients on DBG.
4. Develop (for Dabigatran) and refine (for warfarin) clinical risk prediction rules for hemorrhage.

11.3.a Clinical Data Collection: Both warfarin and DBG cohorts are prospective, inception cohorts. Participants are enrolled at initiation of therapy and followed for up to 2 years. Demographic (age, race, gender, occupation, education, income, and health insurance), lifestyle (exercise, alcohol and smoking) and medical history are documented paying special attention to factors associated with hemorrhage risk (**Table 7**).

- Medical history includes indication for therapy, comorbid conditions, and medications. During follow-up (monthly for warfarin, and quarterly for DBG), factors influencing response such as dose, INR (for warfarin), concurrent medications, adherence are documented.[118-120] The completeness of the data is highlighted in recent reports wherein only 3 of 1563 patients had missing GFR values.[32,37]
- Concomitant medications can influence response to warfarin and DBG[121,122] and independently increase the risk of hemorrhagic complications.[123-126] The increase in risk of hemorrhage can result from co-therapy with CYP2C9 inhibitors (e.g. amiodarone) or inducers (e.g. carbamazepine)[123,124] for warfarin P-gp inhibitors (e.g. amiodarone) or P-gp inducers (e.g. rifampin) for DBG[127-129] or concomitant use of antiplatelet for warfarin and DBG.[130-136] Medication history will be documented by self-report (over the counter drugs, e.g. proton pump inhibitors) with validation through medical records and pharmacy refill records.

Table 7 Overview of measurement strategy for key clinical risk factors associated with risk of hemorrhage	
Prior Bleeding history	Defined ICD-9 diagnosis code of hemorrhage (e.g. intracranial or gastrointestinal bleeding)
Hypertension	BP>140/90 on two consecutive visits, use of an antihypertensive medication
Diabetes Mellitus	Hemoglobin A1c>7.0, use or insulin or oral hypoglycemic agents
Prior Stroke	Ischemic and hemorrhagic strokes will be identified using primary ICD-9 diagnoses
Adherence	Validated 8-question Morisky scale[137-139]
Health-related quality of life	HrQOL using the EQ-5D instrument[140-144]
Medication history	Self-report (over the counter drugs) with validation through pharmacy dispensing records
Kidney impairment[145-147]	Four categories based on estimated glomerular filtration rate (eGFR ml/min/1.73m^2); no /mild chronic kidney disease (CKD; eGFR $\geq$60); moderate-risk CKD (eGFR $\geq$45<60), high-risk CKD (eGFR $\geq$30<45), and very-high-risk CKD (eGFR <30 ml/min/1.73m2)..
The proportional representation across these categories will be 60%, 25%, 10% and 5% respectively	
Antiplatelet agents (AP)	None, low (e.g. aspirin $\leq$162 mg/day), high intensity (e.g. aspirin 325 mg/day, 75mg/day clopidogrel, 10mg/day prasugrel, 90mg bid for ticagrelor or dual anti-platelet therapy).
The proportional representation across these categories will be 43%, 30%, 27% respectively	

- Major hemorrhage will be defined by ISTH criteria.[56,148] This includes fatal events, symptomatic bleeding in a critical area (e.g. intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial) and bleeding with a decrease in hemoglobin $\geq$ 2 g/dl, and/or leading to transfusion $\geq$ 2 units of red blood cells.
- Event Adjudication: 3 blinded examiners review all thromboembolic and hemorrhagic events are reviewed by. The pair-wise inter-rater agreement (Kappa= 0.93 to 0.96) is excellent. Because patients with fatal events are most likely to be lost and it is imperative to ensure documentation of all fatal events, the vital status of such patients is determined by querying the Alabama Dept. of Vital Statistics to verify cause of death and obtain a death certificate. These efforts have ensured low (9%) loss to follow-up.

11.3.b Warfarin cohort currently includes 1647 participants (goal 1800 by 2016). African Americans comprise 43% of the cohort. This cohort has archived DNA and genotype data to enable candidate gene, haplotype, genome-wide association study (GWAS, Illumina 1Mduo). The clinical and genetic data has resulted in many manuscripts[9-11,13-16,19-24,26-33,35-37,44,45,47-49,149-151] This has also allowed us to elucidate differences in warfarin response (**Table 8)** between African Americans (AAs) and European Americans (EAs).[10,11,14-26]

Table 8: Anticoagulation control, over anticoagulation and hemorrhage among 1357 patients			
Variable	**EA**	**AA**	AA spent less time in target INR range (PTTR) compared to European Americans (EA; P<0.0001).
Number of patients	762	595	
Follow-up time (yrs)	1111.3	803.3	There were 156 major hemorrhagic events observed during 1912 years of follow-up (incidence 8.2/100 patient-years; 95% CI: 7.0, 9.5). Gastrointestinal hemorrhage was most common (n=94), followed by hematoma (n=24), genitourinary (n=14), Intracranial hemorrhage (n=12), Hemoptysis (n=10).
% Time In range (PTTR)	57.6%	49.1%	
Episodes of INR >4	811	756	
Major Hemorrhage	68	70	
Incidence of hemorrhage	6.7 [5.2, 8.5]	9.7 [7.5, 12.2]	AAs had a higher incidence of hemorrhage than EAs (p=0.03) and a 70% higher relative risk (p=0.013) after adjustment for clinical and genetic factors compared to EAs.
Risk of hemorrhage (AA vs. EA)		1.7 [1.13, 2.48]	

Leveraging the clinical and genetic data, Dr. Ather will determine the influence of heart failure on warfarin response (dose, anticoagulation control and hemorrhage) in Project 1.

11.3.c Dabigatran (DBG) cohort recruitment was initiated in Feb 2014 and currently includes 408 participants (goal 500 by 2016). African Americans comprise 15% of the cohort. Clinical data collection and review all thromboembolic and hemorrhagic events is as described above over the 2- year follow-up.

- Although warfarin remains widely used, concordant with national trends, the use of NOACs is increasing at UAB. African Americans constitute 12 to 20% of NoAC users at UAB compared to 1.2 to 1.5% in clinical trials (**Table 9**).[92,101,103] This can provide unique opportunity for understanding racial differences in NoACs response and identifying factors associated with risk of hemorrhage.

Table 9: Current users of warfarin, dabigatran, rivaroxaban and apixaban at UAB

	Warfarin (% AA)		Dabigatran(% AA)		Rivaroxaban (% AA)		Apixaban (% AA)	
2012	7074	24.8%	1819	8.2%	652	15.5%	n/a	n/a
2013	6069	28.9%	1147	10.0%	1603	15.7%	181	9.4%
2014	5462	29.1%	848	14.4%	2057	18.9%	788	12.3%

- The current RO1 does not include any genetic/ genomic assessments for DBG. Dr. Shendre (candidate for PhD in epidemiology) has initiated collection and archival of DNA samples (supported by Dr. Limdi).
- Among the NoACs, DBG is associated with a higher risk of hemorrhage. To capitalize on the current DBG cohort supported by Dr. Limdi's RO1 (goal 500; 408 enrolled), Dr. Shendre, with the guidance and assistance of the research associate, will recruit an additional 500 patients to create a 1000 patient cohort. African Americans will comprise 15% of the DBG cohort. This will provide a robust cohort to conduct the candidate-gene analysis proposed in Project 2.

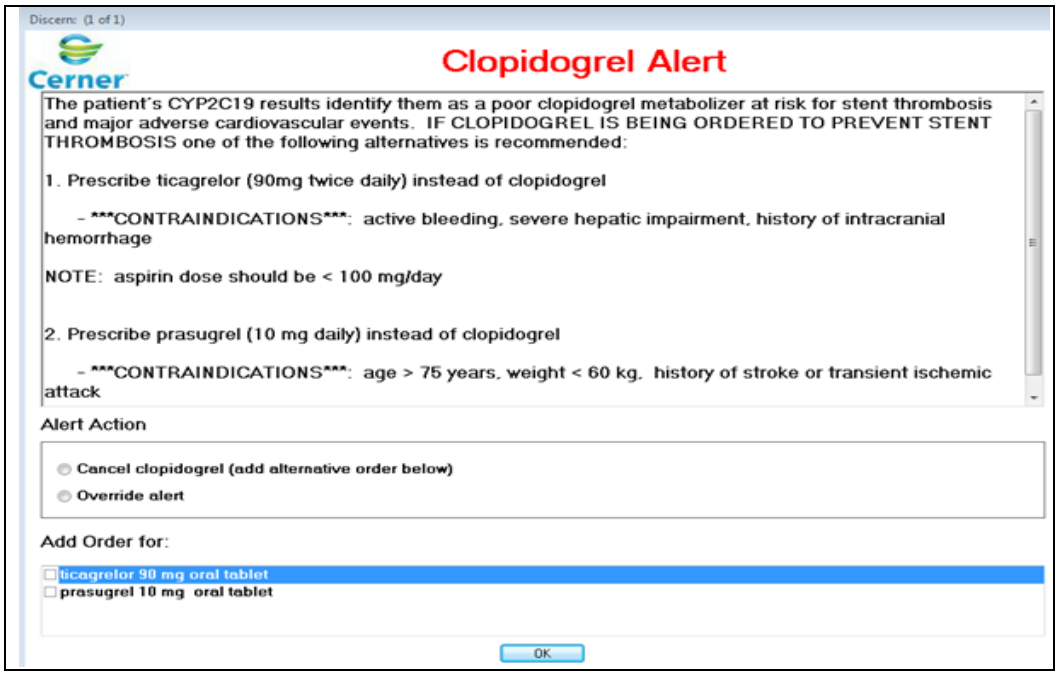
11.4 RESOURCE II: Cohort of patients undergoing percutaneous coronary intervention (PCI):

To facilitate delivery of precision medicine, the University of Alabama at Birmingham (UAB) is establishing infrastructure to integrate genomics into clinical care. Implementation of *CYP2C19* genotype-guided antiplatelet therapy (GGAT) in patients with acute coronary syndrome (ACS) and those undergoing percutaneous coronary intervention (PCI) is ongoing. ACS/PCI patients (30% African American) are prescribed dual-antiplatelet therapy (DAPT), most often, aspirin and clopidogrel. Clopidogrel is activated by cytochrome P450 2C19 (*CYP2C19*).[152,153] Possession of one or two copies (intermediate, poor-metabolizer) of *CYP2C19* loss-of-function (LOF) alleles (e.g. *2, *3) confers an increased risk for major adverse cardiovascular events (MACE) and stent thrombosis in clopidogrel users. [154,155] [156-162] In contrast, possession of the *CYP2C19*17* (gain-of-function; GOF) allele may enhance inhibition and may increase bleeding risk.[163-166]

Although the current standard of care is to initiate DAPT without *CYP2C19* testing (non-GGAT), physicians can choose *CYP2C19* genotype-guided antiplatelet therapy (GGAT) as part of clinical care. Genotyping is done in the Molecular Diagnostic lab using the SPARTAN platform[167] with a 60-90min of sample receipt. For patients possessing *CYP2C19*2 or *3* alleles, an automatic alert (**Figure 1**) is generated to notify physicians.

Figure 1: Clinical Decision support guiding antiplatelet selection in post-PCI patients possessing *CYP2C19* loss-of-function alleles.

For patients with *CYP2C19*1/*1 or *1/*17 or *17/17 genotype the CDS is **not** triggered. The physician can choose dual antiplatelet treatment based on patient-specific clinical factors.



Clinical decision support providing recommendations for alternate antiplatelet therapy based on published guidelines is embedded in the electronic medical record.[168] Therapy is then tailored based on clinical and genetic factors prior to discharge. Adoption of testing in ACS/ PCI patients is evolving, with testing performed in 35-40% of patients. All patients are approached for enrollment in a prospective inception cohort. Over a six month period, in addition to the 111 genotyped for *CYP2C19*, 189 patients who have undergone PCI without GGAT have consented to participate. *CYP2C19* genotype distribution is presented in **Table 10**.

Table 10: *CYP2C19* genotype distribution in the 111 patients tested (≠3 Asians excluded)

	Metabolizer	Observed among 111 patients at UAB			Expected[168]	
***CYP2C19* genotype**	status	N=111 (%)	AA≠ N=19	EA≠ N=89	AA	EA
*1/*1	Normal	40 (36%)	7 (37%)	31 (35%)	21%	33%
*1/*17, *17/*17	Ultra-rapid	40 (36%)	8 (42%)	31 (35%)	45%	40%
*1/*2, *2/*17 or *1/*3	Intermediate	30 (27%)	4 (21%)	26 (29%)	30%	25%
*2/*2, *2/*3 or *3/*3	Poor	1 (1%)	0 (0%)	1 (1%)	4%	2%

In addition to the clinical data collection described in section 11.3, risk factors associated with thromboembolic and hemorrhagic outcomes (**Table 11**) are documented.[169-179]

Table 11: Clinical predictors associated with risk thromboembolic and hemorrhagic outcomes

Hemodynamic and laboratory parameters	**Related to PCI**
Blood pressure, Heart rate	Emergent or urgent procedure
Shock/ Hemodynamic instability	Acute MI (STEMI or NSTEMI)
Platelet count, Anemia, Hematocrit, GFR (ml/min/1.73m^2)	Stent thrombosis (revascularization)
Creatin kinase (CK), creatin kinase-myocardial band (CK-MB), Cardiac Troponin I	Multi-vessel disease, Left main stem disease
	Pre and post-PCI percent blockage, TIMI flow grade
B-type natriuretic peptide (BNP)	Site of and length of lesion (ostia, bifurcation)
ST-segment deviation on ECG	Number of stents

Patients are followed for 1 year and thromboembolic and hemorrhagic outcomes documented as defined below.[55-58] Event adjudication is done as described in section 11.3.

- Thromboembolic complications will include stent thrombosis as defined by Academic Research Consortium[57] and Major Adverse Cardiovascular Events (MACE): defined as non-fatal stroke,[57] non-fatal myocardial infarction (MI),[180] and death secondary to any cardiovascular cause.[57] This includes deaths from MI, sudden cardiac death, heart failure, stroke, and other cardiovascular causes.
- Hemorrhage will be defined as events with a ≥10% hematocrit and/or ≥2g/dL hemoglobin drop or that requires transfusion or surgical intervention. We will also assess bleeding as defined by TIMI-38.[58]
- We expect the incidence of thromboembolic complications to range from 10-30 per 100 patient years (pyrs) and hemorrhage to range from 5-20/ 100 pyrs.

By July 2017, this cohort is expected to enroll 1250 patients with a 1-year prospective follow-up. This is expected to include recruitment of GGAT (goal n=250) and non-GGAT (goal n=1000) patients with DNA and plasma samples archived for research will support new research by Drs. Arora and Irvin (Project 3).

Mentees will leverage these resources and propose new research to address new knowledge gaps. Mentees will learn principles of research, analytic approaches including candidate gene, genome-wide association analysis, and development of clinical prediction rules. More importantly, mentees will work collaboratively on problem solving and proposing alternate approaches for ongoing projects. The experience will engage them in generating hypothesis and pilot data and develop their careers in POR.

11.5 PROJECT 1: Determining the effects of heart failure on warfarin response

11.5.a Rationale: While pharmacogenomics is the cornerstone of precision medicine, variability in response is also influenced by comorbid conditions.[181-184] Therefore, in addition to genomics, we must also focus on understanding the influence of comorbid conditions on drug response. Patients requiring warfarin often have multiple comorbid conditions that influence warfarin response. We have shown that CKD patients require lower warfarin dose and have a higher risk of hemorrhage.[30,145,147,185] Similarly, warfarin dose requirements are lower in patients with acute decompensated heart failure (HF).[186] However, the influence of heart failure (left ventricular ejection fraction LVEF <40%) on warfarin response has not been evaluated. To address this knowledge gap, **Dr. Ather will lead Project 1** using the existing Warfarin Cohort (n=1647; goal n=1800) wherein 10-20% of patients are expected to have LVEF <40%. He will determine the influence of heart failure on warfarin response through two aims:

- **Aim 1:** Elucidate the influence of heart failure on therapeutic warfarin dose
- **Aim 2:** Elucidate the influence of heart failure on anticoagulation control (percent time in target range; PTTR), and risk of hemorrhage.

11.5.b Statistical methods and power: The influence of heart failure on warfarin dose and anticoagulation control will be evaluated using multivariable regression analyses. All analyses will account for demographic (e.g. age, BMI), lifestyle (e.g. smoking), clinical (comorbid conditions, amiodarone use), and genetic factors.

Warfarin dose (mg/day; log transformed to attain normality) will be defined as the average maintenance dose after the attainment of three consecutive INRs in target range measured at least 2 weeks apart. Here we present sample size needed to detect a dose difference (7-10.5mg/week) at 80% power with alpha of 0.05.

Dose	Patients with LVEF< 40 %		
Difference	10%	15%	20%
7 mg/week	1570	1120	880
10.5 mg/week	700	500	395

Proportion of time spent in target range (PTTR) will be estimated for each patient using the Rosendaal linear interpolation method.[187] Time in target range for each patient will be assessed by the percentage of interpolated INR values within the target range of 2.0–3.0 after attainment of first INR in target range. Here, we present sample size needed to detect a 10-20% PTTR difference at 80% power with alpha of 0.05.

PTTR	Patients with LVEF< 40 %		
Difference	10%	15%	20%
10%	1150	1100	875
15%	690	500	390
20%	390	280	220

The influence of heart failure on the risk of major hemorrhage (as defined by the ISTH criteria)[56,148] will be assessed using the counting process format in the proportional hazard (PH) model. Minor hemorrhages (mild nosebleeds, microscopic hematuria, mild bruising, and mild hemorrhoidal bleeding) will be excluded. Here we present sample size needed to detect a 1.75 to 2.5 risk ratio at 80% power with alpha of 0.05.

Relative Risk	Patients with LVEF< 40 %		
	10%	15%	20%
1.75	1930	1340	1040
2.0	1230	860	660
2.5	680	480	390

11.5.c Mentee plans: Ather's (MD, PhD) clinical and research interests are centered on personalized medicine in complex patients with cardiovascular disease (specifically heart failure). He will be co-mentored by Drs. Limdi and Prabhu. The proposed project will provide him with patient-oriented research experience and allow his to explore genetic underpinnings of variability in response to other commonly used medications such as B-blockers. He plans to apply for a K23 award to study predictors of drug response in heart failure patients.

11.6 PROJECT 2: Identifying genetic factors associated with Dabigatran-related hemorrhage.

11.6.a Rationale: Dabigatran (DBG), the first NoAC introduced in the USA, has similar overall risk of hemorrhage compared to warfarin.[188,189] Older age (≥75 years) and kidney impairment are risk factors for DBG-related hemorrhage.[190-198] However, the influence of other clinical (e.g. antiplatelet therapy), demographic (race, gender), and genetic factors associated with DBG-related hemorrhage in a real world population remains largely unexplored. The RE-LY genetics sub-study reported that variants in ATP-binding cassette, sub-family B, member 1 (*ABCB1*) and carboxylesterase 1 (*CES1*) are associated DBG concentrations.[199]

The current RO1 aims to elucidate the influence of kidney impairment and concurrent antiplatelet therapy on risk of DBG-related-hemorrhage. The RO1 did not propose any genomic assessments for the DBG cohort. Dr. Shendre has initiated sample (DNA) collection supported by departmental funds available to Dr. Limdi. Dr. Shendre will leverage this resource for Project 2. She will work with the clinical coordinator, enrolling an additional 500 patients on DBG, to create a 1000 patient DBG cohort (500 to be enrolled as part of the RO1; enrolled 408) and conduct candidate gene analysis in 1000 patients.

- **Aim 3:** Determine the influence of candidate genes, demographic (race, age) and clinical factors (antiplatelet therapy, kidney impairment and heart failure) on DBG-related-hemorrhage. We will specifically assess variants in *ABCB1* (rs4148738) and *CES1* (rs2244613, rs8192935).[200] Genotyping will be conducted by the Heflin genomics core laboratory using pyrosequencing or taqman assays.
- **Aim 4**: Incorporate patient-specific genetic and clinical factors into clinical prediction rules (CPRs) to personalize the prediction of hemorrhage among DBG users.

11.6.b.1 Statistical Analysis and power for Dabigatran-related hemorrhage: The association of kidney function, antiplatelet therapy and variants in *ABCB1* and *CES1* with hemorrhage using time to event analysis

employing the Cox PH model after accounting for clinical factors is listed above. As the minor allele frequencies (MAF) of candidate-gene variants are 45% (rs4148738), 33% (rs8192935) and 18% (rs2244613), the analysis is adequately powered (>80%; alpha=0.05) to detect hazard ratios of ≥2. We have extensive experience with using methodology with warfarin pharmacogenomics (allowing changes in kidney function, interacting medications, anticoagulation control, etc. over time).[21,28,29]

Table 12	**Power (1000 patient cohort) at two-sided alpha=0.05 to detect HR=2.0**			
Event rate in	% of patients with exposure			
unexposed	5%	10%	20%	30%
0.04	0.61	0.86	0.97	0.99
0.05	0.70	0.92	0.99	0.99
0.06	0.77	0.95	0.99	0.99
	Power to detect HR=3.0			
0.04	0.99	0.99	0.97	0.99
0.05	0.99	0.99	0.99	0.99
0.06	0.99	0.99	0.99	0.99

In ***Table 12*** we **conservatively estimate power** to detect a hazard ratio ≥ 2. We assume that patients are enrolled over 2 years, followed for up to 2 years with an attrition rate of 10% under varying rates of hemorrhage (4 to 7/100p-years) in the unexposed, proportion of patients with exposure (1% to 30%) at two-sided alpha level of 0.05.

11.6.b.2 Statistical Analysis- Model development: Dr. Shendre is refining the current CPR for warfarin-related- hemorrhage (e.g. HASBLED) [81,134,201-208] by including genes (*CYP2C9*) known to influence bleeding risk and is using the analysis approach described herein.

We will assign a risk score to predictor variables that are proportional to the magnitude of the effect size in the final multivariable Cox PH model (***Table 13).***

The risk score will be collapsed into "low," "intermediate," and "high" risk groups based on the observed incidence of major hemorrhage. Because there are no definitive or clinically determined cut-points for rates of major hemorrhage at which warfarin would be contraindicated we will choose risk thresholds to optimally aggregate low-risk vs. high-risk groups.

Table 13: Example for assigning risk score based on kidney function (under review)

Kidney Function	Adjusted HR (95% CI); p	Score
eGFR ≥ 60	Referent (HR=1.0)	0.0
eGFR ≥45-60	1.11 [0.55,2.25]; p=0.78	0.0
eGFR ≥30-44	2.11 [1.01,4.41]; p=0.048	2.0
eGFR <30	5.65 [3.11,10.27]; p<0.0001	5.5

A similar approach will be used to identify risk factors for DBG related hemorrhage and develop a clinical prediction rule for DBG-related hemorrhage. Predictors will be incorporated in model building. We will apply backward elimination selection on 1,000 bootstrap samples, with significance level <0.05 for removing a variable. The final model will include variables that meet the threshold in >50% of the bootstrap samples. This method has been used to develop AF risk-prediction models among Framingham and ATRIA participants.[206,209]

11.6.c Mentee plans: Dr. Shendre (MBBS, PhD candidate in Epidemiology) will be co-mentored by Drs. Limdi, Beasley and Brown. She plans to complete her PhD in Epidemiology (May 2016) and join Dr. Limdi's team as a post-doctoral fellow. She will lead Project II and plan to apply for a K23 award (by spring 2019) centered on clinical prediction of hemorrhage among patients taking non-vitamin K antagonist oral anticoagulants including apixaban, rivaroxaban and edoxaban. This well-defined project will allow Dr. Shendre to gain the experience and propose incorporation of rivaroxaban and apixaban to build larger NoAC cohort as part of her K23 application. This will enable further refinement of clinical decision support "warfarin vs. dabigatran or rivaroxaban or apixaban." Moreover, as 15-20% of NoAC users are African American, she will be able to test additional hypotheses to elucidate clinical and genetic underpinnings that may underlie race-specific differences in NoAC response.

11.7 PROJECT 3: Evaluate racial differences in major adverse cardiovascular events in ACS/ PCI patients and determine clinical utility of genotype-guided antiplatelet therapy

11.7.a Rationale: Despite the strength of *CYP2C19*-outcome association,[156-162] adoption of this precision medicine remains limited as evidence of utility is limited. African Americans (AAs) with ACS/PCI experience poor clinical outcomes.[210-221] AAs are under-represented (<1.5%) in clinical trials, and in research supporting *CYP2C19*-outcome associations,[157] There is limited data on predictors that (may) differentially influence poor outcomes in this race group.[222-224] Resource II will be expanded to support Project 3. Drs. Arora and Irvin will gain experience in implementation research, clinical prediction rule development and assessing utility.

- **Aim 5**: Determine differences in thromboembolic and hemorrhagic outcomes among African Americans vs. European Americans and elucidate race-specific effects of *CYP2C19* and clinical factors.
- **Aim 6:** Determine effectiveness (clinical utility) and economic value (cost-effectiveness) of GGAT.

11.7b.1 Analysis approach, power to evaluate racial differences in outcomes: We will assess the effect of *CYP2C19* and clinical factors on risk of thromboembolism and hemorrhage over the 1-year follow-up. Based on the *CYP2C19* genotype distribution (Table 10) we expect prevalence of GOF alleles (*17) to range from 36-42% and LOF alleles (*2, *3) to range from 21-28%. Varying the event rate from 10-30/100p-years, our analysis is powered (>80%; alpha=0.05) to detect hazard ratios (HR) of ≥1.5 for race-adjusted analysis in 1250 patients and race-stratified analysis among EAs (n=875). We are powered to detect HR of ≥1.8 race-stratified analysis among AAs (n=375). For *CYP2C19**race interactions we are powered to detect HR of ≥2.0.

11.7.b.2 Analysis approach, power to evaluate clinical utility: Effectiveness analysis will compare rates of thromboembolism and hemorrhage among patients receiving GGAT (n=250) compared to non-GGAT group (n=1000). Assuming that 25% of patients possess *CYP2C19* LOF alleles associated with an increased risk of thromboembolism and 35% of patients possess *CYP2C19* *17 alleles associated with bleeding, the 1250 patient cohort would provide ≥80% power at alpha of 0.05 to detect ≥6.5% decrease in event rate.

11.7.b.3 Cost-Effectiveness Analyses will be conducted from a third party payer perspective and have a time horizon of one year (corresponding to the study follow-up period). Outcomes will be measured by Quality Adjusted Life Year (QALY) calculated for the one year follow-up using utility weights obtained from the response to the EQ-5D instrument. Utility weights will be obtained at baseline, six and 12 months follow-up.

We will compare costs of the GGAT strategy, which include cost of genotyping and associated antiplatelet therapy plus the cost of medical care in the follow-up period for patients in the GGAT group, to the costs of the non-GGAT strategy which include the cost of antiplatelet therapy plus the cost of medical care in the follow-up period for patients in the non-GGAT group. We will first determine the differences in total costs using a regression model where costs will be the dependent variable, and a binary variable indicating study strategies will be the independent variable. Similar analyses will be used to determine the impact of GGAT on the QALY. We will then determine the 1) net cost of GGAT vs. non-GGAT, and 2) effectiveness, i.e., the difference in QALY between GGAT and non-GGAT. If GGAT is less costly and more effective than non-GGAT, then GGAT will be considered cost-saving. If the GGAT is more expensive and more effective than non-GGAT, we will calculate an Incremental Cost Effectiveness Ratio (ICER) as the ratio of net cost and effectiveness using $50,000 to $100,000/QALY as our threshold. To examine uncertainty we will sample with replacement costs and outcomes from the two study groups and calculate mean costs and outcomes for each bootstrap sample, repeating the procedure 1000 times.[225,226]

11.7.c Mentee plans: The proposed project will provide Dr. Irvin the perfect context to acquire the additional skills in patient-oriented research, clinical translation and implementation to complement her work in genomic discovery work. She plans to apply for a K23 award (spring 2018) using archived samples for additional genomic interrogation in the future, including genome-wide rare and common genetic variant association, developing risk prediction rules using clinical and genetic factors. Dr. Arora will work with Drs. Limdi and Pisu in assessing clinical utility of GGAT, developing risk prediction rules and finally evaluating its effectiveness through implementation. As a clinician scientist he is interested in developing a portfolio centered on implementation of evidence-based interventions to improve care of patients with cardiovascular disease.

11.8 Limitations and alternative strategies and future efforts

1. Project 1: The influence of heart failure (HF) on warfarin response is defined based on LVEF <40% rather than New York Heart Association Functional Classification. Dr. Ather will refine the definition of HF through medical record review and assess HF-warfarin response based on functional class.
2. Project 2: We recognize that the CPRs for DBG related hemorrhage will need to be validated in the future. Model validation and further development will be pursued as part of Dr. Shendre's K23 incorporating other NoACs and using methodology proposed by McGeechan et al and Pencina et al.[227-234]
3. Project 2 proposes a candidate gene approach. We recognize that DBG-related hemorrhage may be influenced by other genes. Moreover, while we are not enrolling patients on Apixaban and Rivaroxaban, Dr. Shendre's will propose expanding assessment of genetic underpinnings of NoAC-related hemorrhage.
4. Project 3: Although we evaluate a MACE and stent thrombosis as a composite endpoint, we recognize that they are clinically distinct endpoints. The skills developed, along with pilot data generated will allow Dr. Irvin to a larger cohort patient cohort with 1 year follow-up as part of his K23 to evaluate each endpoint separately. Moreover the archived DNA samples will allow her to propose additional genomic analysis. We will explore differential benefits from genetic testing by race: African Americans vs. European Americans. Although the study is underpowered to assess race-specific benefits of GGAT, the pilot data generated can then be further developed and validated through aims the K23 grant.

Bibliography and References Cited:

1. Burneo JG, Limdi N, Kuzniecky RI, et al. Neurotoxicity following addition of intravenous valproate to lamotrigine therapy. *Neurology.* 2003;60(12):1991-1992.
2. DeWolfe JL, Knowlton RC, Beasley MT, Cofield S, Faught E, Limdi NA. Hyperammonemia following intravenous valproate loading. *Epilepsy Res.* 2009;85(1):65-71.
3. Dutta S, Faught E, Limdi NA. Valproate protein binding following rapid intravenous administration of high doses of valproic acid in patients with epilepsy. *J Clin Pharm Ther.* 2007;32(4):365-371.
4. Limdi NA, Faught E. The safety of rapid valproic acid infusion. *Epilepsia.* 2000;41(10):1342-1345.
5. Limdi NA, Knowlton RK, Cofield SS, et al. Safety of rapid intravenous loading of valproate. *Epilepsia.* 2007;48(3):478-483.
6. Limdi NA, Shimpi AV, Faught E, Gomez CR, Burneo JG. Efficacy of rapid IV administration of valproic acid for status epilepticus. *Neurology.* 2005;64(2):353-355.
7. Limdi NA, Lemons NV, Gomez CR. Superiority of fixed-dose warfarin for chronic anticoagulation. *J Stroke Cerebrovasc Dis.* 2004;13(3):118-121.
8. Aithal GP, Day CP, Kesteven PJ, Daly AK. Association of polymorphisms in the cytochrome P450 CYP2C9 with warfarin dose requirement and risk of bleeding complications. *Lancet.* 1999;353(9154):717-719.
9. Goldstein JA, Blaisdell JA, Limdi NA. A potentially deleterious new CYP2C9 polymorphism identified in an African American patient with major hemorrhage on warfarin therapy. *Blood Cells Mol Dis.* 2009;42(2):155-158. PMC2662477.
10. Perera MA, Cavallari LH, Limdi NA, et al. Genetic variants associated with warfarin dose in African-American individuals: a genome-wide association study. *Lancet.* 2013;382(9894):790-796. PMCID:3759580.
11. Daneshjou R, Gamazon ER, Burkley B, et al. Genetic variant in folate homeostasis is associated with lower warfarin dose in African Americans. *Blood.* 2014;124(14):2298-2305. PMC4183989.
12. Do AN, Irvin MR, Lynch AI, et al. The effects of angiotensinogen gene polymorphisms on cardiovascular disease outcomes during antihypertensive treatment in the GenHAT study. *Frontiers in pharmacology.* 2014;5:210.
13. Parra EJ, Botton MR, Perini JA, et al. Genome-wide association study of warfarin maintenance dose in a Brazilian sample. *Pharmacogenomics.* 2015:1-11.
14. Limdi NA, Arnett DK, Goldstein JA, et al. Influence of CYP2C9 and VKORC1 on warfarin dose, anticoagulation attainment and maintenance among European-Americans and African-Americans. *Pharmacogenomics.* 2008;9(5):511-526. PMC2757655.
15. Limdi NA, Beasley TM, Allison DB, Rivers CA, Acton RT. Racial differences in the prevalence of Factor V Leiden mutation among patients on chronic warfarin therapy. *Blood Cells Mol Dis.* 2006;37(2):100-106.
16. Limdi NA, Beasley TM, Crowley MR, et al. VKORC1 polymorphisms, haplotypes and haplotype groups on warfarin dose among African-Americans and European-Americans. *Pharmacogenomics.* 2008;9(10):1445-1458.Pmc2586955.
17. Limdi NA, McGwin G, Goldstein JA, et al. Influence of CYP2C9 and VKORC1 1173C/T genotype on the risk of hemorrhagic complications in African-American and European-American patients on warfarin. *Clin Pharmacol Ther.* 2008;83(2):312-321.
18. Limdi NA, Wadelius M, Cavallari L, et al. Warfarin pharmacogenetics: a single VKORC1 polymorphism is predictive of dose across 3 racial groups. *Blood.* 2010;115(18):3827-3834.
19. Schelleman H, Limdi NA, Kimmel SE. Ethnic differences in warfarin maintenance dose requirement and its relationship with genetics. *Pharmacogenomics.* 2008;9(9):1331-1346.
20. Limdi N, Goldstein J, Blaisdell J, Beasley T, Rivers C, Acton R. Influence of CYP2C9 Genotype on warfarin dose among African American and European Americans. *Per Med.* 2007;4(2):157-169. .
21. Limdi NA, McGwin G, Goldstein JA, et al. Influence of CYP2C9 and VKORC1 1173C/T genotype on the risk of hemorrhagic complications in African-American and European-American patients on warfarin. *Clin Pharmacol Ther.* 2008;83(2):312-321. PMCID2683398.
22. Limdi NA, Veenstra DL. Warfarin pharmacogenetics. *Pharmacotherapy.* 2008;28(9):1084-1097. .
23. Cavallari LH, Limdi NA. Warfarin pharmacogenomics. *Curr Opin Mol Ther.* 2009;11(3):243-251.

24. Klein TE, Altman RB, Eriksson N, et al. Estimation of the warfarin dose with clinical and pharmacogenetic data. *N Engl J Med.* 2009;360(8):753-764. PMC2722908.
25. Kimmel SE, French B, Kasner SE, et al. A pharmacogenetic versus a clinical algorithm for warfarin dosing. *N Engl J Med.* 2013;369(24):2283-2293. Pmc3942158.
26. Limdi NA, Brown TM, Yan Q, et al. Race influences warfarin dose changes associated with genetic factors. *Blood.* 2015;126(4):539-545. PMC4513254.
27. Daneshjou R, Tatonetti NP, Karczewski KJ, et al. Pathway analysis of genome-wide data improves warfarin dose prediction. *BMC Genomics.* 2013;14 Suppl 3:S11. PMCID3829086.
28. Limdi NA, Beasley TM, Baird MF, et al. Kidney Function Influences Warfarin Responsiveness and Hemorrhagic Complications. *J Am Soc Nephrol.* 2009;20:912-921. PMC2663833.
29. Limdi MA, Crowley MR, Beasley TM, Limdi NA, Allon M. Influence of kidney function on risk of hemorrhage among patients taking warfarin: a cohort study. *Am J Kidney Dis.* 2013;61(2):354-357. PMC3654383.
30. Limdi NA, Nolin TD, Booth SL, et al. Influence of kidney function on risk of supratherapeutic international normalized ratio-related hemorrhage in warfarin users: a prospective cohort study. *Am J Kidney Dis.* 2015;65(5):701-709. PMC4414676
31. Limdi NA, Limdi MA, Cavallari L, et al. Warfarin Dosing in Patients With Impaired Kidney Function. *Am J Kidney Dis.* 2010;56(5):823-831. PMC2963672.
32. Cosgun E, Limdi NA, Duarte CW. High-dimensional pharmacogenetic prediction of a continuous trait using machine learning techniques with application to warfarin dose prediction in African Americans. *Bioinformatics.* 2011;27(10):1384-1389. PMC3087957.
33. Liu N, Zhao H, Patki A, Limdi NA, Allison DB. Controlling Population Structure in Human Genetic Association Studies with Samples of Unrelated Individuals. *Statistics and its interface.* 2011;4(3):317-326. PMC3269890.
34. Zhang B, Zhi D, Zhang K, Gao G, Limdi NN, Liu N. Practical Consideration of Genotype Imputation: Sample Size, Window Size, Reference Choice, and Untyped Rate. *Statistics and its interface.* 2011;4(3):339-352.
35. Lenzini P, Wadelius M, Kimmel S, et al. Integration of genetic, clinical, and INR data to refine warfarin dosing. *Clin Pharmacol Ther.* 2010;87(5):572-578. PMC2858245.
36. Limdi NA, Wadelius M, Cavallari L, et al. Warfarin pharmacogenetics: a single VKORC1 polymorphism is predictive of dose across 3 racial groups. *Blood.* 2010;115(18):3827-3834. PMC2865873.
37. Horne BD, Lenzini PA, Wadelius M, et al. Pharmacogenetic warfarin dose refinements remain significantly influenced by genetic factors after one week of therapy. *Thromb Haemost.* 2012;107(2):232-240.
38. Counce D, Limdi N, Kuzniecky R. Rasmussen's Encephalitis. *Curr Treat Options Neurol.* 2001;3(6):555-563.
39. Haaz S, Fontaine KR, Cutter G, Limdi N, Perumean-Chaney S, Allison DB. Citrus aurantium and synephrine alkaloids in the treatment of overweight and obesity: an update. *Obes Rev.* 2006;7(1):79-88.
40. Knowlton RC, Elgavish RA, Bartolucci A, et al. Functional imaging: II. Prediction of epilepsy surgery outcome. *Ann Neurol.* 2008;64(1):35-41.
41. Knowlton RC, Elgavish RA, Limdi N, et al. Functional imaging: I. Relative predictive value of intracranial electroencephalography. *Ann Neurol.* 2008;64(1):25-34.
42. Knowlton RC, Razdan SN, Limdi N, et al. Effect of epilepsy magnetic source imaging on intracranial electrode placement. *Ann Neurol.* 2009;65(6):716-723. PMC2729691.
43. Knowlton RC, Kar J, Miller S, et al. Preference-based quality-of-life measures for neocortical epilepsy surgery. *Epilepsia.* 2011;52(5):1018-1020.
44. Zhang B, Zhi D, Zhang K, Gao G, Limdi NA, Liu N. Practical Consideration of Genotype Imputation: Sample Size, Window Size, Reference Choice, and Untyped Rate. *Statistics and its Interface 2011.* 2011;4(3): 339-352. PMC3269888.
45. Chang TI, Gao L, Brown TM, et al. Use of secondary prevention medications among adults with reduced kidney function. *Clin J Am Soc Nephrol.* 2012;7(4):604-611.
46. Irvin MR, Shimbo D, Mann DM, et al. Prevalence and correlates of low medication adherence in apparent treatment-resistant hypertension. *Journal of clinical hypertension (Greenwich, Conn.).* 2012;14(10):694-700. PMC3464920.

47. Kabagambe EK, Beasley TM, Limdi NA. Vitamin K intake, body mass index and warfarin maintenance dose. *Cardiology.* 2013;126(4):214-218.PMC4038335.
48. Thigpen JL, Limdi NA. Reversal of Oral Anticoagulation. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy.* 2013.
49. Shendre A, Beasley TM, Brown TM, Hill CE, Arnett DK, Limdi NA. Influence of Regular Physical Activity on Warfarin Dose and Risk of Hemorrhagic Complications. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy.* 2014;34(6):545-554. PMC4109410
50. Shendre A, Irvin MR, Aouizerat BE, et al. RYR3 gene variants in subclinical atherosclerosis among HIV-infected women in the Women's Interagency HIV Study (WIHS). *Atherosclerosis.* 2014;233(2):666-672. PMC3965606
51. Gutierrez OM, Judd SE, Irvin MR, et al. APOL1 nephropathy risk variants are associated with altered high-density lipoprotein profiles in African Americans. *Nephrol Dial Transplant.* 2015.
52. Thigpen JL, Dillon C, Forster KB, et al. Validity of international classification of disease codes to identify ischemic stroke and intracranial hemorrhage among individuals with associated diagnosis of atrial fibrillation. *Circ Cardiovasc Qual Outcomes.* 2015;8(1):8-14.
53. Aronis KN, Thigpen JL, Tripodis Y, et al. Paroxysmal atrial fibrillation and the hazards of under-treatment. *Int J Cardiol.* 2015;202:214-220.
54. Boehme AK, Pamboukian SV, George JF, et al. Predictors of Thromboembolic Events in Patients with Ventricular Assist Device. *Asaio j.* 2015.
55. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost.* 2005;3(4):692-694.
56. Seto AC, Kenyon K, Wittkowsky AK. Discrepancies in identification of major bleeding events in patients taking warfarin. *Pharmacotherapy.* 2008;28(9):1098-1103.
57. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation.* 2007;115(17):2344-2351.
58. Wiviott SD. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N. Engl. J. Med.* 2007;357:2001-2015.
59. Khoury MJ, Gwinn M, Yoon PW, Dowling N, Moore CA, Bradley L. The continuum of translation research in genomic medicine: how can we accelerate the appropriate integration of human genome discoveries into health care and disease prevention? *Genetics in medicine : official journal of the American College of Medical Genetics.* 2007;9(10):665-674.
60. Deverka PA, Doksum T, Carlson RJ. Integrating molecular medicine into the US health-care system: opportunities, barriers, and policy challenges. *Clin Pharmacol Ther.* 2007;82(4):427-434.
61. Deverka PA, McLeod HL. Harnessing economic drivers for successful clinical implementation of pharmacogenetic testing. *Clin Pharmacol Ther.* 2008;84(2):191-193.
62. Woodcock J. The human genome and translational research: how much evidence is enough? *Health Aff (Millwood).* 2008;27(6):1616-1618.
63. Khoury MJ, Berg A, Coates R, Evans J, Teutsch SM, Bradley LA. The evidence dilemma in genomic medicine. *Health Aff (Millwood).* 2008;27(6):1600-1611.
64. Flockhart DA, Abernethy DR. Finding the right research question: quality science depends on quality careers. *Clin Pharmacol Ther.* 2008;84(3):427-429.
65. Meissner HI, Glasgow RE, Vinson CA, et al. The U.S. training institute for dissemination and implementation research in health. *Implementation science : IS.* 2013;8:12.
66. National Academy of Sciences, National Academy of Engineering, Institute of Medicine. *On Being A Scientist: A Guide to Responsible Conduct in Research.* Third ed. Washington D.C.: The National Academies Press; 2009.
67. Morris AP, Zeggini E. An evaluation of statistical approaches to rare variant analysis in genetic association studies. *Genet Epidemiol.* 2010;34(2):188-193.
68. Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics--2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation.* 2009;119(3):480-486.
69. Go AS. The epidemiology of atrial fibrillation in elderly persons: the tip of the iceberg. *Am J Geriatr Cardiol.* 2005;14(2):56-61.

70. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *Jama.* 2001;285(18):2370-2375.
71. Brand FN, Abbott RD, Kannel WB, Wolf PA. Characteristics and prognosis of lone atrial fibrillation. 30-year follow-up in the Framingham Study. *Jama.* 1985;254(24):3449-3453.
72. Kaarisalo MM, Immonen-Raiha P, Marttila RJ, et al. Atrial fibrillation and stroke. Mortality and causes of death after the first acute ischemic stroke. *Stroke.* 1997;28(2):311-315.
73. Kelly-Hayes M, Wolf PA, Kannel WB, Sytkowski P, D'Agostino RB, Gresham GE. Factors influencing survival and need for institutionalization following stroke: the Framingham Study. *Arch Phys Med Rehabil.* 1988;69(6):415-418.
74. Lamassa M, Di Carlo A, Pracucci G, et al. Characteristics, outcome, and care of stroke associated with atrial fibrillation in Europe: data from a multicenter multinational hospital-based registry (The European Community Stroke Project). *Stroke.* 2001;32(2):392-398.
75. Sacco RL, Wolf PA, Kannel WB, McNamara PM. Survival and recurrence following stroke. The Framingham study. *Stroke.* 1982;13(3):290-295.
76. Steger C, Pratter A, Martinek-Bregel M, et al. Stroke patients with atrial fibrillation have a worse prognosis than patients without: data from the Austrian Stroke registry. *Eur Heart J.* 2004;25(19):1734-1740.
77. Wolf PA, Dawber TR, Thomas HE, Jr., Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. *Neurology.* 1978;28(10):973-977.
78. Wolf PA, Mitchell JB, Baker CS, Kannel WB, D'Agostino RB. Impact of atrial fibrillation on mortality, stroke, and medical costs. *Arch Intern Med.* 1998;158(3):229-234.
79. Singer DE, Albers GW, Dalen JE, et al. Antithrombotic therapy in atrial fibrillation: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest.* 2008;133(6 Suppl):546S-592S.
80. Stroke Risk in Atrial Fibrillation Working G. Comparison of 12 risk stratification schemes to predict stroke in patients with nonvalvular atrial fibrillation. *Stroke.* 2008;39(6):1901-1910.
81. Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. *The American journal of medicine.* 1998;105(2):91-99.
82. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *Jama.* 2001;285(22):2864-2870.
83. Nieuwlaat R, Connolly SJ. Stroke prevention in atrial fibrillation: better use of anticoagulation and new agents will lead to improved outcomes. *Heart.* 2009;95(2):95-97.
84. van Walraven C, Hart RG, Connolly S, et al. Effect of age on stroke prevention therapy in patients with atrial fibrillation: the atrial fibrillation investigators. *Stroke.* 2009;40(4):1410-1416.
85. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest.* 2010;137(2):263-272.
86. Gorin L, Fauchier L, Nonin E, et al. Antithrombotic treatment and the risk of death and stroke in patients with atrial fibrillation and a CHADS2 score=1. *Thromb Haemost.* 2010;103(4):833-840.
87. Lane DA, Lip GY. Anticoagulation for atrial fibrillation patients with CHADS score of 1. *J Cardiovasc Electrophysiol.* 2010;21(5):508-510.
88. Lip GY. Anticoagulation therapy and the risk of stroke in patients with atrial fibrillation at 'moderate risk' [CHADS2 score=1]: simplifying stroke risk assessment and thromboprophylaxis in real-life clinical practice. *Thromb Haemost.* 2010;103(4):683-685.
89. Poli D, Lip GY, Antonucci E, Grifoni E, Lane D. Stroke risk stratification in a "real-world" elderly anticoagulated atrial fibrillation population. *J Cardiovasc Electrophysiol.* 2011;22(1):25-30.
90. Lip GY, Halperin JL. Improving stroke risk stratification in atrial fibrillation. *The American journal of medicine.* 2010;123(6):484-488.
91. Lip GY, Connolly S, Yusuf S, et al. Modification of outcomes with aspirin or apixaban in relation to CHADS(2) and CHA(2)DS(2)-VASc scores in patients with atrial fibrillation: a secondary analysis of the AVERROES study. *Circulation. Arrhythmia and electrophysiology.* 2013;6(1):31-38.
92. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009;361(12):1139-1151.

93. Eriksson BI, Dahl OE, Rosencher N, et al. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. *Lancet.* 2007;370(9591):949-956.
94. Ezekowitz MD, Wallentin L, Connolly SJ, et al. Dabigatran and warfarin in vitamin K antagonist-naive and -experienced cohorts with atrial fibrillation. *Circulation.* 2010;122(22):2246-2253.
95. Flaker G, Ezekowitz M, Yusuf S, et al. Efficacy and Safety of Dabigatran Compared to Warfarin in Patients With Paroxysmal, Persistent, and Permanent Atrial Fibrillation: Results From the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) Study. *J Am Coll Cardiol.* 2012;59(9):854-855.
96. Freeman JV, Zhu RP, Owens DK, et al. Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in atrial fibrillation. *Ann Intern Med.* 2011;154(1):1-11.
97. Friedman RJ, Dahl OE, Rosencher N, et al. Dabigatran versus enoxaparin for prevention of venous thromboembolism after hip or knee arthroplasty: a pooled analysis of three trials. *Thromb Res.* 2010;126(3):175-182.
98. Banerjee A, Lane DA, Torp-Pedersen C, Lip GY. Net clinical benefit of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus no treatment in a 'real world' atrial fibrillation population: a modelling analysis based on a nationwide cohort study. *Thromb Haemost.* 2012;107(3):584-589.
99. Hankey GJ, Patel MR, Stevens SR, et al. Rivaroxaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of ROCKET AF. *Lancet neurology.* 2012;11(4):315-322.
100. Mega JL, Braunwald E, Wiviott SD, et al. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med.* 2012;366(1):9-19.
101. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med.* 2011;365(10):883-891.
102. Alexander JH, Lopes RD, James S, et al. Apixaban with antiplatelet therapy after acute coronary syndrome. *N Engl J Med.* 2011;365(8):699-708.
103. Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. *N Engl J Med.* 2011;364(9):806-817.
104. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011;365(11):981-992.
105. Diener HC, Eikelboom J, Connolly SJ, et al. Apixaban versus aspirin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a predefined subgroup analysis from AVERROES, a randomised trial. *Lancet neurology.* 2012;11(3):225-231.
106. Weitz JI, Eikelboom JW, Samama MM, American College of Chest P. New antithrombotic drugs: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141(2 Suppl):e120S-151S.
107. Melnikova I. The anticoagulants market. *Nat Rev Drug Discov.* 2009;8(5):353-354.
108. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. *N Engl J Med.* 2011;365(21):2002-2012.
109. Budnitz DS, Shehab N, Kegler SR, Richards CL. Medication use leading to emergency department visits for adverse drug events in older adults. *Ann Intern Med.* 2007;147(11):755-765.
110. Wysowski DK, Nourjah P, Swartz L. Bleeding complications with warfarin use: a prevalent adverse effect resulting in regulatory action. *Arch Intern Med.* 2007;167(13):1414-1419.
111. Coca SG, Krumholz HM, Garg AX, Parikh CR. Underrepresentation of renal disease in randomized controlled trials of cardiovascular disease. *Jama.* 2006;296(11):1377-1384.
112. Charytan D, Kuntz RE. The exclusion of patients with chronic kidney disease from clinical trials in coronary artery disease. *Kidney Int.* 2006;70(11):2021-2030.
113. Himmelfarb J. Chronic kidney disease and the public health: gaps in evidence from interventional trials. *Jama.* 2007;297(23):2630-2633.
114. Higashi MK, Veenstra DL, Kondo LM, et al. Association between CYP2C9 genetic variants and anticoagulation-related outcomes during warfarin therapy. *Jama.* 2002;287(13):1690-1698.
115. Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. *Circulation.* 2007;115(21):2689-2696.

116. Landefeld CS, Anderson PA, Goodnough LT, et al. The bleeding severity index: validation and comparison to other methods for classifying bleeding complications of medical therapy. *J Clin Epidemiol.* 1989;42(8):711-718.
117. Steffensen FH, Kristensen K, Ejlersen E, Dahlerup JF, Sorensen HT. Major haemorrhagic complications during oral anticoagulant therapy in a Danish population-based cohort. *J Intern Med.* 1997;242(6):497-503.
118. Lenz TL, Lenz NJ, Faulkner MA. Potential interactions between exercise and drug therapy. *Sports Med.* 2004;34(5):293-306.
119. Shibata Y, Hashimoto H, Kurata C, Ohno R, Kazui T, Takinami M. Influence of physical activity on warfarin therapy. *Thromb Haemost.* 1998;80(1):203-204.
120. Wittkowsky AK, Devine EB. Frequency and causes of overanticoagulation and underanticoagulation in patients treated with warfarin. *Pharmacotherapy.* 2004;24(10):1311-1316.
121. Howard PA, Ellerbeck EF, Engelman KK, Patterson KL. The nature and frequency of potential warfarin drug interactions that increase the risk of bleeding in patients with atrial fibrillation. *Pharmacoepidemiol Drug Saf.* 2002;11(7):569-576.
122. Nutescu EA, Helgason CM. Concomitant drug, dietary, and lifestyle issues in patients with atrial fibrillation receiving anticoagulation therapy for stroke prophylaxis. *Curr Treat Options Cardiovasc Med.* 2005;7(3):241-250.
123. Holbrook AM, Pereira JA, Labiris R, et al. Systematic overview of warfarin and its drug and food interactions. *Archives of Internal Medicine.* 2005;165(10):1095-1106.
124. Kaminsky LS, Zhang ZY. Human P450 metabolism of warfarin. *Pharmacol Ther.* 1997;73(1):67-74.
125. Rettie AE, Jones JP. Clinical and toxicological relevance of CYP2C9: drug-drug interactions and pharmacogenetics. *Annu Rev Pharmacol Toxicol.* 2005;45:477-494.
126. Wittkowsky AK. Warfarin and other coumarin derivatives: pharmacokinetics, pharmacodynamics, and drug interactions. *Semin.* 2003;3(3):221-230.
127. Xiong Q, Lau YC, Lip GY. Pharmacodynamic profile and drug interactions with non-vitamin K antagonist oral anticoagulants: implications for patients with atrial fibrillation. *Expert Opin Drug Metab Toxicol.* 2015;11(6):937-948.
128. Saraf K, Morris P, Garg P, Sheridan P, Storey R. Non-vitamin K antagonist oral anticoagulants (NOACs): clinical evidence and therapeutic considerations. *Postgrad Med J.* 2014;90(1067):520-528.
129. Lee CJ, Ansell JE. Direct thrombin inhibitors. *Br J Clin Pharmacol.* 2011;72(4):581-592.
130. Brewer ES, Reznikov B, Liberman RF, et al. Incidence and predictors of intracranial hemorrhage after minor head trauma in patients taking anticoagulant and antiplatelet medication. *J Trauma.* 2011;70(1):E1-5.
131. Eikelboom JW, Hirsh J. Combined antiplatelet and anticoagulant therapy: clinical benefits and risks. *J Thromb Haemost.* 2007;5 Suppl 1:255-263.
132. Levi M, Eerenberg E, Kamphuisen PW. Bleeding risk and reversal strategies for old and new anticoagulants and antiplatelet agents. *J Thromb Haemost.* 2011;9(9):1705-1712.
133. Quilliam BJ, Lapane KL, Eaton CB, Mor V. Effect of antiplatelet and anticoagulant agents on risk of hospitalization for bleeding among a population of elderly nursing home stroke survivors. *Stroke.* 2001;32(10):2299-2304.
134. Shireman TI, Howard PA, Kresowik TF, Ellerbeck EF. Combined anticoagulant-antiplatelet use and major bleeding events in elderly atrial fibrillation patients. *Stroke.* 2004;35(10):2362-2367.
135. Vedovati MC, Becattini C, Agnelli G. Combined oral anticoagulants and antiplatelets: benefits and risks. *Intern Emerg Med.* 2010;5(4):281-290.
136. Friedman RJ, Kurth A, Clemens A, Noack H, Eriksson BI, Caprini JA. Dabigatran etexilate and concomitant use of non-steroidal anti-inflammatory drugs or acetylsalicylic acid in patients undergoing total hip and total knee arthroplasty: no increased risk of bleeding. *Thromb Haemost.* 2012;108(1):183-190.
137. Morisky DE, Ang A, Krousel-Wood M, Ward HJ. Predictive Validity of A Medication Adherence Measure in an Outpatient Setting. *Journal of clinical hypertension (Greenwich, Conn.).* 2008;10(5):348-354.
138. Cuffee YL, Hargraves JL, Rosal M, et al. Reported racial discrimination, trust in physicians, and medication adherence among inner-city African Americans with hypertension. *Am J Public Health.* 2013;103(11):e55-62.

139. Kelly MS, Moczygemba LR, Gatewood SS. Concordance of Pharmacist Assessment of Medication Nonadherence With a Self-Report Medication Adherence Scale. *J Pharm Pract.* 2014.
140. Luo N, Johnson JA, Shaw JW, Feeny D, Coons SJ. Self-reported health status of the general adult U.S. population as assessed by the EQ-5D and Health Utilities Index. *Med Care.* 2005;43(11):1078-1086.
141. Shaw JW, Johnson JA, Chen S, Levin JR, Coons SJ. Racial/ethnic differences in preferences for the EQ-5D health states: results from the U.S. valuation study. *J Clin Epidemiol.* 2007;60(5):479-490.
142. Berg J, Lindgren P, Nieuwlaat R, Bouin O, Crijns H. Factors determining utility measured with the EQ-5D in patients with atrial fibrillation. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2010;19(3):381-390.
143. Ravens-Sieberer U, Wille N, Badia X, et al. Feasibility, reliability, and validity of the EQ-5D-Y: results from a multinational study. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2010;19(6):887-897.
144. Nowels D, McGloin J, Westfall JM, Holcomb S. Validation of the EQ-5D quality of life instrument in patients after myocardial infarction. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2005;14(1):95-105.
145. Limdi MA, Crowley MR, Beasley TM, Limdi NA, Allon M. Influence of kidney function on risk of hemorrhage among patients taking warfarin: a cohort study. *Am J Kidney Dis.* 2013;61(2):354-357.
146. Wieloch M, Jonsson KM, Sjalander A, Lip GY, Eriksson N, Svensson PJ. Estimated glomerular filtration rate is associated with major bleeding complications but not thromboembolic events, in anticoagulated patients taking warfarin. *Thromb Res.* 2013;131(6):481-486.
147. Limdi NA, Beasley TM, Baird MF, et al. Kidney function influences warfarin responsiveness and hemorrhagic complications. *J Am Soc Nephrol.* 2009;20(4):912-921.
148. Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the S, Standardization Committee of the International Society on T, Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost.* 2005;3(4):692-694.
149. Limdi NA, Wiener H, Goldstein JA, Acton RT, Beasley TM. Influence of CYP2C9 and VKORC1 on warfarin response during initiation of therapy. *Blood Cells Mol Dis.* 2009;43(1):119-128.
150. Limdi NA, Veenstra DL. Expectations, validity, and reality in pharmacogenetics. *J Clin Epidemiol.* 2010;63(9):960-969. PMC2888890.
151. Limdi NA. Warfarin pharmacogenetics: challenges and opportunities for clinical translation. *Frontiers in pharmacology.* 2012;3:183.
152. Close SL. Clopidogrel pharmacogenetics: metabolism and drug interactions. *Drug Metabol Drug Interact.* 2011;26(2):45-51.
153. Farid NA, Kurihara A, Wrighton SA. Metabolism and disposition of the thienopyridine antiplatelet drugs ticlopidine, clopidogrel, and prasugrel in humans. *Journal of clinical pharmacology.* 2010;50(2):126-142.
154. Shuldiner AR, O'Connell JR, Bliden KP, et al. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. *Jama.* 2009;302(8):849-857.
155. Chen BL, Zhang W, Li Q, et al. Inhibition of ADP-induced platelet aggregation by clopidogrel is related to CYP2C19 genetic polymorphisms. *Clin Exp Pharmacol Physiol.* 2008;35(8):904-908.
156. Pare G, Mehta SR, Yusuf S, et al. Effects of CYP2C19 genotype on outcomes of clopidogrel treatment. *The New England journal of medicine.* 2010;363(18):1704-1714.
157. Mega JL, Simon T, Collet JP, et al. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. *Jama.* 2010;304(16):1821-1830.
158. Mega JL, Close SL, Wiviott SD, et al. Genetic variants in ABCB1 and CYP2C19 and cardiovascular outcomes after treatment with clopidogrel and prasugrel in the TRITON-TIMI 38 trial: a pharmacogenetic analysis. *Lancet.* 2010;376(9749):1312-1319.
159. Mega JL. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. *Jama.* 2010;304:1821-1830.
160. Collet JP, Hulot JS, Pena A, et al. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. *Lancet.* 2009;373(9660):309-317.
161. Giusti B, Gori AM, Marcucci R, et al. Cytochrome P450 2C19 loss-of-function polymorphism, but not CYP3A4 IVS10 + 12G/A and P2Y12 T744C polymorphisms, is associated with response variability to

dual antiplatelet treatment in high-risk vascular patients. *Pharmacogenet Genomics.* 2007;17(12):1057-1064.
162. Simon T, Verstuyft C, Mary-Krause M, et al. Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med.* 2009;360(4):363-375.
163. Sibbing D, Koch W, Gebhard D, et al. Cytochrome 2C19*17 allelic variant, platelet aggregation, bleeding events, and stent thrombosis in clopidogrel-treated patients with coronary stent placement. *Circulation.* 2010;121(4):512-518.
164. Cuisset T, Loosveld M, Morange PE, et al. CYP2C19*2 and *17 alleles have a significant impact on platelet response and bleeding risk in patients treated with prasugrel after acute coronary syndrome. *JACC. Cardiovascular interventions.* 2012;5(12):1280-1287.
165. Harmsze AM, van Werkum JW, Hackeng CM, et al. The influence of CYP2C19*2 and *17 on on-treatment platelet reactivity and bleeding events in patients undergoing elective coronary stenting. *Pharmacogenetics and genomics.* 2012;22(3):169-175.
166. Li Y, Tang HL, Hu YF, Xie HG. The gain-of-function variant allele CYP2C19*17: a double-edged sword between thrombosis and bleeding in clopidogrel-treated patients. *Journal of thrombosis and haemostasis : JTH.* 2012;10(2):199-206.
167. Roberts JD, Wells GA, Le May MR, et al. Point-of-care genetic testing for personalisation of antiplatelet treatment (RAPID GENE): a prospective, randomised, proof-of-concept trial. *Lancet.* 2012;379(9827):1705-1711.
168. Scott SA, Sangkuhl K, Stein CM, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. *Clin Pharmacol Ther.* 2013;94(3):317-323.
169. Bawamia B, Mehran R, Qiu W, Kunadian V. Risk scores in acute coronary syndrome and percutaneous coronary intervention: a review. *Am Heart J.* 2013;165(4):441-450.
170. Singh M, Holmes DR, Lennon RJ, Rihal CS. Development and validation of risk adjustment models for long-term mortality and myocardial infarction following percutaneous coronary interventions. *Circulation: Cardiovascular Interventions.* 2010;3(5):423-430.
171. Addala S, Grines CL, Dixon SR, et al. Predicting mortality in patients with ST-elevation myocardial infarction treated with primary percutaneous coronary intervention (PAMI risk score). *Am J Cardiol.* 2004;93(5):629-632.
172. Halkin A, Singh M, Nikolsky E, et al. Prediction of mortality after primary percutaneous coronary intervention for acute myocardial infarction: the CADILLAC risk score. *J Am Coll Cardiol.* 2005;45(9):1397-1405.
173. Maluenda G, Delhaye C, Gaglia MA, Jr., et al. A novel percutaneous coronary intervention risk score to predict one-year mortality. *Am J Cardiol.* 2010;106(5):641-645.
174. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. *JAMA.* 2000;284(7):835-842.
175. Fox CS, Muntner P, Chen AY, et al. Use of evidence-based therapies in short-term outcomes of ST-segment elevation myocardial infarction and non-ST-segment elevation myocardial infarction in patients with chronic kidney disease: a report from the National Cardiovascular Data Acute Coronary Treatment and Intervention Outcomes Network registry. *Circulation.* 2010;121(3):357-365.
176. Sianos G, Morel MA, Kappetein AP, et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention.* 2005;1(2):219-227.
177. Garg S, Sarno G, Garcia-Garcia HM, et al. A new tool for the risk stratification of patients with complex coronary artery disease: the Clinical SYNTAX Score. *Circ Cardiovasc Interv.* 2010;3(4):317-326.
178. Eagle KA, Lim MJ, Dabbous OH, et al. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. *Jama.* 2004;291(22):2727-2733.
179. Granger CB, Goldberg RJ, Dabbous O, et al. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med.* 2003;163(19):2345-2353.
180. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Circulation.* 2012;126(16):2020-2035.
181. Wittkowsky AK, Devine EB. Frequency and causes of overanticoagulation and underanticoagulation in patients treated with warfarin. *Pharmacotherapy.* 2004;24(10):1311-1316.

182. Fang MC, Chang Y, Hylek EM, et al. Advanced age, anticoagulation intensity, and risk for intracranial hemorrhage among patients taking warfarin for atrial fibrillation. *Ann Intern Med.* 2004;141(10):745-752.
183. Hylek EM, Regan S, Go AS, Hughes RA, Singer DE, Skates SJ. Clinical predictors of prolonged delay in return of the international normalized ratio to within the therapeutic range after excessive anticoagulation with warfarin. *Ann Intern Med.* 2001;135(6):393-400.
184. Kim EJ, Ozonoff A, Hylek EM, et al. Predicting outcomes among patients with atrial fibrillation and heart failure receiving anticoagulation with warfarin. *Thromb Haemost.* 2015;114(1).
185. Limdi NA, Limdi MA, Cavallari L, et al. Warfarin dosing in patients with impaired kidney function. *Am J Kidney Dis.* 2010;56(5):823-831.
186. Doecke CJ, Cosh DG, Gallus AS. Standardised initial warfarin treatment: evaluation of initial treatment response and maintenance dose prediction by randomised trial, and risk factors for an excessive warfarin response. *Australian and New Zealand journal of medicine.* 1991;21(3):319-324.
187. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briet E. A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemost.* 1993;69(3):236-239.
188. Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Buller HR, Levi M. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. *Circulation.* 2011;124(14):1573-1579.
189. van Ryn J, Stangier J, Haertter S, et al. Dabigatran etexilate--a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. *Thromb Haemost.* 2010;103(6):1116-1127.
190. Bleeding with dabigatran (Pradaxa). *Med Lett Drugs Ther.* 2011;53(1379-1380):98.
191. Bleeding with dabigatran, rivaroxaban, apixaban. No antidote, and little clinical experience. *Prescrire international.* 2013;22(139):155-159.
192. Eikelboom JW, Wallentin L, Connolly SJ, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. *Circulation.* 2011;123(21):2363-2372.
193. Fawole A, Daw HA, Crowther MA. Practical management of bleeding due to the anticoagulants dabigatran, rivaroxaban, and apixaban. *Cleve Clin J Med.* 2013;80(7):443-451.
194. Harper P, Young L, Merriman E. Bleeding risk with dabigatran in the frail elderly. *N Engl J Med.* 2012;366(9):864-866.
195. Oldgren J, Alings M, Darius H, et al. Risks for stroke, bleeding, and death in patients with atrial fibrillation receiving dabigatran or warfarin in relation to the CHADS2 score: a subgroup analysis of the RE-LY trial. *Annals of internal medicine.* 2011;155(10):660-667, W204.
196. Southworth MR, Reichman ME, Unger EF. Dabigatran and postmarketing reports of bleeding. *N Engl J Med.* 2013;368(14):1272-1274.
197. Wychowski MK, Kouides PA. Dabigatran-induced gastrointestinal bleeding in an elderly patient with moderate renal impairment. *Ann Pharmacother.* 2012;46(4):e10.
198. Sharma M, Cornelius VR, Patel JP, Davies JG, Molokhia M. Efficacy and Harms of Direct Oral Anticoagulants in the Elderly for Stroke Prevention in Atrial Fibrillation and Secondary Prevention of Venous Thromboembolism: Systematic Review and Meta-Analysis. *Circulation.* 2015.
199. Paré G. RE-LY-Genetics: Genetic determinants of dabigatran plasma levels and their relation to clinical response. . Paper presented at: European Society of Cardiology 2012 Congress2012; Munich, Germany.
200. Pare G, Eriksson N, Lehr T, et al. Genetic determinants of dabigatran plasma levels and their relation to bleeding. *Circulation.* 2013;127(13):1404-1412.
201. Landefeld CS, Goldman L. Major bleeding in outpatients treated with warfarin: incidence and prediction by factors known at the start of outpatient therapy. *The American journal of medicine.* 1989;87(2):144-152.
202. Wells PS, Forgie MA, Simms M, et al. The outpatient bleeding risk index: validation of a tool for predicting bleeding rates in patients treated for deep venous thrombosis and pulmonary embolism. *Arch Intern Med.* 2003;163(8):917-920.
203. Kearon C, Ginsberg JS, Kovacs MJ, et al. Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. *N Engl J Med.* 2003;349(7):631-639.

204. Kuijer PM, Hutten BA, Prins MH, Buller HR. Prediction of the risk of bleeding during anticoagulant treatment for venous thromboembolism. *Arch Intern Med.* 1999;159(5):457-460.
205. Ruiz-Gimenez N, Suarez C, Gonzalez R, et al. Predictive variables for major bleeding events in patients presenting with documented acute venous thromboembolism. Findings from the RIETE Registry. *Thromb Haemost.* 2008;100(1):26-31.
206. Fang MC, Go AS, Chang Y, et al. A new risk scheme to predict warfarin-associated hemorrhage: The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. *J Am Coll Cardiol.* 2011;58(4):395-401.
207. Gage BF, Yan Y, Milligan PE, et al. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). *Am Heart J.* 2006;151(3):713-719.
208. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest.* 2010;138(5):1093-1100.
209. Schnabel RB, Sullivan LM, Levy D, et al. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. *Lancet.* 2009;373(9665):739-745.
210. Batchelor WB, Ellis SG, Ormiston JA, et al. Racial differences in long-term outcomes after percutaneous coronary intervention with paclitaxel-eluting coronary stents. *J Interv Cardiol.* 2013;26(1):49-57.
211. Collins SD, Torguson R, Gaglia MA, Jr., et al. Does black ethnicity influence the development of stent thrombosis in the drug-eluting stent era? *Circulation.* 2010;122(11):1085-1090.
212. Gaglia MA, Jr., Steinberg DH, Pinto Slottow TL, et al. Racial disparities in outcomes following percutaneous coronary intervention with drug-eluting stents. *The American journal of cardiology.* 2009;103(5):653-658.
213. Poludasu S, Cavusoglu E, Khan W, Marmur JD. All-cause mortality after drug-eluting stent implantation in African-Americans. *Coron Artery Dis.* 2008;19(8):551-557.
214. Poludasu S, Cavusoglu E, Khan W, Marmur JD. Impact of body mass index on long-term all-cause mortality after percutaneous coronary intervention in African-Americans. *J Invasive Cardiol.* 2009;21(1):20-25.
215. Dodson JA, Arnold SV, Reid KJ, et al. Physical function and independence 1 year after myocardial infarction: observations from the Translational Research Investigating Underlying disparities in recovery from acute Myocardial infarction: Patients' Health status registry. *Am Heart J.* 2012;163(5):790-796.
216. Kamble S, Boyd AS. Health disparities and social determinants of health among African-American women undergoing percutaneous coronary interventions (PCI). *Journal of cultural diversity.* 2008;15(3):132-142.
217. Melsop K, Brooks MM, Boothroyd DB, Hlatky MA. Effect of race on the clinical outcomes in the bypass angioplasty revascularization investigation trial. *Circ Cardiovasc Qual Outcomes.* 2009;2(3):186-190.
218. Napan S, Kashinath R, Orig M, Kadri S, Khadra S. Racial difference in cardiovascular outcomes following percutaneous coronary intervention in a public health service patient population. *J Invasive Cardiol.* 2010;22(4):168-173.
219. Parikh PB, Jeremias A, Naidu SS, et al. Effect of gender and race on outcomes in dialysis-dependent patients undergoing percutaneous coronary intervention. *The American journal of cardiology.* 2011;107(9):1319-1323.
220. Schneider EB, Black JH, 3rd, Hambridge HL, et al. The impact of race and ethnicity on the outcome of carotid interventions in the United States. *J Surg Res.* 2012;177(1):172-177.
221. Gurbel PA, Bliden KP, Cohen E, et al. Race and sex differences in thrombogenicity: risk of ischemic events following coronary stenting. *Blood Coagul Fibrinolysis.* 2008;19(4):268-275.
222. Cresci S, Depta JP, Lenzini PA, et al. Cytochrome p450 gene variants, race, and mortality among clopidogrel-treated patients after acute myocardial infarction. *Circ Cardiovasc Genet.* 2014;7(3):277-286.
223. McDonough CW, McClure LA, Mitchell BD, et al. CYP2C19 metabolizer status and clopidogrel efficacy in the Secondary Prevention of Small Subcortical Strokes (SPS3) study. *Journal of the American Heart Association.* 2015;4(6):e001652.
224. Bucholz EM, Ma S, Normand S-LT, Krumholz HM. Race, Socioeconomic Status, and Life Expectancy After Acute Myocardial Infarction. *Circulation.* 2015;132(14):1338-1346.

225. O'Brien BJ, Briggs AH. Analysis of uncertainty in health care cost-effectiveness studies: an introduction to statistical issues and methods. *Stat Methods Med Res.* 2002;11(6):455-468.
226. Briggs AH. Statistical approaches to handling uncertainty in health economic evaluation. *European journal of gastroenterology & hepatology.* 2004;16(6):551-561.
227. McGeechan K, Macaskill P, Irwig L, Liew G, Wong TY. Assessing new biomarkers and predictive models for use in clinical practice: a clinician's guide. *Arch Intern Med.* 2008;168(21):2304-2310.
228. Janssens AC, Ioannidis JP, Bedrosian S, et al. Strengthening the reporting of Genetic RIsk Prediction Studies (GRIPS): explanation and elaboration. *J Clin Epidemiol.* 2011;64(8):e1-e22.
229. Pencina MJ, D'Agostino RB, Sr., Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. *Stat Med.* 2011;30(1):11-21.
230. Pencina MJ, D'Agostino RB, Vasan RS. Statistical methods for assessment of added usefulness of new biomarkers. *Clin Chem Lab Med.* 2010;48(12):1703-1711.
231. Steyerberg EW, Pencina MJ. Reclassification calculations for persons with incomplete follow-up. *Ann Intern Med.* 2010;152(3):195-196; author reply 196-197.
232. Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the performance of prediction models: a framework for traditional and novel measures. *Epidemiology.* 2010;21(1):128-138.
233. Uno H, Cai T, Pencina MJ, D'Agostino RB, Wei LJ. On the C-statistics for evaluating overall adequacy of risk prediction procedures with censored survival data. *Stat Med.* 2011;30(10):1105-1117.
234. Janssens AC, Ioannidis JP, van Duijn CM, Little J, Khoury MJ, Group G. Strengthening the reporting of Genetic RIsk Prediction Studies: the GRIPS Statement. *PLoS medicine.* 2011;8(3):e1000420.