Background
• Warfarin is difficult to manage because of the wide inter-individual variation in dose requirements, the narrow therapeutic range and the risk of serious bleeding. Interm individual variation in anticoagulation response to warfarin is affected by age, gender, genetic variations, body mass index and use of concomitant medications.1
• Single nucleotide polymorphisms in vitamin K epoxide reductase complex subunit 1 (VKORC1) and the warfarin metabolizing gene cytochrome P450 family 2, subfamily C, polypeptide 1 (CYP2C9) predict approximately 70 to 80% of the percent of dose variance (VKORC1 ~25%, CYP2C9 ~50%). Non-genetic factors (age, sex, etc.) jointly account for another ~15 percent.2
• Because genetic variations affect warfarin response, potential benefits of genetic testing prior to therapy include more accurate initial dosing with the possibility of shorter time to reach a therapeutic international Normalized Ratio (INR) and reduced adverse outcomes, however the practice of using pharmacogenomics guided therapy is controversial.3
• Currently, the Center for Medicare and Medicaid Services (CMS) restricts warfarin genetic testing coverage to individuals who:3
  1. Have not been previously tested for CYP2C9 or VKORC1 alleles; and
  2. Have received fewer than five days of warfarin in the anticoagulation segment for which the testing is ordered; and
  3. Are enrolled in a prospective, randomized, controlled clinical study meeting CMS determined standards.
• The American College of Chest Physicians “2012 Evidenced-Based Management of Anticoagulant Therapy Guidelines” recommend against routine use of pharmacogenetic testing for guiding doses of vitamin K antagonist therapy.4

Methods
• Pharmacy and medical claims data from a 1.2 million member commercially insured population in the Central U.S. were queried to identify members continuously enrolled March 1, 2010 through June 30, 2011.
• The earliest warfarin claim from July 1, 2010 through June 30, 2011 was defined as the index warfarin claim.
• Warfarin new starter was defined as no warfarin claim in the 120 days before the index warfarin claim.
• Warfarin utilizers’ medical claims were queried from March 1, 2010 through June 30, 2011 for the presence of one or more of the following molecular diagnostic related current procedural terminology (CPT) codes: 83909, 83912, 88384, 88385, and 88386, G9143.
• Allowed amounts from each line of the medical claim with a genetic test CPT code were used to calculate total paid.
• CMS criteria, as stated in the background, were used to define appropriateness of genetic testing relative to warfarin therapy.5
• For members new to warfarin therapy, the latest genetic testing date was compared to the index warfarin claim date and categorized into those having testing performed within five days of the warfarin index claim (i.e., appropriate) or greater than five days (i.e., inappropriate).
• All genetic testing found among non-new start warfarin utilizers was defined as inappropriate.
• Among all 2.1 million members (non-continuously and continuously enrolled), claims (adjusted to 30-day supply) per quarter per million members are reported for warfarin, dabigatran, and rivaroxaban from January 1, 2010 through December 31, 2011.

Results
• 948,270 members were continuously enrolled March 1, 2010 through June 30, 2011 and 8,396 unique members had a warfarin claim from July 1, 2010 through June 30, 2011 (Figure 1).
• A genetic testing claim was found in 334 (4.0%) of 8,396 warfarin utilizers and the total paid for genetic testing was $100,512 with a median of $522 per member (25th percentile $72 and 75th percentile $552).
• Inappropriate genetic testing (greater than five days after warfarin initiation) was found in 226 (67.7%) of 334 warfarin utilizers at a cost of $61,932.
• Of the 8,396 warfarin utilizers, 4,003 (47.7%) were new to warfarin therapy and genetic testing codes were found in 212 (5.3%) members. Inappropriate genetic testing was found in 202 (95.2%) of the 212 new warfarin starters at a total paid amount of $24,464 (Table 1).
• Among the 4,393 members new to warfarin therapy, 122 (2.8%) were found to have had an inappropriate genetic testing claim, as they were already on warfarin therapy, at a total paid amount of $324,464 (Table 2).
• Warfarin utilization in Q42010 was 5,696 claims per quarter per million members, an increase of 9.7 percent from the Q42009 to Q42010 and 59-field higher than dabigatran and rivaroxaban combined. (Figure 2)
• Dabigatran utilization in Q42010 was 275 claims per quarter per million members, a 17.5 percent increase from the market launch utilization in Q42010.

Conclusions
• Warfarin claims utilization continues to increase with a 9.7 percent change from Q42009 to Q42010. Although dabigatran utilization has steadily grown and rivaroxaban was recently approved, their use was 19-fold less than warfarin.
• Currently, genetic testing associated with warfarin utilization is not routine at a rate of four per 100 overall and five per 100 warfarin new starts. The non-routine use of warfarin genetic testing is consistent with the 2012 CHEST guidelines which recommend against routine testing.
• If genetic testing had been performed in all new warfarin starters, $604,456 (4,003 members x $152 median test cost) would have been spent by the plan.
• If inappropriate testing, defined as greater than five days after warfarin is newly initiated, remained at a rate of 25% per month ($298,752 or $0.026 per member per month (PMPM)) would have been expended without benefit.
• As pharmacogenomics testing becomes more mainstream, spaces more drug classes and costs increase, health plans will proactively introspect about how to ensure the right member is tested at the right time.

References
1. The genetic testing procedure codes used in the current analysis are not specific to pharmacogenomics for warfarin and could have been performed for other reasons (e.g., cancer).
2. Data are limited to commercial populations in the Central U.S. and therefore may not be generalizable to Medicare or Medicaid populations or commercially insured individuals in other geographic areas.
3. This analysis did not analyze the clinical utility of pharmacogenomics testing via impact on future medical utilization or warfarin dose adjustments.
4. Medical and pharmac care claims data are intended for administrative and payment information purposes and as such they may represent information that is false-positive or -negative.
5. The authors are solely responsible for the content and methods of this study, and the authors are not liable for errors or omissions in reporting results. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.