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On the potential of preemptive genotyping towards preventing medication related adverse events: Results from the South Korean national health insurance database

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The idea that genetic variation can affect the outcome of drug therapy, and in particular the incidence of severe adverse events (AEs) is widely-accepted. However, actual data on how programs that seek to reduce such AEs might perform has been hard to come by. In 2012, we reported an analysis of use of medications with known pharmacogenetic (PG) effects in ~53K 'medical home' patients at our center [1]. Kim and colleagues [2] have now extended this approach to more than 1.3 million patients (a 3% representative sample) with prescriptions in 2011 across South Korea using a resource that covers 90% of the South Korean population. They observed 32% of patients (~428k) were prescribed at least one PG medication associated with a serious AE, and 53,521 unique patients had the variant allele associated with the PG prescription. Assuming that genetically-tailored therapy reduces the AE rate in those with variants to those with the common allele, the authors estimate that 729 serious AEs could have been prevented in this sample. Generalizing to the broader population represented by the sample, they estimate that approximately 24000 serious AEs could have been prevented with an efficient preemptive genotyping program across South Korea.

One way to use genetic information to address this issue is to perform "reactive" genotyping for drug-specific variants when a PG drug is prescribed. Arguments against this approach are the necessary time lags involved, and the potential inefficiencies of such testing given that for many PG drugs, relevant genetic variants may be uncommon. An alternative, preemptive multiplexed genetic testing, is appealing because if implemented into an electronic health system, the genetic data can be available at the time of prescribing which eliminates impediments to optimal patient treatment. Further, data collected from a multiplexed test are available for as many PG variants as are on the panel and the cost difference between testing one or a few dozen genes is minimal. A perceived weakness of the preemptive approach could be that some patients will be tested for drugs to which they do not get exposed. However, the authors found that in 2011 alone, among those with any

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prescription, 47.6%, 21.2% and 9.8% of patients were prescribed at least one, two, and three medications, respectively, with PG effects.

A number of sites have started to implement and evaluate preemptive programs [3, 4]. At our center we have implemented a program of preemptive genotyping, the Pharmacogenomic Resource for Enhanced Decisions in Care and Treatment (PREDICT; [5]). PREDICT uses clinical data available in the electronic medical record to calculate the risk of being prescribed a PG medication on a daily basis and has been implemented into clinical decision support systems across the Vanderbilt University Medical Center (VUMC) clinics [6]. If the risk is high enough, the physician receives an alert that the patient may benefit from (multiplexed) genetic testing. Currently our panel covers 184 functional polymorphisms on 34 genes. In an analysis of the first ~10,000 patients enrolled, Van Driest et al (2014) [7] found that 91% possessed at least one actionable variant across 5 PG medications. Further, because over time patients are prescribed multiple medications with PG effects, Van Driest et al. estimated that the total number of genetic tests conducted would be reduced by nearly 35% with a multiplexed testing program compared to a reactive, single-gene testing strategy.

To conduct the analyses, Kim et al followed the approach we previously described [2]. Using their own data, they were able to identify patients prescribed medications with PG effects in 2011. Combining the number exposed to each PG medication with literature based estimates of variant allele prevalence and the excess risk of each AE associated with variants, the authors estimated the total number of serious AEs that could have been prevented if excess risk was mitigated by the use of alternative therapies. Even though the authors were only provided de-identified prescription records, they took analyses a step further by estimating AE prevalence associated with each medication in their population and this should permit a more accurate estimate of excess risk (e.g., excess risk estimates are based on AE prevalence, variant allele prevalence, and relative effect measures). Concern about inaccurate estimation arises from the fact that, as mentioned by the authors, all prescriptions that occurred in 2011 were used. This includes incident and prevalent cases, and the relative proportions are unknown. To the extent that this sample contains prevalent prescriptions, the sample represents a population that is generally less susceptible to AEs associated with these PG medications than the general population. Ideally, this study would only have considered incident prescriptions, though we recognize this was impossible since the data pull was from 2011, data were de-identified, and there was no way to link patients to prior prescriptions or to future AEs.

This research will overestimate the beneficial impact of preemptive genotyping to the extent that, for example, literature based estimates of effect sizes are optimistic, and to the extent that alternative treatments, while reducing studied AE rates, may increase others. However, estimates provided by the authors will underestimate the impact of preemptive genotyping as more PG medications and alternative treatments are identified.

While we recognize the need for further research into potential benefits of genomic medicine, it is crucial to take these first steps towards understanding the potential benefits of a pre-emptive genotyping program. The authors should be commended for this work, and specifically for attempting to examine this study question on an extremely large scale.

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