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Precision Medicine and Pharmacogenetics: What Does Oncology Have that Addiction Medicine Doesn't?

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Abstract

Background and aims—Precision, personalized, or stratified medicine, which promises to deliver the right treatment to the right patient, is a topic of international interest in both the lay press and the scientific literature. A key aspect of precision medicine is the identification of biomarkers that predict the response to medications (i.e., pharmacogenetics). We examined why, despite the great strides that have been made in biomarker identification in many areas of medicine, only in oncology has there been substantial progress in their clinical implementation. We also considered why progress in this effort has lagged in addiction medicine.

Methods—We compared the development of pharmacogenetic biomarkers in oncology, cardiovascular medicine (where developments are also promising), and addictive disorders.

Results—The first major reason for the success of oncologic pharmacogenetics is ready access to tumor tissue, which allows *in vitro* testing and insights into cancer biology. The second major reason is funding, with cancer research receiving, by far, the largest allocation by the National Institutes of Health (NIH) over the past two decades. The second largest allocation of research funding has gone to cardiovascular disease research. Addictions research received a much smaller NIH funding allocation, despite the major impact that tobacco use, alcohol consumption, and illicit drug use have on the public health and healthcare costs.

Conclusions—Greater support for research on the personalized treatment of addictive disorders can be expected to yield disproportionately large benefits to the public health and substantial reductions in healthcare costs.

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Keywords

Personalized Medicine; Precision Medicine; Stratified Medicine; Pharmacogenetics; Oncology; Cardiovascular Medicine; Addiction Medicine

Diagnostic tests and medical treatments have traditionally been developed and evaluated using population data, a “one-size fits all” approach that leaves little room for individual variation (1). In recent years, the identification of biomarkers has yielded unique patient predictors of therapeutic and adverse effects of medications, i.e., pharmacogenetics, which has enhanced their clinical utility and safety (2). Pharmacogenetics, a key dimension of precision medicine, targets treatments to the needs of individual patients using genetic biomarkers to identify those for whom a specific treatment is best suited (3).

The genetic variation of greatest relevance to drug development has been categorized into four broad groups by the Food and Drug Administration (4), all of which can affect the benefit–risk profile of a drug: 1) genes relevant to the drug’s pharmacokinetics; 2) genes that encode intended or unintended drug targets or other pathways related to the drug’s pharmacologic effects (i.e., pharmacodynamics); 3) genes that, though not directly related to a drug’s pharmacology, can predispose to toxicities; and 4) genes that influence disease susceptibility or progression.

Growth in the Discovery and Use of Pharmacogenetics in Medicine

A review of drug labels for the period 1945–2005 revealed that, of the 1,200 labels approved by the FDA, about 10% (i.e., 121) contained information that could be used by the prescriber to personalize treatment based on a genetic test (5). Although the genomic biomarkers in 52 labels (43%) were microbial, the majority (69 or 57%) of the biomarkers were in humans, of which 43 (62%) identified variants in genes encoding cytochrome P450 enzymes.

The most recent tally (6) shows that the labels of 165 FDA-approved drugs (or drug combinations) contain information on 64 different pharmacogenomics biomarkers. Although 55 of the biomarkers are unique to one drug, the majority of drugs are associated with variants (e.g., in cytochrome p450 genes) that are relevant to multiple drugs. Biomarker information is most common in the label of medications used to treat cancer (n=71, 43.0%), followed by psychiatric disorders (n=30, 18.2%), infectious diseases (n=18, 10.9%), and cardiovascular disorders (n=12, 7.3%). Importantly, it has been estimated that only 15% of the identified genetic associations are supported by data from randomized controlled trials (RCTs) (7). Thus, despite substantial growth in the number of medication labels with pharmacogenomic information over the past two decades, the most compelling data (i.e., those derived from RCTs) supporting the utility of the biomarkers remains limited.

The effects of more than one-third of the drugs (61 or 37.0%), including all of the psychiatric medications, are associated with variation in cytochrome P450 genes, which affect the pharmacokinetics of the drug. Because pharmacokinetics can readily be ascertained from plasma drug concentrations using standardized methods, genetic

moderators of pharmacokinetic effects are more easily identified than pharmacodynamic variants. In contrast, pharmacodynamic differences are complex traits that vary widely both between individuals and within individuals over time, making them more difficult to identify. Validation of pharmacodynamic effect moderators also requires precision in the measurement of treatment outcomes and can be affected by differences in drug exposure (e.g., based on variable medication adherence), which commonly limits the effectiveness of pharmacotherapy and may be particularly problematic in patients with addictive disorders (6, 8).

Early successes in oncologic and cardiovascular pharmacogenetics have stimulated interest in pharmacogenetic research in other areas of medicine, including addiction medicine (2, 3, 9–13). An important consideration in addiction medicine that differentiates it from cancer and cardiovascular medicine is the heavy reliance on psychosocial treatments for addiction. Although a full discussion of this topic is beyond the scope of this review, there have been some important efforts in this area. Project MATCH, the largest study of psychosocial treatment of addiction, sought to identify patient predictors of treatment response in individuals with an alcohol use disorder (14). That effort, however, failed to identify robust moderator variables (15). More recent efforts to personalize psychosocial interventions to treat alcohol dependence have been on a smaller scale and include the use of adaptive treatment approaches (16).

Precision Medicine: Advances in Oncologic, Cardiovascular, and Addiction Medicine

As we discuss below in detail, the two key determinants of the success of efforts to develop precision medicine are the availability of tissue for *in vitro* study and the allocation of research funds.

Oncologic Pharmacogenetics

Precision medicine has been most successful in the treatment of cancer, where the analysis of genetic variation in both tumor (somatic) and host (germline) tissues have yielded biomarkers that are routinely applied clinically. Several FDA-approved medications, used to treat a variety of cancers (e.g., lung, breast, and gastrointestinal tumors), can be paired with biomarkers to personalize treatment (2). Although germline variation that affects the development of a tumor can also help to predict the therapeutic and adverse effects of anticancer drugs (17, 18), most of the pharmacogenetic options in oncology involve somatic or acquired mutations, which often predict the pharmacodynamic effects of oncologic drugs (19–22).

One well-studied pharmacogenomic approach with diverse oncologic applications is the use of protein kinase-inhibiting drugs to treat tumors characterized by specific mutations, such as those in the epidermal growth factor receptor gene, *EGFR*. The overexpression of the EGFR protein is linked to a generally poor prognosis in multiple types of cancer (e.g., head and neck cancer, non-small-cell lung cancer (NSCLC)) (22). Somatic mutations within the kinase-encoding domain of the gene affect the response to the EGFR inhibitors gefitinib and

erlotinib, so that NSCLC patients with EGFR overexpression, for example, are more likely to respond to such treatments. The robustness of this effect is demonstrated by retrospective studies, which show that patients with any type of *EGFR* mutation or sensitivity to gefitinib and erlotinib had a 75% response rate, compared to a 10% response rate in patients lacking these features (22).

Other types of EGFR mutations, such as exon 19 deletions, also predict a better pharmacotherapeutic response (22), though the longer survival rates in these cases may be attributable to either the drug treatment or the presence of the EGFR mutations themselves. Further, the identification of mutations in potential drug targets has enabled the development of novel drugs to treat various types of cancer previously considered untreatable, such as vemurafenib, a BRAF kinase inhibitor used to treat metastatic melanoma when positive for a *BRAF* V600E mutation (23).

Cardiovascular Pharmacogenetics

Although the package inserts for a variety of cardiovascular medications contain pharmacogenomic information (24), some of which is potentially actionable (e.g., *CYP2C19* for clopidogrel use, *CYP2C9* and *VKORC1* for warfarin use, and *ADRB1* for buncindolol use), there are no cardiovascular medications for which a pharmacogenetic moderator is currently in widespread clinical use (24, 25). This lack of clinical utility is due, in part, to the availability of much less expensive, and perhaps equally effective, methods to gauge and monitor individuals' drug response (e.g., the international normalized ratio [INR] test for warfarin), which has limited the need for genetic testing (25). Despite a lack of completed, well-designed and adequately powered RCTs demonstrating incremental benefit from the use of pharmacogenetic markers in cardiovascular medicine, a number of promising RCTs are currently underway. These include the Pharmacogenetic Prediction of Metoprolol Effectiveness for *CYP2D6*/metoprolol (NCT02293096) and the Genetics Informatics Trial [GIFT] of Warfarin to Prevent DVT for *CYP2C9, VKORC1, CYP4F2*/warfarin (NCT01006733), which can be expected to yield clinically important findings in the coming five years, as these studies are completed.

Addiction Pharmacogenetics

In contrast to clinically relevant pharmacogenetic findings in oncology and a promising literature in cardiovascular medicine, addiction pharmacogenetic findings have not been replicable (9–13). This lack of replicability is likely due to heterogeneity in both the samples and the criteria used to identify treatment response, small sample sizes, a reliance on candidate gene studies, and a failure to adjust statistically for multiple comparisons. The field is also limited by a failure to follow-up on some promising findings, largely due to inadequate funding for such efforts, a topic that is discussed in detail below.

Although among addictive disorders the most robust pharmacogenetic literature concerns nicotine dependence treatments, initial findings of genetic moderation based on candidate gene studies of the dopaminergic, serotonergic, and opioidergic systems (12, 13) have generally not been replicated. More recent studies have examined variation in the nicotinic acetylcholine receptor (nAChRs) gene cluster on chromosome 15. Rs1051730, a SNP in

CHRNA3, which encodes the alpha-3 nicotinic receptor (13, 27), was first identified in genomewide association studies (GWAS) as a contributor to the heaviness of smoking (28, 29). Despite subsequent studies showing that the rs1051730*T allele reduces the probability of cessation success among treatment-seeking smokers (30, 31), a recent large study (32) and a meta-analysis (33) showed no effect of the SNP on the response to nicotine replacement therapy. Another polymorphism in the chromosome 15 cluster, rs16969968, which maps to *CHRNA5*, has been associated with both heaviness of smoking and nicotine dependence (30, 31). However, a recent meta-analysis (33) showed no association between rs16969968 and the response to smoking cessation treatment. Thus, the existing research linking nAChRs genetic variants to response to nicotine dependence treatments remains inconclusive (12).

Identifying Biomarkers of Treatment Response

Advances in identifying pharmacogenetic moderators in oncology and cardiovascular medicine have resulted from the application of a variety of molecular genetic approaches. In contrast, the vast majority of substance use disorder pharmacogenetic studies have been limited to a candidate gene approach. Candidate gene approaches to pharmacogenetics are most useful when a drug interacts with receptors or other “druggable” targets or is subject to metabolism or transport by a protein, particularly when there are known functional polymorphisms in the genes that encode the candidate proteins. Thus, the utility of candidate gene studies depends on knowledge of the biology of the disorder and its treatment. Although candidate gene studies based on a hypothesized mechanism of action may have greater statistical power than agnostic approaches such as GWAS or whole genome sequencing (WGS), the likelihood of selecting the “right” candidate can be vanishingly small. Because the pathophysiology of addictive disorders is not as well understood as oncologic or cardiovascular disorders, candidate gene studies of addiction are more speculative than in these areas of medicine. Further, a recent review of pharmacogenetic studies of substance use disorders indicated that, of 12 candidate gene studies of opioid or cocaine abuse treatment trials, two-thirds had sample sizes less than 200 and were focused on a single or a small number of genetic variants (10), limiting the statistical power to identify genetic moderator effects.

Diverse approaches used to identify genetic moderators of cancer therapies have resulted in the identification of several *clinically applicable* pharmacokinetic gene-medication pairs, including variation in *CYP2D6*, which moderates the metabolism of tamoxifen, and variation in *SLCO1B1*, which moderates the absorption of methotrexate (18). In cardiovascular medicine, diverse approaches have identified *clinically relevant* (though not currently applicable) pharmacokinetic gene-medication pairs, including *CYP2C19*/clopidogrel and *CYP2C9*/warfarin, and pharmacodynamic pairs, including *VKORC1*/warfarin and *ADRB1*/bucindolol (20, 36). In addiction medicine, gene-medication pairs identified using a candidate gene approach include a non-synonymous substitution (rs1799971) in *OPRM1* (which encodes the mu-opioid receptor) and naltrexone for treating alcohol dependence (37), a variant (rs2832407) in *GRIK1* (which encodes the GluK1 subunit of the kainate receptor) and topiramate treatment of heavy drinking (38), two variants (5′-HTTLPR and rs1042173) in *SLC6A4* (which encodes the serotonin transporter)

and ondansetron (39), and a variant (rs678849) in *OPRD1* (which encodes the delta-opioid receptor) and buprenorphine or methadone treatment of opioid dependence (40). However, these gene-medication pairs have either failed to replicate in a prospective study design (*OPRM1*/naltrexone (41) or have not yet been evaluated prospectively (*GRIK1*-topiramate, *SLC6A4*/ondansetron, *OPRD1*/opioid agonists). As discussed below, in regard to smoking cessation treatment, although variation in *CYP2A6* has not proven to be feasible as a biomarker, the nicotine-metabolite ratio, a genetically informed biomarker, has been shown prospectively to be clinically useful (42).

Theoretically agnostic approaches such as GWAS and WGS have been used to identify pharmacogenetic candidates for cancer and cardiovascular treatments. The association of the non-coding SNP rs4363657 in *SLCO1B1* with statin myopathy (43) was demonstrated using GWAS. The finding was obtained in a sample of only 85 subjects with myopathy and 90 controls, selected from among individuals treated with simvastatin 80 mg daily. Rs4363657 was in near-complete linkage disequilibrium with the nonsynonymous SNP rs4149056, which is linked to statin metabolism. Compared with T-allele homozygotes, the odds ratio for myopathy with each copy of the rs4149056*C allele was 4.5 and it was 16.9 in C-allele homozygotes (43). The finding was replicated in a second trial of simvastatin. GWAS has also been used to confirm the role of candidate genes thought to influence drug-response phenotypes (e.g., *VKORC1* (rs9923231) and *CYP2C9* (rs1057910 and rs1799853) with warfarin response (44). WGS was used to identify rare coding variants in *KCNE1* (a potassium channel gene) and *ACN9* (a gluconeogenesis pathway gene) as risk factors for drug-induced long QT syndrome (45).

A major success in nicotine addiction pharmacotherapy was the identification of a biomarker of nicotine clearance, i.e., the ratio of the nicotine metabolite 3’hydroxycotinine to cotinine, referred to as the nicotine metabolite ratio (NMR), which moderates nicotine dependence treatment (46). The metabolism of nicotine occurs by the cytochrome P450 enzyme CYP2A6 (47). Polymorphisms that affect enzyme activity–and nicotine metabolism–have been identified in the *CYP2A6* gene (48). Individuals with *CYP2A6* null variants–genetically slow metabolizers of nicotine–have less severe nicotine dependence and are more likely to quit smoking than those with wild-type alleles (49–52). Unfortunately, the feasibility of using *CYP2A6* variants to predict the response to treatments for nicotine dependence is low, because: 1) genotyping is complex and costly, 2) *CYP2A6* variants that account for substantial variance in response have yet to be identified, and 3) *CYP2A6* variants do not account for influences on smoking behavior attributable to factors such as race and sex (53, 54). (See ref. 55 for a comprehensive database on variation in *CYP2A6*).

Conversely, the NMR serves as a reliable, less complex, and inexpensive alternative to genotyping (46, 56–61). NMR is independent from the time since the last cigarette and it can be measured using saliva, urine, or plasma (53), making specimen collection and evaluation methods routine.

Four studies of the relationship between baseline NMR and response to transdermal nicotine showed a consistent pattern: slow metabolizers of nicotine had significantly higher quit rates from the patch but fast metabolizers did not (52, 62–64). In a fifth study, the non-nicotine

medication bupropion significantly enhanced quit rates for fast metabolizers of nicotine, but not for slow metabolizers (65). These studies led to the first prospective NMR-stratified pharmacogenetic trial of treatments for nicotine dependence (42), which represents a notable departure from the generally small size of addiction pharmacogenetic studies (10,11). Over 1,200 smokers were characterized as slow or fast metabolizers of nicotine and randomly assigned to receive placebo patch and placebo pill, nicotine patch and placebo pill, or varenicline and placebo patch. At the end of treatment and six-month follow-up, fast metabolizers of nicotine had significantly higher quit rates when treated with varenicline than nicotine patch. In contrast, slow metabolizers of nicotine exhibited similar quit rates across the two treatments, but reported more severe adverse effects of varenicline treatment. Thus, the NMR is the only biomarker replicated across studies and demonstrated in a prospective trial to moderate treatment for nicotine dependence or any other substance use disorder.

Precision medicine: Moving forward

Two main factors help to explain the major successes to date in cancer precision medicine. First, as pointed out earlier, access to tumor tissue, in which somatic mutations can be identified, allows for tailored therapies, which has yielded most of the pharmacogenomic therapy recommendations in the field (17). In contrast, brain tissue, of greatest interest to understanding the pathophysiology of addictive disorders, is relatively inaccessible. Neuroimaging (e.g., functional magnetic resonance imaging, positron emission tomography), which is non-invasive and provides a high degree of measurement precision, has the potential to yield useful sub-phenotypes to elucidate the etiology of addictive disorders and their response to treatment. However, because there are substantial methodological challenges in this approach, including high equipment and implementation costs, which limit the size of study samples and extensive variability across studies in neuroimaging protocols, neurobehavioral task probes, and analytic strategies, few findings have been fully replicated (66).

Second, cancer precision medicine in the United States has benefitted from the high levels of philanthropic and public funding available for cancer research, advantages that, to a lesser extent, also exist for cardiovascular research. Since 1946, for example, the American Cancer society has contributed U.S. $4.6 billion to cancer research (67) and since 1949 the American Heart Association has contributed more than U.S. $4.0 billion to cardiovascular and stroke research (68). This situation contrasts sharply with addictive disorders, for which there is little non-governmental research support. The most established non-governmental, addiction-related organizations are Alcoholics Anonymous and Narcotics Anonymous, which emphasize anonymity to counter the stigma associated with addiction and enhance the recovery efforts of their members.

A much greater source of support for basic and clinical research on the etiology, pathophysiology, and treatment of disease is the U.S. National Institutes of Health (NIH). Personalized or precision medicine has become a national priority, as evidenced by $215 million for a Precision Medicine Initiative contained in the FY2016 U.S. budget. The goal of the funding is to advance innovative approaches to disease prevention and treatment (69).

Approximately one-third of the precision medicine initiative of 2015 and all of the 2016 National Cancer Moonshot Initiative (70) are expressly directed to cancer research, increasing the likelihood that oncology will continue to dominate developments in precision medicine.

Although additional investment in precision oncology is likely to enhance its current state of readiness, a review of NIH appropriations over more than two decades provides a background against which developments in precision medicine can best be understood. Since 1993, total NIH appropriations have exceeded $500 billion dollars (71). During this time, the largest share of NIH appropriations has gone to the National Cancer Institute (NCI: $85 billion or 17% of the total), approximately 70% more than funding for the National Heart, Lung, and Blood Institute (NHLBI: $50 billion or 10% of the total). These high levels of funding reflect the fact that cardiovascular disease and malignant neoplasms are the top two leading causes of death in the United States (72). During this period, allocations to NIDA and NIAAA combined were $25 billion or 5% of the total NIH budget. Further, the Tobacco Control Research Branch of NCI allocated approximately $82 million (73) for tobacco research, representing about 2.6% of the total NCI research budget (74). Although only a small portion of the total NCI research budget, it substantially augments the funding for addiction research provided to NIDA and NIAAA.

Of note, these funding allocations are out of all proportion to the mortality rates of the diseases that are the focus of the NIH institutes. It has been estimated that 33.5% of all cancer deaths result from alcohol or tobacco use (75, 76), with more than 80% of lung cancer deaths and more than 28% of deaths due to cardiovascular disease attributable to smoking (77) and 15% of breast cancer deaths to alcohol consumption (75). In addition, hepatitis C viral infection, which is most commonly transmitted through intravenous drug use, is now the most important cause of liver cancer (78). Death rates from liver cancer have increased annually from 2003–2012, while deaths from other kinds of cancer have decreased during this time (79).

Because more than one-third of all cancer deaths could be averted by preventing tobacco and alcohol use, it would appear that, as in other areas of health research, funding for addiction precision medicine could be money well spent. Although there is limited evidence that precision medicine will reduce healthcare costs, identifying healthy individuals at elevated risk of disease and targeting them with efficacious treatments is one of its most important potential benefits (80). By enabling preventive measures to be targeted towards those who could benefit most, personalized or precision medicine has the potential to generate substantial value for society (81). This return may be particularly great for individuals using alcohol and drugs by identifying those at greatest risk of adverse consequences, including dependence.

In 2014, the number of people of all ages in the United States living with a cancer diagnosis exceeded 14.5 million (82), while the number diagnosed with heart disease was 27.6 million (83). In that year, the estimated number of adults (18 or older) with tobacco dependence was 30.6 million, while 16.3 million had an alcohol use disorder, and 6.2 million had an illicit drug use disorder (84). Although alcohol, tobacco, and other drug use disorders often co-

occur (85, 86), so that the total number of individuals with an addictive disorder is less than the sum of these, addictive disorders may be as prevalent as cancer and heart disease combined.

In 2009, the total cost of healthcare and lost productivity due to cancer in the United States was $216.6 billion (87). In 2011, cardiovascular disease and stroke cost the nation an estimated $316.6 billion in health care costs and lost productivity (88). Addictive disorders also have an important impact on both healthcare and non-healthcare costs. In 2010, the estimated cost of excessive alcohol use was $249 billion, with 77% of the cost attributable to binge drinking (89). Direct and indirect costs in the United States attributable to smoking for the years 2009–2012 were between $289 and $332.5 billion annually (77). The cost in 2007 of illicit drugs was $193 billion, the majority of which ($120.3 billion) was due to lost productivity (90).

The U.S. Surgeon General recently issued a report, “Alcohol, Drugs, and Health” (91), which reviews the harms related to substance misuse and abuse disorders, along with the neurobiological basis for substance use disorders and evidence-based interventions to prevent and treat them. In addition to educating the public, the report could help to generate greater industry funding for addiction treatment, for which there are many fewer FDA-approved drugs than for treating cancer or cardiovascular disease. The lack of investment by the pharmaceutical industry in addiction treatments is likely due to the perception that such drugs are unlikely to be highly profitable. The Affordable Care Act of 2010, which expanded coverage for addiction treatment, was anticipated to expand the variety of substance abuse treatment providers and shift services toward outpatient programs and integrated care, resulting in greater patient access to medically based and person-centered treatment (92). However, current plans by the U.S. Congress and the President to repeal the ACA could undermine this progress, particularly as it applies to addiction medicine.

Advances in addiction precision medicine will likely come from concerted efforts in the identification of moderators of treatment response in parallel with the discovery of variation contributing to the genetic risk of addictive disorders, such as those of the Psychiatric Genomics Consortium (PGC) (93), as well as other biomarkers of risk [e.g., in the Adolescent Brain Cognitive Development (ABCD) Study (94), and the National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA) (95)]. Efforts are underway by the PGC to aggregate large GWAS samples of alcohol- and drug-dependent individuals for meta- and mega-analyses. However, the success of these efforts will depend on greater funding for the collection of large GWAS-suitable datasets to facilitate pathway- and network-informed interpretation that, along with polygenic risk score analyses, could substantially augment the available pharmacological targets for addiction treatment trials (96). Additional research funding would also make possible the extension of these findings to pharmacogenetics through the aggregation of large treatment trials that use similar study designs and medications and that collect blood or saliva samples for DNA extraction and genotyping. Based on these stringent requirements and initiatives favoring cancer precision medicine, it may be many years before addiction precision medicine will impact clinical care.

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References

1. Evers K. Personalized medicine in psychiatry: ethical challenges and opportunities. Dialogues Clin Neurosci. 2009 Dec; 11(4):427–34. [PubMed: 20135900]
2. Hamburg MA, Collins FS. The path to personalized medicine. N Engl J Med. 2010 Jul 22; 363(4): 301–4. [PubMed: 20551152]
3. Jameson JL, Longo DL. Precision medicine—Personalized, problematic, and promising. N Engl J Med. 2015; 372(23):2229–2234. [PubMed: 26014593]
4. Food and Drug Administration. Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling. Silver Spring; 2013. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm337169.pdf
5. Frueh FW, Amur S, Mummaneni P, Epstein RS, Aubert RE, DeLuca TM, Verbrugge RR, Burckart GJ, Lesko LJ. Pharmacogenomic biomarker information in drug labels approved by the United States Food and Drug Administration: prevalence of related drug use. Pharmacotherapy. 2008 Aug 1; 28(8):992–998. [PubMed: 18657016]
6. U.S. Food and Drug Administration. Table of Pharmacogenomic Biomarkers in Drug Labeling. https://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm
7. Wang B, Canestaro WJ, Choudhry NK. Clinical evidence supporting pharmacogenomic biomarker testing provided in US Food and Drug Administration drug labels. JAMA Intern Med. 2014 Dec 1; 174(12):1938–1944. [PubMed: 25317785]
8. Vermeire E, Hearnshaw H, Van Royen P, Denekens J. Patient adherence to treatment: three decades of research. A comprehensive review. J Clin Pharm Ther. 2001 Oct 30; 26(5):331–342. [PubMed: 11679023]
9. Sturgess JE, George TP, Kennedy JL, Heinz A, Müller DJ. Pharmacogenetics of alcohol, nicotine and drug addiction treatments. Addict Biol. 2011 Jul 1; 16(3):357–76. [PubMed: 21362114]
10. Jones JD, Comer SD. A review of pharmacogenetic studies of substance-related disorders. Drug Alcohol Depend. 2015 Jul 1.152:1–14. [PubMed: 25819021]
11. Jones JD, Comer SD, Kranzler HR. The pharmacogenetics of alcohol use disorder. Alcohol Clin Exp Res. 2015 Mar 1; 39(3):391–402. [PubMed: 25703505]
12. Tanner JA, Chenoweth MJ, Tyndale RF. Pharmacogenetics of nicotine and associated smoking behaviors. Curr Top Behav Neurosci. 2015; 23:37–86. [PubMed: 25655887]
13. Chen LS, Horton A, Bierut L. Pathways to precision medicine in smoking cessation treatments. Neurosci Lett. 2016 May 18. pii: S0304-3940(16)30345-7. Epub ahead of print. doi: 10.1016/j.neulet.2016.05.033
14. Project MATCH Research Group. Project MATCH: Rationale and methods for a multisite clinical trial matching patients to alcoholism treatment. Alcohol Clin Exp Res. 1993; 17(6):1130–1145. [PubMed: 8116822]
15. Project MATCH Research Group. Matching alcoholism treatments to client heterogeneity: Project MATCH three-year drinking outcomes. Alcohol Clin Exp Res. 1998; 22(6):1300–1311. [PubMed: 9756046]
16. Kranzler HR, McKay JR. Personalized treatment of alcohol dependence. Curr Psychiatry Rep. 2012 Oct 1; 14(5):486–493. [PubMed: 22810115]
17. McLeod HL. Cancer pharmacogenomics: early promise, but concerted effort needed. Science. 2013 Mar 29; 339(6127):1563–1566. [PubMed: 23539596]
18. Wheeler HE, Maitland ML, Dolan ME, Cox NJ, Ratain MJ. Cancer pharmacogenomics: strategies and challenges. Nature Rev Genet. 2013 Jan 1; 14(1):23–34. [PubMed: 23183705]
19. Filipski KK, Mechanic LE, Long R, Freedman AN. Pharmacogenomics in oncology care. Front Genet. 2014 Apr 8.5:73. [PubMed: 24782887]

20. Hertz DL, Rae J. Pharmacogenetics of cancer drugs. Annu Rev Med. 2015 Jan 14.66:65–81. [PubMed: 25386932]
21. Patel JN. Cancer pharmacogenomics: implications on ethnic diversity and drug response. Pharmacogenet Genomics. 2015 May 1; 25(5):223–230. [PubMed: 25751395]
22. Ikediobi ON. Somatic pharmacogenomics in cancer. Pharmacogenomics J. 2008 Oct 1; 8(5):305–14. [PubMed: 18679398]
23. Bollag G, Hirth P, Tsai J, Zhang J, Ibrahim PN, Cho H, Spevak W, Zhang C, Zhang Y, Habets G, Burton EA, Wong B, Tsang G, West BL, Powell B, Shellooe R, Marimuthu A, Nguyen H, Zhang KY, Artis DR, Schlessinger J, Su F, Higgins B, Iyer R, D'Andrea K, Koehler A, Stumm M, Lin PS, Lee RJ, Grippo J, Puzanov I, Kim KB, Ribas A, McArthur GA, Sosman JA, Chapman PB, Flaherty KT, Xu X, Nathanson KL, Nolop K. Clinical efficacy of a RAF inhibitor needs broad target blockade in *BRAF*-mutant melanoma. Nature. 2010 Sep 30; 467(7315):596–599. [PubMed: 20823850]
24. Pereira NL, Sargent DJ, Farkouh ME, Rihal CS. Genotype-based clinical trials in cardiovascular disease. Nat Rev Cardiol. 2015 Aug 1; 12(8):475–87. [PubMed: 25940926]
25. Turner RM, Pirmohamed M. Cardiovascular pharmacogenomics: expectations and practical benefits. Clin Pharmacol Ther. 2014 Mar 1; 95(3):281–93. [PubMed: 24322971]
26. Herman AI, DeVito EE, Jensen KP, Sofuoglu M. Pharmacogenetics of nicotine addiction: role of dopamine. Pharmacogenomics. 2014 Feb; 15(2):221–34. [PubMed: 24444411]
27. Bough KJ, Lerman C, Rose JE, McClernon FJ, Kenny PJ, Tyndale RF, David SP, Stein EA, Uhl GR, Conti DV, Green C, Amur S. Biomarkers for smoking cessation. Clin Pharmacol Ther. 2013 Jun; 93(6):526–38. [PubMed: 23588313]
28. Caporaso N, Gu F, Chatterjee N, Sheng-Chih J, Yu K, Yeager M, Chen C, Jacobs K, Wheeler W, Landi MT, Ziegler RG, Hunter DJ, Chanock S, Hankinson S, Kraft P, Bergen AW. Genome-wide and candidate gene association study of cigarette smoking behaviors. PloS one. 2009 Feb 27.4(2):e4653. [PubMed: 19247474]
29. Liu JZ, Tozzi F, Waterworth DM, Pillai SG, Muglia P, Middleton L, Berrettini W, Knouff CW, Yuan X, Waeber G, Vollenweider P, Preisig M, Wareham NJ, Zhao JH, Loos RJ, Barroso I, Khaw KT, Grundy S, Barter P, Mahley R, Kesaniemi A, McPherson R, Vincent JB, Strauss J, Kennedy JL, Farmer A, McGuffin P, Day R, Matthews K, Bakke P, Gulsvik A, Lucae S, Ising M, Brueckl T, Horstmann S, Wichmann HE, Rawal R, Dahmen N, Lamina C, Polasek O, Zgaga L, Huffman J, Campbell S, Kooner J, Chambers JC, Burnett MS, Devaney JM, Pichard AD, Kent KM, Satler L, Lindsay JM, Waksman R, Epstein S, Wilson JF, Wild SH, Campbell H, Vitart V, Reilly MP, Li M, Qu L, Wilensky R, Matthai W, Hakonarson HH, Rader DJ, Franke A, Wittig M, Schäfer A, Uda M, Terracciano A, Xiao X, Busonero F, Scheet P, Schlessinger D, St Clair D, Rujescu D, Abecasis GR, Grabe HJ, Teumer A, Völzke H, Petersmann A, John U, Rudan I, Hayward C, Wright AF, Kolcic I, Wright BJ, Thompson JR, Balmforth AJ, Hall AS, Samani NJ, Anderson CA, Ahmad T, Mathew CG, Parkes M, Satsangi J, Caulfield M, Munroe PB, Farrall M, Dominiczak A, Worthington J, Thomson W, Eyre S, Barton A, Mooser V, Francks C, Marchini J. Wellcome Trust Case Control Consortium. Meta-analysis and imputation refines the association of 15q25 with smoking quantity. Nat Genet. 2010 May; 42(5):436–40. DOI: 10.1038/ng.572 [PubMed: 20418889]
30. Munafò MR, Johnstone EC, Walther D, Uhl GR, Murphy MF, Aveyard P. CHRNA3 rs1051730 genotype and short-term smoking cessation. Nicotine Tob Res. 2011 Oct; 13(10):982–8. DOI: 10.1093/ntr/ntr106 [PubMed: 21690317]
31. Bergen AW, Javitz HS, Krasnow R, Nishita D, Michel M, Conti DV, Liu J, Lee W, Edlund CK, Hall S, Kwok PY, Benowitz NL, Baker TB, Tyndale RF, Lerman C, Swan GE. Nicotinic acetylcholine receptor variation and response to smoking cessation therapies. Pharmacogenet Genomics. 2013 Feb; 23(2):94–103. [PubMed: 23249876]
32. Tyndale RF, Zhu AZ, George TP, Cinciripini P, Hawk LW Jr, Schnoll RA, Swan GE, Benowitz NL, Heitjan DF, Lerman C. PGRN-PNAT Research Group. Lack of associations of CHRNA5-A3-B4 genetic variants with smoking cessation treatment outcomes in Caucasian smokers despite associations with baseline smoking. PLoS One. 2015 May 26.10(5):e0128109. eCollection 2015. doi: 10.1371/journal.pone.0128109 [PubMed: 26010901]

33. Leung T, Bergen A, Munafò MR, De Ruyck K, Selby P, De Luca V. Effect of the rs1051730–rs16969968 variant and smoking cessation treatment: a meta-analysis. Pharmacogenomics. 2015; 16(7):713–20. [PubMed: 25950378]
34. Ware JJ, van den Bree MB, Munafò MR. Association of the CHRNA5-A3-B4 gene cluster with heaviness of smoking: a meta-analysis. Nicotine Tob Res. 2011 Dec 1; 13(12):1167–75. [PubMed: 22071378]
35. Chen LS, Baker TB, Piper ME, Breslau N, Cannon DS, Doheny KF, Gogarten SM, Johnson EO, Saccone NL, Wang JC, Weiss RB, Goate AM, Bierut LJ. Interplay of genetic risk factors (CHRNA5-CHRNA3-CHRNB4) and cessation treatments in smoking cessation success. Am J Psychiatry. 2012 Jul; 169(7):735–42. [PubMed: 22648373]
36. Johnson JA, Cavallari LH. Pharmacogenetics and cardiovascular disease–Implications for personalized medicine. Pharmacol Rev. 2013 Jul 1; 65(3):987–1009. [PubMed: 23686351]
37. Oslin DW, Berrettini W, Kranzler HR, Pettinati H, Gelernter J, Volpicelli, O'Brien CP. A functional polymorphism of the mu-opioid receptor gene is associated with naltrexone response in alcohol-dependent patients. Neuropsychopharmacology. 2003 Jun 18.28:1546–1552. [PubMed: 12813472]
38. Kranzler HR, Covault J, Feinn R, Armeli S, Tennen H, Arias AJ, Gelernter J, Pond T, Oncken C, Kampman KM. Topiramate treatment for heavy drinkers: moderation by a GRIK1 polymorphism. Am J Psychiatry. 2011; 168:265–75. [PubMed: 21247998]
39. Johnson BA, Ait-Daoud N, Seneviratne C, Roache JD, Javors MA, Wang XQ, Liu L, Penberthy JK, DiClemente CC, Li MD. Pharmacogenetic approach at the serotonin transporter gene as a method of reducing the severity of alcohol drinking. Am J Psychiatry. 2011; 168:265–75. [PubMed: 21247998]
40. Crist RC, Clarke TK, Ang A, Ambrose-Lanci LM, Lohoff FW, Saxon AJ, Ling W, Hillhouse MP, Bruce RD, Woody G, Berrettini WH. An intronic variant in OPRD1 predicts treatment outcome for opioid dependence in African-Americans. Neuropsychopharmacology. 2013 Sep 1; 38(10): 2003–10. [PubMed: 23612435]
41. Oslin DW, Leong SH, Lynch KG, Berrettini W, O'Brien CP, Gordon AJ, Rukstalis M. Naltrexone vs placebo for the treatment of alcohol Dependence: A randomized clinical trial. JAMA Psychiatry. 2015 May; 72(5):430–7. [PubMed: 25760804]
42. Lerman C, Schnoll RA, Hawk LW, Cinciripini P, George TP, Wileyto EP, Swan GE, Benowitz NL, Heitjan DF, Tyndale RF. PGRN-PNAT Research Group. Use of the nicotine metabolite ratio as a genetically informed biomarker of response to nicotine patch or varenicline for smoking cessation: a randomised, double-blind placebo-controlled trial. Lancet Respir Med. 2015 Feb 28; 3(2):131–138. [PubMed: 25588294]
43. Link E, Parish S, Armitage J, Bowman L, Heath S, Matsuda F, Gut I, Lathrop M, Collins R. SEARCH Collaborative Group. *SLCO1B1* variants and statin-induced myopathy—a genomewide study. N Engl J Med. 2008 Aug 21.359:789–799. [PubMed: 18650507]
44. Takeuchi F, McGinnis R, Bourgeois S, Barnes C, Eriksson N, Soranzo N, Whittaker P, Ranganath V, Kumanduri V, McLaren W, Holm L, Lindh J, Rane A, Wadelius M, Deloukas P. A genome-wide association study confirms VKORC1, CYP2C9, and CYP4F2 as principal genetic determinants of warfarin dose. PLoS Genet. 2009 Mar.5(3):e1000433. [PubMed: 19300499]
45. Weeke P, Mosley JD, Hanna D, Delaney JT, Shaffer C, Wells QS, Van Driest S, Karnes JH, Ingram C, Guo Y, Shyr Y, Norris K, Kannankeril PJ, Ramirez AH, Smith JD, Mardis ER, Nickerson D, George AL Jr, Roden DM. Exome sequencing implicates an increased burden of rare potassium channel variants in the risk of drug-induced long QT interval syndrome. J Am Coll Cardiol. 2014 Apr 15; 63(14):1430–1437. [PubMed: 24561134]
46. Allenby CE, Boylan KA, Lerman C, Falcone M. Precision medicine for tobacco dependence: Development and validation of the nicotine metabolite ratio. J Neuroimmune Pharmacol. 2016 Sep; 11(3):471–83. [PubMed: 26872457]
47. Hukkanen J, Jacob P, Benowitz NL. Metabolism and disposition kinetics of nicotine. Pharmacol Rev. 2005 Mar 1; 57(1):79–115. [PubMed: 15734728]
48. Piliguian M, Zhu AZ, Zhou Q, Benowitz NL, Ahluwalia JS, Sanderson Cox L, Tyndale RF. Novel CYP2A6 variants identified in African Americans are associated with slow nicotine metabolism in vitro and in vivo. Pharmacogenet Genomics. 2014 Feb; 24(2):118–128. [PubMed: 24305170]

49. Chenoweth MJ, O'Loughlin J, Sylvestre MP, Tyndale RF. CYP2A6 slow nicotine metabolism is associated with increased quitting by adolescent smokers. PharmacogenetGenomics. 2013 Apr; 23(4):232–235.
50. Kubota T, Nakajima-Taniguchi C, Fukuda T, Funamoto M, Maeda M, Tange E, Ueki R, Kawashima K, Hara H, Fujio Y, Azuma J. CYP2A6 polymorphisms are associated with nicotine dependence and influence withdrawal symptoms in smoking cessation. The Pharmacogenomics J. 2006 Mar 1; 6(2):115–119. [PubMed: 16402086]
51. Gu DF, Hinks LJ, Morton NE, Day IN. The use of long PCR to confirm three common alleles at the CYP2A6 locus and the relationship between genotype and smoking habit. Ann Hum Genet. 2000 Sep 1; 64(5):383–390. [PubMed: 11281276]
52. Ho MK, Mwenifumbo JC, Al Koudsi N, Okuyemi KS, Ahluwalia JS, Benowitz NL, Tyndale RF. Association of nicotine metabolite ratio and CYP2A6 genotype with smoking cessation treatment in African-American light smokers. Clin Pharmacol Ther. 2009 Jun 1; 85(6):635–643. [PubMed: 19279561]
53. West O, Hajek P, McRobbie H. Systematic review of the relationship between the 3-hydroxycotinine/cotinine ratio and cigarette dependence. Psychopharmacology. 2011 Nov 1; 218(2):313–322. [PubMed: 21597990]
54. Mwenifumbo JC, Tyndale RF. Molecular genetics of nicotine metabolism. Handb Exp Pharmacol. 2009; (192):235–259. [PubMed: 19184652]
55. [Accessed: 2017-03-03] The Human Cytochrome P450 (CYP) Allele Nomenclature Database: Allele Nomenclature for Cytochrome P450 enzymes. Available at: http://www.cypalleles.ki.se/ (Archived by WebCite® at http://www.webcitation.org/6ohCkxzXP)
56. Dempsey D, Tutka P, Jacob P, Allen F, Schoedel K, Tyndale RF, Benowitz NL. Nicotine metabolite ratio as an index of cytochrome P450 2A6 metabolic activity. Clin Pharmacol Ther. 2004 Jul 1; 76(1):64–72. [PubMed: 15229465]
57. Benowitz NL, Hukkanen J, Jacob P III. Nicotine chemistry, metabolism, kinetics and biomarkers. Handb Exp Pharmacol. 2009; (192):29–60. [PubMed: 19184645]
58. Hamilton DA, Mahoney MC, Novalen M, Chenoweth MJ, Heitjan DF, Lerman C, Tyndale RF, Hawk LW. Test-Retest Reliability and Stability of the Nicotine Metabolite Ratio Among Treatment-Seeking Smokers. Nicotine Tob Res. 2015 Dec 1; 17(12):1505–9. [PubMed: 25732567]
59. Lea RA, Dickson S, Benowitz NL. Within-subject variation of the salivary 3HC/COT ratio in regular daily smokers: prospects for estimating CYP2A6 enzyme activity in large-scale surveys of nicotine metabolic rate. J Anal Toxicol. 2006 Jul 1; 30(6):386–389. [PubMed: 16872570]
60. Mooney ME, Li ZZ, Murphy SE, Pentel PR, Le C, Hatsukami DK. Stability of the nicotine metabolite ratio in ad libitum and reducing smokers. Cancer Epidemiol Biomarkers Prev. 2008 Jun 1; 17(6):1396–1400. [PubMed: 18559554]
61. Tanner JA, Novalen M, Jatlow P, Huestis MA, Murphy SE, Kaprio J, Kankaanpaa A, Galanti L, Stefan C, George TP, Benowitz NL, Lerman C, Tyndale RF. Nicotine metabolite ratio (3-Hydroxycotinine/Cotinine) in plasma and urine by different analytical methods and laboratories: implications for clinical implementation. Cancer Epidemiol Biomarkers Prev. 2015 Aug 1; 24(8): 1239–1246. [PubMed: 26014804]
62. Kaufmann A, Hitsman B, Goelz PM, Veluz-Wilkins A, Blazekovic S, Powers L, Leone FT, Gariti P, Tyndale RF, Schnoll RA. Rate of nicotine metabolism and smoking cessation outcomes in a community-based sample of treatment-seeking smokers. Addict Behav. 2015 Dec 31.51:93–99. [PubMed: 26240944]
63. Schnoll RA, Patterson F, Wileyto EP, Tyndale RF, Benowitz N, Lerman C. Nicotine metabolic rate predicts successful smoking cessation with transdermal nicotine: A validation study. Pharmacol Biochem Behav. 2009 Mar 31; 92(1):6–11. [PubMed: 19000709]
64. Lerman C, Kaufmann V, Rukstalis M, Patterson F, Perkins K, Audrain-McGovern J, Benowitz N. Individualizing nicotine replacement therapy for the treatment of tobacco dependence: a randomized trial. Ann Intern Med. 2004 Mar 16; 140(6):426–433. [PubMed: 15023708]
65. Patterson F, Schnoll RA, Wileyto EP, Pinto A, Epstein LH, Shields PG, Hawk LW, Tyndale RF, Benowitz N, Lerman C. Toward personalized therapy for smoking cessation: A randomized

placebo-controlled trial of bupropion. Clin Pharmacol Ther. 2008 Sep 1; 84(3):320–5. [PubMed: 18388868]

66. Falcone M, Smith RM, Chenoweth MJ, Bhattacharjee AK, Kelsoe JR, Tyndale RF, Lerman C. Pharmacogenomics Research Network Central Nervous System Working Group. Neuroimaging in psychiatric pharmacogenetics research: the promise and pitfalls. Neuropsychopharmacology. 2013 Nov; 38(12):2327–37. [PubMed: 23793356]
67. American Cancer Society. [Accessed: 2017-03-03] Fast Facts About American Cancer Society Research. http://www.cancer.org/research/acsresearchupdates/more/fast-facts-about-american-cancer-society-research(Archived by WebCite® at http://www.webcitation.org/6ohBOSQRM)
68. American Heart Association, Inc. [Accessed: 2017-03-03] Available from: https://www.guidestar.org/profile/13-5613797(Archived by WebCite® at http://www.webcitation.org/6ohBb5vH4)
69. The White House Office of the Press Secretary. [Accessed: 2017-03-03] FACT SHEET: President Obama's Precision Medicine Initiative. 2015 Jan 30. Available from: https://www.whitehouse.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative(Archived by WebCite®at http://www.webcitation.org/6ohBjZdD3)
70. National Cancer Institute. Cancer Moonshot. National Institute of Health; Available from: https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative(Archived by WebCite® at http://www.webcitation.org/6ohBpdrpw) [Accessed: 2017-03-03]
71. National Institutes of Health. [Accessed: 2017-03-03] The NIH Almanac | National Institutes of Health (NIH). Available from: https://www.nih.gov/about-nih/what-we-do/nih-almanac/appropriations-section-1(Archived by WebCite® at http://www.webcitation.org/6ohC4ayQm)
72. Centers for Disease Control and Prevention. National Center for Health Statistics. Centers for Disease Control and Prevention; 2016. Leading Causes of Death [Internet]. Available from: http://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm(Archived by WebCite® at http://www.webcitation.org/6ohCJYMbO) [Accessed: 2017-03-03]
73. National Cancer Institute. [Accessed: 2017-03-03] Cancer Control and Population Sciences. Available from: http://maps.cancer.gov/overview/DCCPSGrants/grantlist.jsp?method=dynamic&program=brp&branch=TCRB&menu=program(Archived by WebCite® at http://www.webcitation.org/6ohCM34gN)
74. Department of Health and Human Services, National Insitutes of Health. [Accessed: 2017-03-03] FY 2016 Budget [Internet]. Available from: https://www.cancer.gov/about-nci/budget/congressional-justification/fy2016-nci-congressional-justification.pdf(Archived by WebCite® at http://www.webcitation.org/6ohCTTEMJ)
75. Nelson DE, Jarman DW, Rehm J, Greenfield TK, Rey G, Kerr WC, Miller P, Shield KD, Ye Y, Naimi TS. Alcohol-attributable cancer deaths and years of potential life lost in the United States. Am J Public Health. 2013 Apr; 103(4):641–648. [PubMed: 23409916]
76. Balogh EP, Dresler C, Fleury ME, Gritz ER, Kean TJ, Myers ML, Nass SJ, Nevidjon B, Toll BA, Warren GW, Herbst RS. Reducing tobacco-related cancer incidence and mortality: Summary of an Institute of Medicine Workshop. Oncologist. 2014 Jan 1; 19(1):21–31. [PubMed: 24304712]
77. US Department of Health and Human Services. The Health Consequences of Smoking: 50 Years of Progress: A Report of the Surgeon General. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014.
78. American Cancer Society. [Accessed: 2017-03-03] Liver Cancer Risk Factors [Internet]. 2016. Available from: http://www.cancer.org/cancer/livercancer/detailedguide/liver-cancer-risk-factors(Archived by WebCite® at http://www.webcitation.org/6ohDHbX3O)
79. American Cancer Society. [Accessed: 2017-03-03] Cancer Statistics 2016: A Presentation from the American Cancer Society. 2016. Available from: http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-047064.pptx(Archived by WebCite® at http://www.webcitation.org/6ohDIycJF)
80. Dzau VJ, Ginsburg GS. Realizing the full potential of precision medicine in health and health care. JAMA. 2016 Oct 25; 316(16):1659–60. [PubMed: 27669484]

81. Dzau VJ, Ginsburg GS, Van Nuys K, Agus D, Goldman D. Aligning incentives to fulfill the promise of personalised medicine. Lancet. 2015 May 23; 385(9982):2118–2119. [PubMed: 25957453]
82. National Cancer Institute. Cancer Statistics [Internet]. National Cancer Institute; 2016. Available From: https://www.cancer.gov/about-cancer/understanding/statistics(Archived by WebCite® at http://www.webcitation.org/6ohDU4Epe) [Accessed: 2017-03-03]
83. Centers for Disease Control and Prevention. Heart Disease [Internet]. National Center for Health Statistics; Available from: http://www.cdc.gov/nchs/fastats/heart-disease.htm(Archived by WebCite® at http://www.webcitation.org/6ohDVmpVd) [Accessed: 2017-03-03]
84. Substance Abuse and Mental Health Services Administration [Internet]. [Accessed: 2017-03-03] Results from the 2014 National Survey on Drug Use and Health: Detailed Tables [Internet]. 2015. Available from: http://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs2014/NSDUH-DetTabs2014.htm#topofpage(Archived by WebCite® at http://www.webcitation.org/6ohDfL6FZ)
85. Kessler RC, Crum RM, Warner LA, Nelson CB, Schulenberg J, Anthony JC. Lifetime co-occurrence of DSM-III-R alcohol abuse and dependence with other psychiatric disorders in the National Comorbidity Survey. Arch Gen Psychiatry. 1997 Apr 1; 54(4):313–21. [PubMed: 9107147]
86. Stinson FS, Grant BF, Dawson DA, Ruan WJ, Huang B, Saha T. Comorbidity between DSM-IV alcohol and specific drug use disorders in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Drug Alcohol Depend. 2005 Oct 1; 80(1):105–16. [PubMed: 16157233]
87. American Association for Cancer Research. [Accessed: 2017-03-03] Cancer Progress Report. Available from: http://cancerprogressreport.org/2014/Pages/cancer2014.aspx?Page=2(Archived by WebCite® at http://www.webcitation.org/6ohDhb73V)
88. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jiménez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER 3rd, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW, Turner MB. Writing Group Members; American Heart Association Statistics Committee; Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics—2016 Update. A Report From the American Heart Association. Circulation. 2016 Jan 26; 133(4):e38–360. [PubMed: 26673558]
89. Centers for Disease Control and Prevention. Excessive Drinking Is Draining the U.S. Economy. Centers for Disease Control and Prevention; 2016. Available from: http://www.cdc.gov/features/costsofdrinking/index.html(Archived by WebCite® at http://www.webcitation.org/6ohDpGyR9) [Accessed: 2017-03-03]
90. National Institute on Drug Abuse (NIDA). Trends & Statistics [Internet]. National Institute on Drug Abuse (NIDA); 2015 Aug. Available from: https://www.drugabuse.gov/related-topics/trends-statistics(Archived by WebCite® at http://www.webcitation.org/6ohDqHRDE) [Accessed: 2017-03-03]
91. U.S. Department of Health and Human Services (HHS), Office of the Surgeon General, Facing Addiction in America. The Surgeon General's Report on Alcohol, Drugs, and Health. Washington, DC: HHS; Nov. 2016
92. Buck JA. The looming expansion and transformation of public substance abuse treatment under the Affordable Care Act. Health Aff (Millwood). 2011 Aug; 30(8):1402–10. [PubMed: 21821557]
93. Sullivan PF. The psychiatric GWAS consortium: big science comes to psychiatry. Neuron. 2010 Oct 21; 68(2):182–6. [PubMed: 20955924]
94. [Accessed: 2017-03-03] Adolescent Brain Cognitive Development Study. Available at: https://addictionresearch.nih.gov/abcd-study(Archived by WebCite® at http://www.webcitation.org/6ohE92Bll)
95. National Consortium on Alcohol and Neurodevelopment in Adolescence. [Accessed: 2017-03-03] https://niaaa.nih.gov/research/major-initiatives/national-consortium-alcohol-and-neurodevelopment-adolescence(Archived by WebCite® at http://www.webcitation.org/6ohEAGmMG)

96. Breen G, Li Q, Roth BL, O'Donnell P, Didriksen M, Dolmetsch R, O'Reilly PF, Gaspar HA, Manji H, Huebel C, Kelsoe JR, Malhotra D, Bertolino A, Posthuma D, Sklar P, Kapur S, Sullivan PF, Collier DA, Edenberg HJ. Translating genome-wide association findings into new therapeutics for psychiatry. Nat Neurosci. 2016 Oct 26; 19(11):1392–1396. [PubMed: 27786187]