Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
CHAPTER FOUR

Clinical Perspectives on Targeting Therapies for Personalized Medicine

Donald R.J. Singer*,1, Zoulikha M. Zaïr†

*Fellowship of Postgraduate Medicine, London, United Kingdom
†Warwick Medical School, University of Warwick, Coventry, United Kingdom
1Corresponding author: e-mail address: fpm.chandos@gmail.com; drjsinger@gmail.com

Contents

1. Introduction 80
2. What Are Personalized Medicines? 81
3. Rare Diseases 81
4. Evidence for Precision Medicines from Real World Data 82
5. Using “Real World” Data 82
6. Ethical Concerns 83
7. Adaptive Trial Design 84
8. Companion Diagnostics 85
9. Biological Treatments 86
10. Case Studies: Targets for Precision Medicines and Companion Diagnostics 88
  10.1 Drug Transporter Proteins 88
  10.2 Pleiotropic Effects of Statins 89
  10.3 Flecainide: Potential Off-Target Mechanism for Sudden Death 91
  10.4 EGF Receptor 2 Antagonism with Trastuzmab 91
  10.5 Diagnostic Markers to Guide Selection of Anti-cancer Tyrosine Kinase Receptor Inhibitors 93
  10.6 Multiple Companion Diagnostics to Guide Selection of Anti-cancer Tyrosine Kinase Receptor Inhibitors to Treat Colorectal Cancer 96
  10.7 Immunological Targets in Neuropsychiatry 97
  10.8 Targeting the Genetic Abnormality in Cystic Fibrosis 100
  10.9 Drug Selection Based on Pharmacogenetic Variants in Drug-Metabolizing Enzymes 100
  10.10 Histocompatibility Antigen Companion Diagnostics 101
11. Network Pharmacology 101
12. Future Developments 103
Acknowledgments 104
References 104
Abstract

Expected benefits from new technology include more efficient patient selection for clinical trials, more cost-effective treatment pathways for patients and health services and a more profitable accelerated approach for drug developers. Regulatory authorities expect the pharmaceutical and biotechnology industries to accelerate their development of companion diagnostics and companion therapeutics toward the goal of safer and more effective personalized medicine, and expect health services to fund and prescribers to adopt these new therapeutic technologies.

This review discusses the importance of a range of new approaches to developing new and reprofiled medicines to treat common and serious diseases, and rare diseases: new network pharmacology approaches, adaptive trial designs with enriched populations more likely to respond safely to treatment, as assessed by companion diagnostics for response and toxicity risk and use of "real world" data.

Case studies are described of single and multiple protein drug targets in several important therapeutic areas. These case studies also illustrate the value and complexity of use of selective biomarkers of clinical response and risk of adverse drug effects, either singly or in combination.

1. INTRODUCTION

Francis Collins, Director of the US National Institutes of Health, has stated that “the 21st century is the century of biology. The nation that invests in biomedical research will reap untold rewards in its economy and the health of its people” (Collins, 2015). This assertion reflects optimism on two fronts: that better characterization of disease will lead to more effective and safer use of current treatments for common long-term medical disorders; and that new biomedical technology and expertise will accelerate development of improved treatments or new treatments where none currently exist. Of particular interest are new approaches to currently refractory cancers, resolving acquired resistance to cancer chemotherapy and resistance to antimicrobial chemotherapy, the ability to deal rapidly with epidemic viral diseases such as Ebola hemorrhagic fever, SARS (Severe Acute Respiratory Syndrome), and MERS (Middle Eastern Respiratory Syndrome), developing disease-modifying treatment for rare inherited diseases, and improving treatment for endemic infections in the developing world for which current treatments are toxic, poorly effective, or not available.

Personalizing use of medicines needs to involve development of the right drugs in parallel with biomarkers of response, both for disease outcomes and for adverse drug reactions (ADRs). Accelerated drug development usually
means more dependence on surrogate markers of response. Regulators need to ensure that long-term monitoring and reporting is systematic for clinically important endpoints and coupled to the right to continued licensing of medicines for clinical use.

This review will consider the extent to which this promise may be met with respect to precision medicine—the application of molecular approaches to improving effectiveness and safety in the use of medicines within stratified groups of patients with well-defined genotypes and phenotypes. This review also discusses the importance of timely development of companion diagnostics to improve treatment planning in selected patients by increasing the likelihood of effectiveness and reducing the risk of adverse effects from an associated companion therapeutic.

2. WHAT ARE PERSONALIZED MEDICINES?

The USA drugs regulatory authority the Food and Drugs Administration, when describing personalized medicines (Marburger & Kvamme, 2008), notes that this does not mean “the creation of drugs or medical devices that are unique to a patient but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not.”

This reflects the clinical practicality of delivering “personalizing” medicines, as precision medicine: a stratified approach to treatment of smaller subgroups of patients, as technology to test for biomarkers of drug effectiveness and toxicity becomes increasingly affordable.

3. RARE DISEASES

Around 7300 rare genetic diseases have been included in the registry prepared by the US National Organization for Rare Disorders (NORD, 2015). NORD has also provided support for the development of rare disease registries within the ambit of the European Union. These registries will play a vital role in identifying patients and their families willing to take part in research into new and improved treatments for serious rare diseases. However, even when these registries are pooled, new approaches will be needed to obtain clinical data on the safety and effectiveness of treatments in very small groups of patients.
4. EVIDENCE FOR PRECISION MEDICINES FROM REAL WORLD DATA

A major challenge in developing drugs for precision medicine concerns achieving adequate sample size both for insight into efficacy and safety of medicines: obtaining sufficient statistical power for understanding use of medicines in smaller subsets of patients with heterogeneous variants of common diseases and in the often very small numbers of patients with individual rare diseases. Interest is rapidly growing in the idea of complementing results of “gold standard” formal randomized controlled trials (RCTs) with use of “real world data” (Sun et al., 2015). To be as effective as possible, accessed data should be homogeneous in content and standard in use of taxonomy within health system electronic health records, within disease registries, observational cohorts, and other relevant health data sets.

The quality of “big data” obtained from within electronic health records will need to be improved, supported by new ethical approaches to patient confidentiality to ensure as far as possible completeness of the information in EHRs. In addition, new statistical approaches will be needed to analyze these complex real world data sets.

To these ends, public–private partnerships supported by the European Union’s Innovative Medicines Initiatives are currently exploring new approaches that will be needed within two major programmes: Accelerated Development of Appropriate Patient Therapies (ADAPT SMART, 2015) and IMI Get Real (Schmidt, Klungel, & Groenwold, 2016), both projects funded by the EU Innovative Medicines Initiative. A current limiting factor is the estimated shortfall of 125,000 data analysts needed across the EU alone for effective development, maintenance, and analysis of current and envisaged very large clinical datasets.

In the United States, the 2007 Food and Drugs Administration Amendment Act provided for instruments toward clinical database development, including with regard to informed patient consent, with the aim of providing access to health data on 100 m individuals, by using systems to be supported by 18 data-partners and 35 subcontractors.

5. USING “REAL WORLD” DATA

The Sentinel Initiative (Southworth, Reichman, & Unger, 2013) is a Harvard-based database sourced from patient data derived from insurance
claim reports and other administrative data. The Sentinel Initiative (Southworth et al., 2013) is already beginning to be used to assess “in world” risk from selected drugs and vaccines, providing reports on issues of drug safety concern within months, rather than the years needed for RCTs. Outcomes for the FDA regulators from projects arising from this initiative have included questions on a trivalent flu vaccine and febrile seizures, with no increase in risk observed. Sentinel and other international databases have also identified the need for new warnings in patient information leaflet that the live rotavirus vaccine Rotarix may cause intussusception (Rha et al., 2014) and that the angiotensin Type 1 receptor olmesartan may cause sprue as an important adverse effect (FDA, 2013).

A study of the Sentinel database to assess links between dabigatran and bleeding risk illustrates some of the challenges to use of the data. Dabigatran was licensed as an orally active alternative to reducing risk of embolic stroke in patients with atrial fibrillation due to nonvalvular causes. RE-LY, the initial RCT, indicated that dabigatran was better than warfarin at preventing stroke, with similar overall bleeding risk (Connolly et al., 2009). Following the market authorization for dabigatran, the FDA received an expectedly large number of reports of serious bleeding episodes associated with the drug. This was interpreted as possibly due to underreporting about bleeding due to the much older drug warfarin and overreporting for the new drug dabigatran. Other possible reasons included inability to obtain sufficient personal data on individuals featured in the ADR reports, including for details of patient populations, comorbidity, concurrent medications, drug dose and whether it had been adjusted for renal function (Southworth et al., 2013). The Sentinel database suggested that in fact, as in the RE-LY RCT, bleeding risk from intracranial and gastrointestinal hemorrhages for dabigatran was similar to that from warfarin (Southworth et al., 2013). However, the authors of the Sentinel report noted that its limitations also included lack of adjustment for some key variables, including confounding by indication for the treatment (Freemantle et al., 2013), and lack of validation about whether an insurance claim code reflected an actual bleeding episode (Southworth et al., 2013). Further analyses are planned to aim to adjust as far as possible for these key factors.

6. ETHICAL CONCERNS

Barriers to patients’ willingness for their data to be made available for clinical researchers have to be anticipated and resolved so that patients will as
far as possible not to be deterred from allowing their clinical data to be used. Patients’ concerns include that by agreeing to testing with regard to their personal risk of subtypes of serious diseases and their likelihood of responding to treatment, there may be an adverse impact on their financial position, e.g., on employability, eligibility for a mortgage and other loans, and obtaining insurance cover.

By voluntary agreement, insurance companies in some jurisdictions have previously waived access to knowledge of the results of testing for biomarkers of risk of serious disease and by implication of reduced likelihood of optimal response to treatment. This area may need statutory protection if these voluntary agreements prove insufficient to protect patients and the public from the impact of testing for personal risk, when serious and/or currently untreatable disease risks are identified. Of note, the genetic testing company 23andMe reports having genotyped 1 million people worldwide, of whom about 80% are reported to have consented to let their data be used for research (Chen, 2015).

Precision medicine testing may result in depriving patients of treatments, when in clinical practice the benefits of these treatments may be better than anticipated from formal clinical trials (Singer & Watkins, 2012). The response to treatment may be influenced by compensatory effects of many factors, including other treatments that affect drug-metabolizing enzymes or drug binding, effects of comorbidity and lifestyle factors on pharmacokinetics, single-nucleotide polymorphisms (SNPs) or copy number polymorphisms (CNPs) in genes for other metabolic pathways, and differences in alternative signaling pathways (Singer & Watkins, 2012).

This raises the major ethical question: what level of certainty about the potential benefit of a “precision medicine” is acceptable in patients with no other treatment options, or much less effective or toxic options within current therapy?

7. ADAPTIVE TRIAL DESIGN

Growing interest in development of stratified medicines is leading to the increasing importance of subgroup analyses in confirmatory clinical trials and in particular achieving adequate statistical power in relatively small subgroups of patients (Ogbagaber, Karp, & Wahed, 2015; Shan, Wilding, Hutson, & Gerstenberger, 2015; Stallard, Hamborg, Parsons, & Friede, 2014).

For example, the B-Raf protein regulates normal cell growth and the $BRAF\,V600E$-activating gene mutation is important for tumor growth in
late-stage malignant melanoma in around 50% of patients with this aggressive tumor type (Chapman et al., 2011; McArthur et al., 2014). As an example of adaptive trial design, the B-Raf enzyme inhibitor vemurafenib has only been assessed for treating malignant melanoma in patients who have the above mutation (Chapman et al., 2011; McArthur et al., 2014), reducing costs of developing the drug. This mutation occurs in around 8% of colorectal and other solid cancers (Yang et al., 2012), suggesting that the BRAF V600E companion diagnostic could be used for adaptive trial design when studying treatment with inhibitors of B-Raf for these additional types of cancer.

New adaptive designs for clinical trials include monitoring the relative effectiveness of treatments in subgroups of interest, with the option then to alter the recruitment strategy for future patient entry into trials. These adaptive approaches need new analytical methods and resolution of discussion with regulators about use of resulting data in applications for licensing new drugs and devices evaluated in this way (Stallard et al., 2014).

These medicine adaptive pathways to patients (MAPPs) aim to support new types of clinical trials that adapt to a given patient’s response (Schulthess, Chlebus, Bergstrm, & Baelen, 2014). These MAPPs are intended to lead to accelerated but limited commercial marketing authorization for a patient group to benefit from a new therapeutic agent, while additional clinical endpoints are validated.

8. COMPANION DIAGNOSTICS

For precision medicine, diagnostics are needed both for the initial decision to prescribe and, if so, whether dose modification is needed in the light of genetic or functional information on individual variability in pharmacokinetics. Further tests are needed after a drug treatment has been started to monitor disease outcome and to monitor for adverse effects.

The concept of combination diagnostics (Singer & Watkins, 2012) was applied initially in the 1980s, mainly in veterinary and dental practice. The further term theranostics—used interchangeably with the phrase Companion Diagnostics—describes mandatory safety or efficacy diagnostic tests to be used before a companion drug can be prescribed (Singer & Watkins, 2012).

The US drugs regulatory authority the FDA defines a companion diagnostic device as an “in vitro diagnostic device or an imaging tool that provides information that is essential for the safe and effective use of a corresponding
therapeutic product” (FDA, 2015a). The therapeutic and its companion diagnostic are defined as a combination product (FDA, 2015b).

Within the jurisdictions of the FDA and other national regulatory authorities (Crabb, Marlow, Bell, & Newland, 2012), a companion diagnostic device with a particular therapeutic product is “stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product, as well as in the labeling of any generic equivalents and biosimilar equivalents of the therapeutic product” (FDA, 2015a). This means that the Companion Diagnostic test must be performed before a new partner therapeutic can be prescribed.

Understanding whether these tests will improve cost–effectiveness needs consideration of the costs of performing and interpreting assays for these biomarkers of drug transport, drug costs compared to other treatment options if they exist, the epidemiology of these biomarkers, and whether there is heterogeneity in their tissue expression (Singer & Watkins, 2012).

Licensing by national regulators of pharmacogenetic companion diagnostics to coincide with approval for a new drug has the aims of both improving safety in use of potentially toxic drugs and minimizing future treatment costs resulting from better treatment effectiveness. The USA FDA has already licensed several companion diagnostic devices for use with a corresponding therapeutic product (FDA, 2015a).

It is ideal on clinical and cost grounds that effective companion diagnostic devices are identified prior to licensing of a treatment (Fig. 1). This now forms part of strategy for major pharmaceutical companies with, for example, ~50% of new drugs under development by Roche having diagnostics developed in parallel.

This is important both to ensure that effective treatments can be selected and that patients can be protected from predictable significant ADRs. It is also important for effective planning of the costs of a new treatment where those costs will include additional mandated testing. Agreeing reimbursement of the combined costs of testing and treatment is much more difficult when genetic biomarkers and other companion diagnostic devices are identified after initial drug licensing.

9. BIOLOGICAL TREATMENTS

Biologics as biopharmaceuticals are typically a class of therapeutic proteins synthesized by biological processes enabled by recombinant DNA technology. Monoclonal antibodies (MCA) are similar to the antibody
proteins that the human immune system uses but MCA are designed specifically to block a biochemical or specific cellular target in the body. Examples of MCA for therapeutic use are given in the case studies below. Receptor constructs (fusion proteins) are usually based on a naturally occurring receptor linked to an immunoglobulin frame. The receptor provides the construct with specificity with the immunoglobulin-structure conferring stability.

Nucleic acid biologics are also attractive as potential new therapeutic agents, based on the ability of current technology to achieve rapid synthesis of small interfering RNAs to inhibit gene expression. For example, the public–private RNAi consortium based at the Broad Institute in Boston has synthesized 160,000 RNAi constructs for evaluation for potential therapeutic use, targeted against 15,000 human and 15,000 mouse genes (Broad, 2015). Noncoding microRNAs may also provide biological options for treatment targets (Pichler & Calin, 2015). However, delivery to tissues of interest remains a major limiting factor.

The biologics class of medicines has clinical indications for treating a wide range of organ-based and systemic diseases. Their high cost has led to interest in the development of biosimilars (Ramanan & Grampp, 2014). These can be licensed at much lower cost, however, differences in

Figure 1 Economic attractiveness of companion diagnostics to pharmaceutical and biotechnology companies. Reproduced with permission from Davis, Furstenthal, and Desai (2009).
manufacturing and quality control may lead to the risk of unexpected serious adverse effects, for example, pure red cell aplasia resulting from patient antibodies being formed to a biosimilar to erythropoietin (EPO) (Macdougall et al., 2012). These antibodies to EPO not only neutralize the biological activity of the administered biological EPO but also endogenous EPO, thus stopping red cell production by the bone marrow (Macdougall et al., 2012).

10. CASE STUDIES: TARGETS FOR PRECISION MEDICINES AND COMPANION DIAGNOSTICS

10.1 Drug Transporter Proteins

Drug transporter proteins are involved in the pharmacokinetics of many drugs and are categorized according to their role in either cellular uptake or elimination of transported molecules (Wen et al., 2015; Zair, Eloranta, Stieger, & Kullak-Ublick, 2008). Influx transporters (Fig. 2), comprising organic anion transporter proteins (OATPs), organic anion transporters (OATs), and organic cation transporters (OCTs), transport drugs across
epithelial barriers such as enterocytes, hepatocytes, and renal tubule cells (Hagenbuch & Stieger, 2013; Zair et al., 2008). Efflux transporters (Fig. 2), common among which are members of the ATP-binding cassette (ABC) superfamily, are responsible for cellular efflux and drug resistance (Holland, 2011; Zair et al., 2008). Perturbations in transporter-mediated drug uptake dramatically influence drug pharmacokinetics, manifestations including subtherapeutic drug concentration, drug resistance (Wen et al., 2015), and/or adverse effects.

Particular SNPs and CNPs (Sebat et al., 2004) may alter drug transporter protein expression and function and thus alter drug pharmacokinetics (Franke, Gardner, & Sparreboom, 2010; Megaraj et al., 2011; Niemi, Pasanen, & Neuvonen, 2011). It is thus important that drug design and development take account of potential effects on candidate bioactive compounds of variability in drug transporter activity.

Testing for pharmacogenetic and functional variants in drug transporters also provides opportunities for developing new companion diagnostics. Thus, a patient’s drug transporter profile may be useful in predicting treatment response (Zair et al., 2008), as well as risk of adverse effects from treatments of cancer, and a wide range of other therapeutic classes. For instance, increased OATP1B1 protein levels are seen in tumors of the colon, endometrium, esophagus, lung, prostate, stomach, testis, and bladder, and genetic variation both in OATP1B1 and in OATP1B3 contribute to the in vitro cytotoxicity of paclitaxel in ovarian cancer cells (Svoboda et al., 2011). OATP1B1 genetic variants were also associated with increased irinotecan-induced treatment response and survival in colorectal cancer patients in a prospective multicenter study (Huang et al., 2013). Regarding efflux transporters, SNPs in genes expressing ABCB1 multidrug resistance protein variants have been related to substrate and inhibitor-dependent functional modifications in in vitro studies and reduced expression in tissues. Furthermore, ABCB1 proteins have been shown to have a potent ability to interact with numerous clinically important kinase inhibitors, including imatinib, gefitinib, and erlotinib, conferring cancer treatment resistance (Gong & Kim, 2013; Ozvegy-Laczka et al., 2004; Shi et al., 2007; Sugimoto, Tsukahara, Ishikawa, & Mitsuhashi, 2005).

10.2 Pleiotropic Effects of Statins

Statins provide an illustrative case study for the pleiotropic effects of drugs and for the potential for development of companion diagnostics. Statins are well-recognized to reduce the incidence and severity of ischaemic heart
disease and atheromatous vascular complications in the brain and other circulations by inhibiting the key rate-limiting enzyme for cholesterol synthesis HMG CoA reductase (Goldstein & Brown, 1990), and by upregulation of LDL receptors to increase cholesterol scavenging (Ma et al., 1986). However, statins also have important pleiotropic actions (Koh, Sakuma, & Quon, 2011; Liao & Laufs, 2005), independent of their lipid-lowering properties. These pleiotropic actions may contribute both to the cardiovascular benefits of statins and to their adverse effects. For example, direct (Hauck et al., 2007; Hermida et al., 2013; Rajtik et al., 2012; Thuc et al., 2010; Zheng & Hu, 2005) and indirect evidence (Jenkins, Grieve, Yacoub, & Singer, 1996; Ozawa et al., 2009) in experimental models and in patients suggests that beneficial effects of statins may include improving cardiac function by effects independent of their cholesterol-lowering effects, by modulating a range of signaling pathways, including mitigation of apoptosis (Rajtik et al., 2012).

However, recent secondary research suggests that part of the cardiovascular benefits in some patients on statin treatment may be offset by the increased incidence of Type 2 diabetes mellitus which may be caused by the drug as a pleiotropic effect (Sattar et al., 2010). In a meta-analysis of 13 statin trials (91,140 participants), 2226 assigned statins and 2052 assigned control developed diabetes over an average of 4 years. Statin therapy was associated with a 9% increase in risk for incident diabetes (95% confidence interval (CI) 2–17%) (Sattar et al., 2010).

The most serious adverse affect that limits ability to take long-term statin treatment is rhabdomyolysis—injury to skeletal muscle cells leading to leak of myoglobin into the circulation and risk of acute kidney failure. An SNP with population prevalence of 15% has now been identified linked to serious statin–induced myopathy, the SNP found in 60% of affected patients in the initial report (Ghatak, Faheem, & Thompson, 2010; Link et al., 2008). Findings arose from a genomewide association study (GWAS) in 85 subjects with confirmed or developing myopathy and 90 controls. All were on a high daily dose of simvastatin (80 mg) as part of a trial with ~12,000 participants.

The GWAS showed a single highly significant graded association of myopathy with the rs4363657 SNP within SLCO1B1 on chromosome 12 (odds ratio for myopathy: 4.5 (95% CI 2.6–7.7) per copy of the C allele; 16.9 (95% CI 4.7–61.1) in CC vs. TT homozygotes). This region encodes the organic anion-transporting polypeptide OATP1B1 that regulates hepatic uptake of statins and is in nearly complete linkage disequilibrium with the rs4149056 SNP that is linked to statin metabolism. The association of rs4149056 with myopathy was replicated in a trial of 40 mg
of simvastatin daily, which also showed an association between rs4149056 and the cholesterol-lowering effects of simvastatin. No SNPs in any other region were clearly associated with myopathy.

Drugs metabolized by the OATP1B1 variant accumulate to higher concentrations in blood than with the normally functioning transport protein. Statins affected include simvastatin, pravastatin, and rosuvastatin. Other drugs transported less well and with adverse effects potentially attributable to the abnormal variant OATP1B1 protein include the antimetabolite methotrexate (Buxhofer-Ausch et al., 2013), the SN-38 active metabolite of the cancer chemotherapy irinotecan (Fujita et al., 2014), the antiviral agent lopinavir (Williamson et al., 2013), and the antibiotic rifampicin (Niemi et al., 2006). However, data for rifampicin suggest that other transporters may compensate for altered uptake of the drug by the OATP1B1 protein (Niemi et al., 2006).

10.3 Flecainide: Potential Off-Target Mechanism for Sudden Death

Ventricular arrhythmias are a major cause of sudden cardiac death. The anti-arrhythmic drug flecainide blocks the Nav1.5 sodium channel in the heart, slowing conduction of cardiac electrical impulse (Investigators, 1989). However, in a treatment trial with the antiarrhythmic drug flecainide led to a 25% excess mortality compared to placebo (Investigators, 1989). New chemical genomic methods allow unrecognized pleiotropic beneficial and harmful targets for medicines to be identified. If these targets are genetically variable in their expression, potentially beneficial drugs might be made available to selected patients who do not have the high-risk genotype(s) and phenotype(s). Magic Tag® is an example of technology for new target discovery through allowing immobilization of bioactive molecules coupled with bacteriophage display, followed by an ELISA assay, to test for interactions of drugs with new putative protein targets (Dilly et al., 2007; Ladwa, Dilly, Clark, Marsh, & Taylor, 2008). Using these methods, an alternative initiation of translation was exemplified for flecainide as a potential toxicity factor by showing its binding to protein products of genes linked to sudden cardiac death (Taylor, Clark, Marsh, Singer, & Dilly, 2013).

10.4 EGF Receptor 2 Antagonism with Trastuzmab

Human epidermal growth factor 2 (HER2) (Gijsen et al., 2010) is a normal pathway for cell growth and division. These growth receptors may be 100 times overexpressed in cancer cells. The first Companion Diagnostic was the
HercepTest, an immunohistochemistry assay to detect HER2 (Gijsen et al., 2010) receptor positive breast cancers (Hurvitz et al., 2012; Slamon et al., 2011; Stern et al., 2015). Trastuzumab was developed as an antibody against HER2. It binds to domain IV of the extracellular segment of the receptor, leading to reduced cell proliferation due to arrest of cells in G1 phase of the cell cycle (Le, Pruefer, & Bast, 2005). Mechanisms for this include activation of the tumor suppressor p27 through inhibiting at least six major intracellular signaling pathways (Le et al., 2005). Trastuzumab also inhibits angiogenesis (Banerjee, Dowsett, Ashworth, & Martin, 2007), attributable in part to reduction in expression of vascular endothelial growth factor (VEGF) and reduced activity of the PI3 kinase/Akt pathway (Kou, Vatish, & Singer, 2007; Le et al., 2005). Use of trastuzumab to treat breast cancer is conditional on the HER2 companion diagnostic test confirming that a breast cancer expresses EGF receptor 2. Around ~30% of breast cancer patients express EGF receptor 2 and thus may benefit from this biological drug. The HER2 test was approved in 1999 by the FDA (Roche & Ingle, 1999), and then by NICE (Crabb et al., 2012) and other regulatory agencies, as a companion diagnostic for use with trastuzumab as the companion therapeutic agent: the first example of formal regulatory licensing of a companion diagnostic.

The Cochrane Collaboration publishes secondary research on treatment outcomes. A 2014 Cochrane Review reported on the benefits of trastuzumab-containing therapies for HER2-positive metastatic breast cancer (Balduzzi et al., 2014). Hazard ratios for overall survival were 0.82 (95% CI 0.71–0.94, P = 0.004) and 0.61 (95% CI 0.54–0.70, P < 0.00001) for progression-free survival. The authors concluded that contamination of control study arms by allowing addition of trastuzumab at the end of a trial may have led to the true effectiveness of the antibody being underestimated (Balduzzi et al., 2014).

Trastuzumab is ineffective against EGF receptor 2 negative cancers and may cause serious adverse effects, including allergic reactions and heart failure (relative risk from the drug: 3.49 (90% CI 1.88–6.47, P = 0.0009)) (Balduzzi et al., 2014). EGF receptor 2 testing avoids exposing patients to unnecessary risk without benefit and reduces costs of unnecessary treatment.

EGF receptor 2 has been identified as a treatment target in other cancers and trastuzumab is now also indicated for treatment of EGF receptor 2 positive metastatic gastric cancer (Gomez-Martin et al., 2014) and gastroesophageal junction adenocarcinoma (Gomez-Martin et al., 2014). Further randomized controlled studies are assessing the effects of adding trastuzumab
to combination chemotherapy against advanced HER2 positive gastric cancer in Japan (Kataoka et al., 2015), a country where the incidence of gastric cancer is very high by international comparison (Charvat et al., 2015).

Cancer chemotherapy trials have evolved to evaluating MCA in combination to target treatment against multiple cancer pathways simultaneously, aiming for additive or synergistic effects, with preclinical or clinical results available for 25 antibody combinations (Henricks, Schellens, Huitema, & Beijnen, 2015). For example, trastuzumab and pertuzumab (an inhibitor of EGF receptor 2 dimerization) have already been shown to be a beneficial combination as double treatment against the EGF receptor 2 receptor for treating HER2-positive metastatic breast cancer, with median progression-free survival increasing from 12 to 18 months (hazard ratio for progression or death, 0.62; 95% CI 0.51–0.75; \( P < 0.001 \)) with adding pertuzumab to trastuzumab combined with the microtubule assembly inhibitor paclitaxel (Baselga et al., 2012). There was no significant increase in serious adverse effects with this antibody combination (Baselga et al., 2012).

It was expected that combining antibodies would be less toxic than conventional combination chemotherapy for cancer. However, a meta-analysis of 4 RCTs of 2069 patients with advanced colorectal cancer suggests that the combination of bevacizumab (an antiangiogenic antibody against VEGF) with cetuximab or panitumumab (antibodies against EGF receptor 1) led to poorer survival and worse toxicity (Lv et al., 2015).

Further studies are needed to assess to what extent differences in outcomes are due to the antibodies themselves, characteristics of the cancers treated or patient factors.

### 10.5 Diagnostic Markers to Guide Selection of Anti-cancer Tyrosine Kinase Receptor Inhibitors

Chronic myeloid leukemia (CML) was the first human cancer linked to an acquired genetic abnormality, the Philadelphia translocation (Quintas-Cardama & Cortes, 2009). This provided the opportunity for developing both new diagnostics and selective drugs to target the resulting mutation. This has been identified as an enzyme with tyrosine kinase activity resulting from fusion of part of the breakpoint cluster region (bcr) gene from chromosome 22 with the abl gene on chromosome 9 (Quintas-Cardama & Cortes, 2009). The fused Bcr-Abl protein is continuously active and is coupled to the interleukin 3 beta(c) receptor subunit, increasing cell turnover and
impairing DNA repair (Quintas-Cardama & Cortes, 2009). Imatinib was developed as the first clinically effective tyrosine kinase receptor inhibitor (TKI) for treating patients with CML who are positive for the BCR-ABL1 mutation (Hochhaus et al., 2009; Hughes et al., 2010; O’Brien et al., 2003). The disease commonly proceeds to an accelerated phase and then to a blast crisis with very poor clinical outcome. The International Randomized Study of Interferon versus STI571 (IRIS) trial of untreated CML in chronic phase assessed benefits of randomization to imatinib (n = 553) versus interferon-alpha plus cytarabine (n = 553) (Hochhaus et al., 2009). In a 6-year update from IRIS in patients receiving imatinib as first-line therapy, there were no reports of disease progression to accelerated phase or blast crisis (Hochhaus et al., 2009). The estimated event-free survival at 6 years was 83%, with a 93% estimated rate of freedom from progression to accelerated phase and then to a blast crisis; estimated overall survival was 88%, 95% survival for CML-related deaths (Hochhaus et al., 2009).

Identifying Bcr-Abl as a treatment target also provided a diagnostic to predict treatment response (Millot et al., 2014). The BCR-ABL1 transcript level early after Bcr-Abl inhibitory treatment predicts short-term clinical response and longer term outcome. For example, in a French trial of imatinib for CML treatment in 40 children, those with a BCR-ABL1/ABL ratio > 10% at 3 months starting the drug had a larger spleen and higher white cell count compared with those with a lower ratio (Millot et al., 2014). Children with BCR-ABL1/ABL ≤ 10% 3 months after starting treatment had higher rates of complete cytogenetic and molecular responses after 12 months and better progression-free survival on median follow-up of 71 months (range, 22–96 months) (Millot et al., 2014).

However, point mutations in the kinase domain of Bcr-Abl are a reason for resistance developing to imatinib, with >90 mutations already known to confer resistance (Soverini et al., 2011). New TKIs (see below) have therefore been developed with different profiles for pathways associated with resistance and adverse effects.

Tyrosine kinases are also targets for treating a range of other cancers. For example, the c-KIT tyrosine kinase promotes growth of gastrointestinal stromal tumors (GIST). Patients who have a c-KIT positive GIST are also responsive to imatinib (Joensuu et al., 2012, 2015). Further inhibitors effective against a multiple range of receptor tyrosine kinases (e.g., sunitinib (Montemurro et al., 2013), nilotinib (Blay et al., 2015; Hughes et al., 2014; Kim et al., 2015; Shimoni et al., 2015), dasatanib (Iriyama et al., 2015; Shah et al., 2014), and sorafenib (Flaherty et al., 2015; Zhu et al.,

Donald R.J. Singer and Zoulikha M. Zaïr
Tyrosine kinase receptor-driven cancers, with the expectation that using inhibitors with actions against multiple receptor tyrosine kinases (Jain et al., 2013; Manley et al., 2010), e.g., both causing direct inhibition of cancer growth and anti-angiogenesis, may improve their anti-cancer effectiveness (Montemurro et al., 2013).

| Inhibitor                        | Main Receptor Tyrosine Kinase and Other Kinase Targets | Tumors Licensed for Treatment                                                                 |
|----------------------------------|-------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| Dasatinib (Iriyama et al., 2015; Shah et al., 2014) | Bcr-Abl and Src family tyrosine kinase                | Ph+ CML and Ph+ ALL                                                                          |
| Imatinib (Hochhaus et al., 2009; Joensuu et al., 2012, 2015) | Bcr-Abl, c-kit, and PDGFR                             | Ph+ CML, Ph+ ALL, GIST, PDGF receptor gene rearrangement myelodysplastic/myeloproliferative diseases, rearrangements, systemic mastocytosis, and hypereosinophilic syndrome +/- chronic eosinophilic leukemia with FIP1L1-PDGFRα fusion kinase deletion |
| Nilotinib (Blay et al., 2015; Hughes et al., 2014; Kim et al., 2015; Shimoni et al., 2015) | Bcr-Abl, DDR-1 and -2, PDGFR alpha and beta, c-kit, and CSF-1R | Imatinib-resistant Ph+ CML                                                                    |
| Sorafenib (Flaherty et al., 2015; Zhu et al., 2015) | Primary kidney cancer (advanced renal cell carcinoma), advanced primary liver cancer (hepatocellular carcinoma), and radioactive iodine resistant advanced thyroid carcinoma | Advanced primary renal cell carcinoma, advanced primary (hepatocellular carcinoma), and advanced thyroid carcinoma resistant to radioactive iodine |
| Sunitinib (Montemurro et al., 2013) | VEGFRs, PDGFRs, and c-kit                            | Renal cell carcinoma and imatinib-resistant GIST                                              |

ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia; CSF-1-R, colony stimulating factor 1 receptor; DDR, discoidin domain deceptor; Ph+, Philadelphia chromosome positive; PDGFR, platelet-derived growth factor receptor; VEGFR, vascular endothelial growth factor receptor.
Several companion diagnostic markers may need to be combined before selecting effective treatments for cancer. This is seen, for example, with the need for combined EGFR-1 and \textit{KRAS} testing for selected cancers.

The transmembrane EGF receptor 1 (HER1) is a target for anti-cancer treatment for a range of cancers, including breast cancer, colorectal cancer, and head and neck cancer (Bemanian et al., 2015; Bennett et al., 2011). The human monoclonal antibody panitumumab inhibits growth of selected EGF receptor 1-dependent tumors by binding to the extracellular domain of the receptor to prevent pathway activation (Bennett et al., 2011). However, \textit{KRAS}, the protein product of the proto-oncogene \textit{KRAS} with GTPase activity, helps to initiate EGF receptor 1-associated cell signaling and mutations of \textit{KRAS} make it constitutively active in many cancers. Patients with these constitutively active variants of GTPase encoded by \textit{KRAS} fail to respond to panitumumab (Amado et al., 2008; Peeters et al., 2009).

A \textit{KRAS} Companion Diagnostic was approved by the FDA after licensing of panitumumab to predict response to the antibody in patients with EGF receptor 1-expressing refractory, progressive, and metastatic colorectal cancer (Mack, 2009). Regulators have limited approval of panitumumab for use in patients with metastatic colorectal cancer expressing both EGF receptor 1 and confirmed using a companion \textit{KRAS} diagnostic to have non-mutated suppressible \textit{KRAS} (Mack, 2009).

The \textit{KRAS} test is also used to predict response to the EGF receptor 1 antagonist cetuximab, a chimeric (mouse/human) monoclonal antibody used to treat patients with metastatic colorectal cancer or head and neck cancer who do not have \textit{KRAS}-activating mutations. 37% of patients with metastatic colon cancer in the study by Van Cutsem et al. (2011) were eligible for adding cetuximab to their treatment: this prolonged overall survival from 23.5 to 20.0 months (hazard ratio: 0.80). In that study, the \textit{BRAF} mutation was a strong indicator of adverse prognosis (Van Cutsem et al., 2011).

In contrast, for treatment response of locally advanced or metastatic non-small cell lung cancer to gefitinib, a small molecule selective inhibitor of EGF receptor tyrosine kinase (EGF receptor 1-TK), activating mutations of EGF receptor 1-TK need to be present (Carotenuto et al., 2011; Hirsch et al., 2006).
10.7 Immunological Targets in Neuropsychiatry

A key advance in precision approaches to treating brain disease has come from insight into the immunological basis of a wide range of neuropsychiatric disorders (Baumeister, Russell, Pariante, & Mondelli, 2014), from acute psychosis, to depression (Horowitz & Zunszain, 2015) and dementia. A possible association between altered immunity and schizophrenia was suggested over a century ago, with support from both epidemiological and genetic studies for links between infection, inflammation, and schizophrenia (Khandaker et al., 2015).

Evidence acquired over the past decade has led to development of new immunological biomarkers, with the implication that anti-inflammatory treatment may be disease and/or symptom modifying in some psychiatric diseases—from syndromes to well-phenotyped disease subtypes.

10.7.1 Inflammation as a Target in Acute Psychosis

Raised inflammatory markers are typical of many settings associated with psychosis, including psychological stress, the puerperal period (Bergink et al., 2015), and infective syndromes. Several inflammatory markers may be raised in first psychosis. Tumor necrosis factor-alpha (TNF-alpha) was reported (Di Nicola et al., 2013) to be ~threefold higher in adult patients with first psychosis versus controls. For example, C-reactive protein (CRP) has been reported to be raised in patients with first psychosis and even higher in patients with first psychosis who also have a history of psychological trauma in with childhood (Di Nicola et al., 2013; Hepgul et al., 2012). In a meta-analysis of results on associations between childhood stress and inflammation in adults with first psychosis, Baumeister et al. identified 18 studies of 16,870 individuals for the inflammatory marker CRP, 15 studies of 3751 individuals for interleukin-6 (IL-6), and 10 studies of 881 individuals for TNF-alpha (Baumeister, Akhtar, Ciufolini, Pariante, & Mondelli, 2015). All three inflammatory markers were raised in adults with first psychosis, independent of age, gender, and body mass index (Baumeister et al., 2015).

10.7.2 Anti-inflammatory Treatment of Neuropsychiatric Disorders

The above observations raise the question whether anti-inflammatory treatment would be helpful in complementing classical pharmacological treatments in psychiatry. Evidence from a double-blind randomized
placebo-controlled trial of the COX-2 inhibitor celecoxib in 46 subjects suggests that it is an effective adjuvant therapy for manic episodes of bipolar mood disorder without psychotic features. Patients with raised cortisol and inflammatory markers have a poorer response to treatment of a first psychosis (Mondelli et al., 2015). Raison et al. conducted a double-blind, placebo-controlled RCT of three infusions of the TNF-alpha antagonist infliximab in 60 outpatients with major depression either on a stable antidepressant regimen \( n = 37 \) or medication free \( n = 23 \) for 4 weeks or more and were moderately resistant to treatment (Raison et al., 2013). Infliximab was infused at 5 mg/kg at baseline and after 2 and 6 weeks of a 12-week study. There was no overall effect of the treatment on depression scores. However, baseline concentrations of TNF and its soluble receptors were significantly higher in infliximab–treated clinical responders versus nonresponders. Furthermore, patients with the highest level of high-sensitivity C-reactive protein (hs-CRP) were most likely to response to the anti-TNF-alpha treatment (Raison et al., 2013) and to have significantly greater decreases in hs-CRP from baseline to week 12 versus placebo–treated responders.

10.7.3 New Targets for Treating Dementia

The common forms of dementia are degenerative, typically affecting the elderly. They tend to by insidious in onset, slowly progressive, with little in the way of neurological features, and with the brain on MRI scan becoming atrophic. The two major degenerative dementias are commonly either caused by Alzheimer’s disease, characterized by cerebral plaques of beta-amyloid or neurofibrillary tangles or atheromatous vascular disease, with similar cardiovascular risk factors and treatments as for coronary artery and peripheral vascular disease, i.e., management of hypercholesterolemia, hypertension, smoking, diabetes mellitus, and chronic kidney disease.

Autoimmune dementia is now being increasingly recognized as amenable to anti-inflammatory treatment, with good outcomes if intensive immunosuppressive and anti-inflammatory treatment is started early after presentation. In their pioneering paper, Vincent and colleagues reported an association between antibodies against potassium channels and limbic encephalitis (Vincent et al., 2004), which they recognized as a potentially immunotherapy-responsive form of encephalitis. Clues to the diagnosis are now recognized to include onset in the younger or middle aged, a subacute onset, the presence of confusion or delirium, rapid progression (e.g., accelerated forgetting over hours to days and weeks), overt neurological
features, focal signal change on brain magnetic resonance imaging, and supportive initial and serial immunological tests.

Historically, brain biopsies were commonly performed to obtain pathological confirmation of the diagnosis. Biopsies have now largely been superseded both because of improvements in brain imaging and algorithm-supported guidance (Schott et al., 2010) for diagnostic options. Suspicion of auto-immune etiology is now usually based on detection of a spectrum of antibodies (Camdessanche et al., 2002; Carvajal-Gonzalez et al., 2014; FDA, 2011; Hart, Maddison, Newsom-Davis, Vincent, & Mills, 2002; Vincent et al., 2004; Wright et al., 2015) complemented by observing recovery on general anti-inflammatory treatment or specific biological treatments targeted against selective inflammatory cytokines. If these patients are untreated, dense amnesia may occur associated with severe brain injury, including major atrophy of the hippocampus.

10.7.4 Systemic Inflammation as a Target for Treating Neurodegeneration

A typical clinical syndrome is seen in the elderly patient who becomes transiently severely confused in association with an episode of infection of the urinary tract or chest. Earlier hypotheses for mechanisms included disorientation when the infection was treated in the hospital setting away from a familiar home environment, toxic effects on brain neurones from systemic inflammatory cytokines generated in response to the infection and direct effects of bacteremia on brain cells.

A new concept is that priming of microglial and endothelial cells in the brain, by a minor, subclinical inflammatory or other insult, may lead to these cells becoming hyperresponsive to inflammatory stimuli during a subsequent infection, microglial cells then themselves having toxic effects on neighboring brain neurones to cause confusion. In experimental studies, mouse microglial cells activated by very low concentration lipopolysaccharide became hyperresponsive to stimulation by live Salmonella typhimurium, the effects being much greater in the aged than in control young mouse brains (Lunnon et al., 2011).

Systemic inflammation results in altered blood–brain barrier permeability after 2 months, still present after 6 months (Nagele, Han, Demarshall, Belinka, & Nagele, 2011). Thus, understanding the pathways for microglial priming and subsequent responsiveness may lead to new possible targets for a range of serious psychiatric disorders: in at-risk patients, prophylaxis, against microglial activation between and during events of infection may reduce the
incidence and severity of infection-associated confusion. Current work is focused on addressing the microglial mechanisms responsible and a recent safety study suggests that the anti-TNF-alpha antibody etanercept may protect from confusion (Butchart et al., 2015). A larger randomized controlled treatment trial powered to look at efficacy endpoints is currently planned.

10.8 Targeting the Genetic Abnormality in Cystic Fibrosis

Cystic fibrosis is inherited as an autosomal recessive condition. Clinical disease occurs when there are loss-of-function mutations in both copies of the gene for the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Affected homozygous patients have thicker secretions in the lungs, leading to recurrent chest infections and respiratory failure. Thick secretions from the pancreas may also lead to malabsorption due to failure of digestive enzymes to enter the lumen of the small intestine. Public–private partnerships have led to discovery of modulators of selected abnormalities in the CFTR protein. There are multiple molecular defects associated with different mutations in the CFTR protein (Collawn, Fu, Bartoszewski, & Matalon, 2014).

The phe508del CFTR mutation causes the disease by limiting how much CFTR protein reaches the surface of bronchial epithelial cells (Wainwright et al., 2015). Lumacaftor increases trafficking of phe508del CFTR to the cell surface and ivacaftor enhances chloride transport of CFTR on the cell surface (Wainwright et al., 2015). In combination, these drugs resulting in modest improvements in lung function and ~30% reduction in the number of respiratory infections (Wainwright et al., 2015).

10.9 Drug Selection Based on Pharmacogenetic Variants in Drug-Metabolizing Enzymes

Tests that are mandatory, recommended, or under consideration because of within individual variability in drug-metabolizing enzymes include thiopurine methyl transferase testing (McLeod & Siva, 2002) for thiopurine drugs (azathioprine, 6-mercaptopurine) to minimize risk of serious bone marrow suppression, UDP-1A1 to reduce risk of irinotecan-induced diarrhea (McLeod & Siva, 2002), CYP2C19 testing for risk of resistance to the antiplatelet prodrug clopidogrel (Mega et al., 2010), CYP2C9 and vitamin K epoxyreductase testing for anticoagulant response to warfarin (Avery et al., 2011; Maitland-van der Zee et al., 2014), and markers of poor metabolizer CYP2D6 activity for risk of resistance to tamoxifen (Welzen et al., 2015) and blunted pain relief from the prodrug codeine (Crews et al., 2014).
Testing for UDP-glucuronosyltransferase (UGT) gene variations illustrates how to avoid an important preventable adverse effect of the anti-cancer drug irinotecan, which prevents DNA from uncoiling by inhibiting the enzyme topoisomerase 1, and so reduces cell growth in selected colorectal and lung cancers (Lévesque et al., 2013). The main dose-limiting toxicity of irinotecan treatment is diarrhea, secondary to enteric injury following biliary excretion of SN-38 (Lévesque et al., 2013). The active metabolite of irinotecan SN-38 is glucoronidated by hepatic UGTs and those with low activity are at increased risk of serious diarrhea (Lévesque et al., 2013). Patients homozygous for UGT1A1*28 are also at greater risk of neutropenia from irinotecan than those with one or two copies of the wild-type allele UGT1A1*1 (Lévesque et al., 2013).

10.10 Histocompatibility Antigen Companion Diagnostics

Histocompatibility antigen (HLA) companion diagnostics are useful for reducing risk of the serious drug-induced skin ADRs: Stevens–Johnson Syndrome and toxic epidermal necrolysis. Serious skin hypersensitivity reactions (Stevens–Johnson Syndrome) due to the antiretroviral agent abacavir were shown be associated with the gene HLA-B*5701 (Pavlos, Mallal, & Phillips, 2012). Prospective screening significantly reduced the incidence of clinical suspected hypersensitivity from 8% to 3% (Pavlos et al., 2012). Approval for clinical use of abacavir should now be coupled to a lower risk result from the HLA-B*5701 diagnostic test (Pavlos et al., 2012).

Carbamazepine is used to treat epilepsy and neuropathic pain, bipolar disorder, and acute manic and mixed episodes associated with bipolar disorder. Stevens–Johnson Syndrome and toxic epidermal necrolysis are associated with the presence of the HLA-B*1502 allele (FDA, 2007). FDA advice is that “Patients with ancestry from areas in which HLA-B*1502 is present should be screened for the HLA-B*1502 allele before starting treatment with carbamazepine” (FDA, 2007). The patient populations at the greatest risk are from Asia, including South Asia (FDA, 2007). Innovative approaches are needed to make these HLA tests available cost effectively on a national scale.

11. NETWORK PHARMACOLOGY

It is being increasingly recognized that drugs in clinical use may have several potential beneficial or adverse effects. Finding these pleiotropic
benefit and risk targets allows multiple indications for new drugs, the opportunity to reprofile use of existing drugs for which safety profiles in other contexts are already established, and to predict potential adverse effects of treatments. The concept of network pharmacology (Hopkins, 2008) arises from the observation that many drugs share the same type of ADR-causing mechanism and that many drugs share similar therapeutic effects (Janga & Tzakos, 2009; Pujol, Mosca, Farres, & Aloy, 2010). These beneficial or adverse effects may be through actions on known or hidden targets, which may be unmasked through considering networks of known disease mechanisms and known drug targets (Fig. 3), complemented by discovery work in silico and using a wide range of “omic,” chemical biology (Taylor et al., 2013), pharmacology, and clinical methods (Watkins, Marsh, Taylor, & Singer, 2010).

Emerging tools offer a platform to identify and explore molecular complexity of a particular disease. These tools are helping both in identifying targets for new therapeutics and in supporting companion diagnostics by, identification of new disease genes and pathways, molecular relationships among apparently distinct disease phenotypes, the biological significance of disease-associated mutations, new biomarkers for complex diseases, and thus new drug targets (Barabasi, Gulbahce, & Loscalzo, 2011).

Network pharmacology approaches provide important potential tools for accelerating development of precision medicines both in strategy for reprofiling existing drugs by helping to identify previous unrecognized treatment targets and for improving benefit-risk profiles when developing new therapeutic agents (Watkins et al., 2010).

An example of this approach is the Cancer Cell Map Initiative (CCMI), a new venture aimed at “systematically detailing these complex interactions among cancer genes and how they differ between diseased and healthy states” (Krogan, Lippman, Agard, Ashworth, & Ideker, 2015). The initiative aims to create cancer cell maps for different tumor types as a tool for targeting disrupted molecular networks, and as a way to accelerate the development of precision medicines against cancers. Developing further targeted medicines for cancer chemotherapy needs to involve detailed understanding of the molecular networks which allow both oncogenesis—initial formation of a cancer, allow cancer cells to develop resistance to treatment, and recognition that, within individual patients, there may be heterogeneity within cancer tissue of mechanisms for sustained cancer growth and resistance to endogenous tumor immunity and cancer chemotherapy.
President Obama announced a Precision Medicine initiative in his State of the Union Address in 2015 (Riley, 2015). This provides a strong signal that the health policy community is being successful in persuading government leaders and funders that precision will be better both for the health of patients and for the financial health of the economy. For the life

**Figure 3** A network-centric view of drug action maps drug-target (polypharmacology) networks to biological networks. In center part of the biological network, nodes (proteins) targeted by same drug are represented in the same color. Drug efficacy and toxicity are understood by actions at specific nodes and hubs. *Reproduced with permission from Hopkins (2007).*
science community, major new investment is expected to support chemists, biochemists, geneticists, data analysts, and a wide range of health professionals to develop public–private partnerships. Members should include experts from academia, health systems, pharmaceutical and smaller biotechnology companies, and patient charities, to accelerate development and implementation in clinical practice of new precision medicines. This will need corresponding radical changes by drug regulators to ensure that a streamlined system can process in a timely way drug submission data based on new methodologies focusing on precision medicines for small subgroups of patients (Riley, 2015).

ACKNOWLEDGMENTS

D.S. holds a patent for siRNA technology. He has worked with but has no financial interest in the Magic Tag® chemical genomics technology. D.S. is a member of the Healthcare Professionals Working Party of the European Medicines Agency.

REFERENCES

ADAPT SMART: An enabling platform for the coordination of Medicines Adaptive Pathways to Patients (MAPPs) activities. (2015). http://www.adaptsmart.eu. Accessed on 5th November, 2015.

Amado, R. G., Wolf, M., Peeters, M., Van Cutsem, E., Siena, S., Freeman, D. J., et al. (2008). Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. Journal of Clinical Oncology, 26(10), 1626–1634. http://dx.doi.org/10.1200/jco.2007.14.7116.

Avery, P. J., Jorgensen, A., Hamberg, A. K., Wadelius, M., Pirmohamed, M., & Kamali, F. (2011). A proposal for an individualized pharmacogenetics-based warfarin initiation dose regimen for patients commencing anticoagulation therapy. Clinical Pharmacology and Therapeutics, 90(5), 701–706. http://dx.doi.org/10.1038/clpt.2011.186.

Balduzzi, S., Mantarro, S., Guarneri, V., Tagliabue, L., Pistotti, V., Moja, L., et al. (2014). Trastuzumab-containing regimens for metastatic breast cancer. The Cochrane Database of Systematic Reviews, 6, Cd006242. http://dx.doi.org/10.1002/14651858.CD006242.pub2.

Banerjee, S., Dowsett, M., Ashworth, A., & Martin, L. A. (2007). Mechanisms of disease: Angiogenesis and the management of breast cancer. Nature Clinical Practice. Oncology, 4(9), 536–550. http://dx.doi.org/10.1038/ncponc0905.

Barabasi, A. L., Gulbahce, N., & Loscalzo, J. (2011). Network medicine: A network-based approach to human disease. Nature Reviews. Genetics, 12(1), 56–68. http://dx.doi.org/10.1038/nrg2918.

Baselga, J., Cortes, J., Kim, S. B., Im, S. A., Hegg, R., Im, Y. H., et al. (2012). Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. The New England Journal of Medicine, 366(2), 109–119. http://dx.doi.org/10.1056/NEJMoai1113216.

Baumeister, D., Akhtar, R., Ciufolini, S., Pariante, C. M., & Mondelli, V. (2015). Childhood trauma and adulthood inflammation: A meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-alpha. Molecular Psychiatry. http://dx.doi.org/10.1038/mp.2015.67.
Baumeister, D., Russell, A., Pariante, C. M., & Mondelli, V. (2014). Inflammatory biomarker profiles of mental disorders and their relation to clinical, social and lifestyle factors. Social Psychiatry and Psychiatric Epidemiology, 49(6), 841–849. http://dx.doi.org/10.1007/s00127-014-0887-z.

Bemanian, V., Sauer, T., Touma, J., Lindstedt, B. A., Chen, Y., Odegaard, H. P., et al. (2015). The epidermal growth factor receptor (EGFR / HER-1) gatekeeper mutation T790M is present in European patients with early breast cancer. PLoS One, 10(8). e0134398. http://dx.doi.org/10.1371/journal.pone.0134398.

Bennett, L., Zhao, Z., Barber, B., Zhou, X., Peeters, M., Zhang, J., et al. (2011). Health-related quality of life in patients with metastatic colorectal cancer treated with panitumumab in first- or second-line treatment. British Journal of Cancer, 105(10), 1495–1502. http://dx.doi.org/10.1038/bjc.2011.409.

Bergink, V., Laursen, T. M., Johannsen, B. M., Kushner, S. A., Meltzer-Brody, S., & Munk-Olsen, T. (2015). Pre-eclampsia and first-onset postpartum psychiatric episodes: A Danish population-based cohort study. Psychological Medicine, 45(16), 3481–3489. http://dx.doi.org/10.1017/S0033291715001385.

Blay, J. Y., Shen, L., Kang, Y. K., Rutkowski, P., Qin, S., Nosov, D., et al. (2015). Nilotinib versus imatinib as first-line therapy for patients with unresectable or metastatic gastrointestinal stromal tumours (ENESTg1): A randomised phase 3 trial. The Lancet Oncology, 16(5), 550–560. http://dx.doi.org/10.1016/s1470-2045(15)70105-1.

Broad. (2015). The RNAi consortium at the broad institute. https://www.broadinstitute.org/rmai/trc. Accessed on 5th November, 2015.

Butchart, J., Brook, L., Hopkins, V., Teeling, J., Püntener, U., Culliford, D., et al. (2015). Etanercept in Alzheimer disease: A randomized, placebo-controlled, double-blind, phase 2 trial. Neurology, 84, 2161–2168.

Buxhofer-Ausch, V., Secky, L., Wlcek, K., Svoboda, M., Kounnis, V., Brasoulis, E., et al. (2013). Tumor-specific expression of organic anion-transporting polypeptides: Transporters as novel targets for cancer therapy. Journal of Drug Delivery, 2013, 863539. http://dx.doi.org/10.1155/2013/863539.

Camdessanche, J. P., Antoine, J. C., Honnorat, J., Vial, C., Petiot, P., Convers, P., et al. (2002). Paraneoplastic peripheral neuropathy associated with anti-Hu antibodies. A clinical and electrophysiological study of 20 patients. Brain, 125(Pt 1), 166–175.

Carotenuto, P., Roma, C., Rachiglio, A. M., Pasquale, R., Franco, R., Antinolfi, G., et al. (2011). Optimizing response to gefitinib in the treatment of non-small-cell lung cancer. Pharmacogenomics and Personalized Medicine, 4, 1–9. http://dx.doi.org/10.2147/PGPM.S6626.

Carvajal-Gonzalez, A., Leite, M. I., Waters, P., Woodhall, M., Coutinho, E., Balint, B., et al. (2014). Glycine receptor antibodies in PERM and related syndromes: Characteristics, clinical features and outcomes. Brain, 137(Pt 8), 2178–2192. http://dx.doi.org/10.1093/brain/awu142.

Chapman, P. B., Hauschild, A., Robert, C., Haanen, J. B., Ascierto, P., Larkin, J., et al. (2011). Improved survival with vemurafenib in melanoma with BRAF V600E mutation. The New England Journal of Medicine, 364(26), 2507–2516. http://dx.doi.org/10.1056/NEJMoa1103782.

Charvat, H., Sasazuki, S., Inoue, M., Iwasaki, M., Sawada, N., Shimazu, T., et al. (2015). Prediction of the 10-year probability of gastric cancer occurrence in the Japanese population: The JPHC study cohort II. International Journal of Cancer. http://dx.doi.org/10.1002/ijc.29705.

Chen, C. Genetic-testing startup 23andMe seeks to raise $150 million. Bloomberg Business. July 7, 2015. http://www.bloomberg.com/news/articles/2015-07-06/genetic-testing-startup-23andme-seeks-to-raise-150-million.
Freemantle, N., Marston, L., Walters, K., Wood, J., Reynolds, M. R., & Petersen, I. (2013). Making inferences on treatment effects from real world data: Propensity scores, confounding by indication, and other perils for the unwary in observational research. *BMJ, 347*, f6409. http://dx.doi.org/10.1136/bmj.f6409.

Fujita, K., Sugiura, T., Okumura, H., Umeda, S., Nakamichi, N., Watanabe, Y., et al. (2014). Direct inhibition and down-regulation by uremic plasma components of hepatic uptake transporter for SN-38, an active metabolite of irinotecan, in humans. *Pharmaceutical Research, 31*(1), 204–215. http://dx.doi.org/10.1007/s11095-013-1153-x.

Ghatak, A., Faheem, O., & Thompson, P. D. (2010). The genetics of statin-induced myopathy. *Atherosclerosis, 210*(2), 337–343. http://dx.doi.org/10.1016/j.atherosclerosis.2009.11.033.

Gijsen, M., King, P., Perera, T., Parker, P. J., Harris, A. L., Larijani, B., et al. (2010). HER2 phosphorylation is maintained by a PKB negative feedback loop in response to anti-HER2 herceptin in breast cancer. *PLoS Biology, 8*(12). e1000563. http://dx.doi.org/10.1371/journal.pbio.1000563.

Goldstein, J. L., & Brown, M. S. (1990). Regulation of the mevalonate pathway. *Nature, 343*(6257), 425–430. http://dx.doi.org/10.1038/343425a0.

Gomez-Martin, C., Lopez-Rios, F., Aparicio, J., Barriuso, J., Garcia-Carbonero, R., Pazo, R., et al. (2014). A critical review of HER2-positive gastric cancer evaluation and treatment: From trastuzumab, and beyond. *Cancer Letters, 351*(1), 30–40. http://dx.doi.org/10.1016/j.canlet.2014.05.019.

Hagenbuch, B., & Stieger, B. (2013). The SLCO (former SLC21) superfamily of transporters. *Molecular Aspects of Medicine, 34*(2–3), 396–412. http://dx.doi.org/10.1016/j.mam.2012.10.009.

Hart, I. K., Maddison, P., Newsom-Davis, J., Vincent, A., & Mills, K. R. (2002). Phenotypic variants of autoimmune peripheral nerve hyperexcitability. *Brain, 125*(Pt. 8), 1887–1895.

Hauck, L., Harms, C., Grothe, D., An, J., Gertz, K., Kronenberg, G., et al. (2007). Critical role for FoxO3a-dependent regulation of p21CIP1/WAF1 in response to statin signaling in cardiac myocytes. *Circulation Research, 100*(1), 50–60. http://dx.doi.org/10.1161/01.RES.0000254704.92532.b9.

Henricks, L. M., Schellens, J. H., Huitema, A. D., & Beijnen, J. H. (2015). The use of combinations of monoclonal antibodies in clinical oncology. *Cancer Treatment Reviews, 41*(10), 859–867. http://dx.doi.org/10.1016/j.ctrv.2015.10.008.

Hepgul, N., Pariente, C. M., Dipasquale, S., DiForti, M., Taylor, H., Marques, T. R., et al. (2012). Childhood malnutrition is associated with increased body mass index and increased C-reactive protein levels in first-episode psychosis patients. *Psychological Medicine, 42*(9), 1893–1901. http://dx.doi.org/10.1017/S0033291711002947.

Hermida, N., Markl, A., Hamelet, J., Van Assche, T., Vanderper, A., Herijgers, P., et al. (2013). HMGCoA reductase inhibition reverses myocardial fibrosis and diastolic dysfunction through AMP-activated protein kinase activation in a mouse model of metabolic syndrome. *Cardiovascular Research, 99*(1), 44–54. http://dx.doi.org/10.1093/cvr/cvr070.

Hirsch, F. R., Varella-Garcia, M., Bunn, P. A., Jr., Franklin, W. A., Dzaidzusko, R., Thatcher, N., et al. (2006). Molecular predictors of outcome with gefitinib in a phase III placebo-controlled study in advanced non-small-cell lung cancer. *Journal of Clinical Oncology, 24*(31), 5034–5042. http://dx.doi.org/10.1200/JCO.2006.06.3958.

Hochhaus, A., O’Brien, S. G., Guilhot, F., Druker, B. J., Branford, S., Foroni, L., et al. (2009). Six-year follow-up of patients receiving imatinib for the first-line treatment
of chronic myeloid leukemia. *Leukemia*, 23(6), 1054–1061. http://dx.doi.org/10.1038/leu.2009.38.

Holland, I. B. (2011). ABC transporters, mechanisms and biology: An overview. *Essays in Biochemistry*, 50(1), 1–17. http://dx.doi.org/10.1042/bse0500001.

Hopkins, A. L. (2007). Network pharmacology. *Nature Biotechnology*, 25(10), 1110–1111. http://dx.doi.org/10.1038/nbt1007-1110.

Hopkins, A. L. (2008). Network pharmacology: The next paradigm in drug discovery. *Nature Chemical Biology*, 4(11), 682–690. http://dx.doi.org/10.1038/nchembio.118.

Horowitz, M. A., & Zunszain, P. A. (2015). Neuroimmune and neuroendocrine abnormalities in depression: Two sides of the same coin. *Annals of the New York Academy of Sciences*, 1351(1), 68–79. http://dx.doi.org/10.1111/nyas.12781.

Huang, L., Zhang, T., Xie, C., Liao, X., Yu, Q., Feng, J., et al. (2013). SLCO1B1 and SLC19A1 gene variants and irinotecan-induced rapid response and survival: A prospective multicenter pharmacogenetics study of metastatic colorectal cancer. *PLoS One*, 8(10). e77223. http://dx.doi.org/10.1371/journal.pone.0077223.

Hughes, T. P., Hochhaus, A., Branford, S., Muller, M. C., Kaeda, J. S., Foroni, L., et al. (2010). Long-term prognostic significance of early molecular response to imatinib in newly diagnosed chronic myeloid leukemia: An analysis from the International Randomized Study of Interferon and STI571 (IRIS). *Blood*, 116(19), 3758–3765. http://dx.doi.org/10.1182/blood-2010-03-273979.

Hughes, T. P., Saglio, G., Kantarjian, H. M., Guilhot, F., Niederwieser, D., Rosti, G., et al. (2014). Early molecular response predicts outcomes in patients with chronic myeloid leukemia in chronic phase treated with frontline nilotinib or imatinib. *Blood*, 123(9), 1353–1360. http://dx.doi.org/10.1182/blood-2013-06-510396.

Hurvitz, S. A., Betting, D. J., Stern, H. M., Quinaux, E., Stinson, J., Seshagiri, S., et al. (2012). Analysis of Fc gamma receptor IIIa and IIa polymorphisms: Lack of correlation with outcome in trastuzumab-treated breast cancer patients. *Clinical Cancer Research*, 18(12), 3478–3486. http://dx.doi.org/10.1158/1078-0432.ccr-11-2294.

Investigators, T. C. A. S. T. C. (1989). Preliminary report: Effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *The New England Journal of Medicine*, 321(6), 406–412. http://dx.doi.org/10.1056/nejm198908103210629.

Iriyama, N., Fujisawa, S., Yoshida, C., Wakita, H., Chiba, S., Okamoto, S., et al. (2015). Early cytotoxic lymphocyte expansion contributes to a deep molecular response to dasatinib in patients with newly diagnosed chronic myeloid leukemia in the chronic phase: Results of the D-first study. *American Journal of Hematology*, 90(9), 819–824. http://dx.doi.org/10.1002/ajh.24096.

Jain, P., Kantarjian, H., Nazha, A., O’Brien, S., Jabbour, E., Romo, C. G., et al. (2013). Early responses predict better outcomes in patients with newly diagnosed chronic myeloid leukemia: Results with four tyrosine kinase inhibitor modalities. *Blood*, 121(24), 4867–4874. http://dx.doi.org/10.1182/blood-2013-03-490128.

Janga, S. C., & Tzakos, A. (2009). Structure and organization of drug-target networks: Insights from genomic approaches for drug discovery. *Molecular BioSystems*, 5(12), 1536–1548. http://dx.doi.org/10.1039/B908147j.

Jenkins, G. H., Grieve, L. A., Yacoub, M. H., & Singer, D. R. (1996). Effect of simvastatin on ejection fraction in cardiac transplant recipients. *The American Journal of Cardiology*, 78(12), 1453–1456.

Joensuu, H., Eriksson, M., Sundby Hall, K., Hartmann, J. T., Pink, D., Schutte, J., et al. (2012). One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: A randomized trial. *JAMA*, 307(12), 1265–1272. http://dx.doi.org/10.1001/jama.2012.347.

Joensuu, H., Eriksson, M., Sundby Hall, K., Reichardt, A., Hartmann, J. T., Pink, D., et al. (2015). Adjuvant imatinib for high-risk GI stromal tumor: Analysis of a randomized
trial. Journal of Clinical Oncology. http://dx.doi.org/10.1200/jco.2015.62.9170. Epub ahead of print.

Kataoka, K., Tokunaga, M., Mizusawa, J., Machida, N., Katayama, H., Shitara, K., et al. (2015). A randomized Phase II trial of systemic chemotherapy with and without trastuzumab followed by surgery in HER2-positive advanced gastric or esophagogastric junction adenocarcinoma with extensive lymph node metastasis: Japan Clinical Oncology Group study JCOG1301 (Trigger Study). Japanese Journal of Clinical Oncology, 45(11), 1082–1086. http://dx.doi.org/10.1093/jjco/hyv134.

Khandaker, G. M., Cousins, L., Deakin, J., Lennox, B. R., Yolken, R., & Jones, P. B. (2015). Inflammation and immunity in schizophrenia: Implications for pathophysiology and treatment. The Lancet Psychiatry, 2(3), 258–270. http://dx.doi.org/10.1016/S2215-0366(14)00122-9.

Kim, D. Y., Joo, Y. D., Lim, S. N., Kim, S. D., Lee, J. H., Lee, J. H., et al. (2015). Nilotinib combined with multiagent chemotherapy for newly diagnosed Philadelphia-positive acute lymphoblastic leukemia. Blood, 126(6), 746–756. http://dx.doi.org/10.1182/blood-2015-03-636548.

Koh, K. K., Sakuma, I., & Quon, M. J. (2011). Differential metabolic effects of distinct statins. Atherosclerosis, 215(1), 1–8. http://dx.doi.org/10.1016/j.atherosclerosis.2010.10.036.

Kou, B., Vatish, M., & Singer, D. R. (2007). Effects of angiotensin II on human endothelial cells survival signalling pathways and its angiogenic response. Vascular Pharmacology, 47(4), 199–208. http://dx.doi.org/10.1016/j.vph.2007.06.011.

Krogn, N. J., Lippman, S., Agard, D. A., Ashworth, A., & Ideker, T. (2015). The cancer cell map initiative: Defining the hallmark networks of cancer. Molecular Cell, 58(4), 690–698. http://dx.doi.org/10.1016/j.molcel.2015.05.008.

Ladwa, S. R., Dilly, S. J., Clark, A. J., Marsh, A., & Taylor, P. C. (2008). Rapid identification of a putative interaction between beta2-adrenoreceptor agonists and ATF4 using a chemical genomics approach. ChemMedChem, 3(5), 742–744. http://dx.doi.org/10.1002/cmdc.200700317.

Le, X. F., Pruefer, F., & Bast, R. C., Jr. (2005). HER2-targeting antibodies modulate the cyclin-dependent kinase inhibitor p27Kip1 via multiple signaling pathways. Cell Cycle, 4(1), 87–95.

Lévesque, E., Bélanger, A. S., Harvey, M., Couture, F., Jonker, D., Innocenti, F., et al. (2013). Refining the UGT1A haplotype associated with irinotecan-induced hematotoxicity in metastatic colorectal cancer patients treated with 5-fluorouracil/irinotecan-based regimens. The Journal of Pharmacology and Experimental Therapeutics, 345, 95–101.

Liao, J. K., & Laufs, U. (2005). Pleiotropic effects of statins. Annual Review of Pharmacology and Toxicology, 45(1), 89–118. http://dx.doi.org/10.1146/annurev.pharmtox.45.120403.095748.

Link, E., Parish, S., Armitage, J., Bowman, L., Heath, S., Matsuda, F., et al. (2008). SLCO1B1 variants and statin-induced myopathy—A genomewide study. The New England Journal of Medicine, 359(8), 789–799. http://dx.doi.org/10.1056/NEJMoa0801936.

Lunnon, K., Teeling, J. L., Tutt, A. L., Cragg, M. S., Glennie, M. J., & Perry, V. H. (2011). Systemic inflammation modulates Fc receptor expression on microglia during chronic neurodegeneration. Journal of Immunology, 186, 7215–7224.

Lv, Y., Yang, Z., Zhao, L., Zhao, S., Han, J., & Zheng, L. (2015). The efficacy and safety of adding bevacizumab to cetuximab- or panitumumab-based therapy in the treatment of patients with metastatic colorectal cancer (mCRC): A meta-analysis from randomized control trials. International Journal of Clinical and Experimental Medicine, 8(1), 334–345.

Ma, P. T., Gil, G., Südhof, T. C., Bilheimer, D. W., Goldstein, J. L., & Brown, M. S. (1986). Mevinolin, an inhibitor of cholesterol synthesis, induces mRNA for low density lipoprotein receptor in livers of hamsters and rabbits. Proceedings of the National Academy of Sciences
of the United States of America, 83(21), 8370–8374. http://dx.doi.org/10.1073/pnas.83.21.8370.

Macdougall, I. C., Roger, S. D., de Francisco, A., Goldsmith, D. J., Schellekens, H., Ebbers, H., et al. (2012). Antibody-mediated pure red cell aplasia in chronic kidney disease patients receiving erythropoiesis-stimulating agents: New insights. *Kidney International, 81*(8), 727–732. http://dx.doi.org/10.1038/ki.2011.500.

Mack, G. S. (2009). FDA holds court on post hoc data linking KRAS status to drug response. *Nature Biotechnology, 27*(2), 110–112. http://dx.doi.org/10.1038/nbt0209-110c.

Maitland-van der Zee, A. H., Daly, A. K., Kamali, F., Manolopoulous, V. G., Verhoef, T. I., Wadelius, M., et al. (2014). Patients benefit from genetics-guided coumarin anticoagulant therapy. *Clinical Pharmacology and Therapeutics, 96*(1), 15–17. http://dx.doi.org/10.1038/clpt.2014.44.

Manley, P. W., Drueckes, P., Fendrich, G., Furet, P., Liebetanz, J., Martiny-Baron, G., et al. (2010). Extended kinase profile and properties of the protein kinase inhibitor nilotinib. *Biochimica et Biophysica Acta, 1804*(3), 445–453. http://dx.doi.org/10.1016/j.bbabap.2009.11.008.

Marburger, J. H., III, & Kvamme, E. F. (2008). President’s Council of Advisors on Science and Technology. *Priorities for personalized medicine*. Office of Science Technology and Policy: Washington, DC, USA.

McArthur, G. A., Chapman, P. B., Robert, C., Larkin, J., Haanen, J. B., Dummer, R., et al. (2014). Safety and efficacy of vemurafenib in BRAF(V600E) and BRAF(V600K) mutation-positive melanoma (BRIM-3): Extended follow-up of a phase 3, randomised, open-label study. *The Lancet Oncology, 15*(3), 323–332. http://dx.doi.org/10.1016/s1470-2045(14)70012-9.

McLeod, H. L., & Siva, C. (2002). The thiopurine S-methyltransferase gene locus—Implications for clinical pharmacogenomics. *Pharmacogenomics, 3*(1), 89–98. http://dx.doi.org/10.1517/14622416.3.1.89.

Mega, J. L., Simon, T., Collet, J. P., Anderson, J. L., Antman, E. M., Bliden, K., et al. (2010). Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: A meta-analysis. *Journal of the American Medical Association, 304*(16), 1821–1830. http://dx.doi.org/10.1001/jama.2010.1543.

Megaraj, V., Zhao, T., Paumi, C. M., Gerk, P. M., Kim, R. B., & Vore, M. (2011). Functional analysis of nonsynonymous single nucleotide polymorphisms of multidrug resistance-associated protein 2 (ABCC2). *Pharmacogenetics and Genomics, 21*(8), 506–515. http://dx.doi.org/10.1097/FPC.0b013e328348c786.

Millot, F., Guilhot, J., Baruchel, A., Petit, A., Bertrand, Y., Mazingue, F., et al. (2014). Impact of early molecular response in children with chronic myeloid leukemia treated in the French Glivec phase 4 study. *Blood, 124*(15), 2408–2410. http://dx.doi.org/10.1182/blood-2014-05-578567.

Mondelli, V., Ciufolini, S., Belvederi Murri, M., Bonaccorso, S., Di Forti, M., Giordano, A., et al. (2015). Cortisol and inflammatory biomarkers predict poor treatment response in first episode psychosis. *Schizophrenia Bulletin, 41*(5), 1162–1170. http://dx.doi.org/10.1093/schbul/sbv028.

Montemurro, M., Gelderblom, H., Bitz, U., Schutte, J., Blay, J. Y., Joensuu, H., et al. (2013). Sorafenib as third- or fourth-line treatment of advanced gastrointestinal stromal tumour and pretreatment including both imatinib and sunitinib, and nilotinib: A retrospective analysis. *European Journal of Cancer, 49*(5), 1027–1031. http://dx.doi.org/10.1016/j.ejca.2012.10.009.

Nagele, E., Han, M., Demarshall, C., Belinka, B., & Nagele, R. (2011). Diagnosis of Alzheimer’s disease based on disease-specific autoantibody profiles in human sera. *PLoS One, 6*(8), e23112.
Niemi, M., Kivisto, K. T., Diczfalusy, U., Bodin, K., Bertilsson, L., Fromm, M. F., et al. (2006). Effect of SLCO1B1 polymorphism on induction of CYP3A4 by rifampicin. *Pharmacogenetics and Genomics, 16*(8), 565–568. http://dx.doi.org/10.1097/01.fpc.0000215070.52212.0e.

Niemi, M., Pasanen, M. K., & Neuvonen, P. J. (2011). Organic anion transporting polypeptide 1B1: A genetically polymorphic transporter of major importance for hepatic drug uptake. *Pharmacological Reviews, 63*(1), 157–181. http://dx.doi.org/10.1124/pr.110.002857.

NORD. (2015). NORD (National Organization for Rare Disorders). http://rarediseases.org/. Accessed on 5th November, 2015.

O’Brien, S. G., Guilhot, F., Larson, R. A., Gathmann, I., Baccarani, M., Cervantes, F., et al. (2003). Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *The New England Journal of Medicine, 348*(11), 994–1004. http://dx.doi.org/10.1056/NEJMoa022457.

Ogbagaber, S. B., Karp, J., & Wahed, A. S. (2015). Design of sequentially randomized trials for testing adaptive treatment strategies. *Statistics in Medicine*. 10.1002/sim.6747. Epub ahead of print.

Ozawa, T., Oda, H., Oda, M., Hosaka, Y., Kashimura, T., Ozaki, K., et al. (2009). Improved cardiac function after sirolimus-eluting stent placement in diabetic patients by pioglitazone: Combination therapy with statin. *Journal of Cardiology, 53*(3), 402–409. http://dx.doi.org/10.1016/j.jcc.2009.01.011.

Ozvegy-Laczka, C., Hegedus, T., Varady, G., Ujhelly, O., Schuetz, J. D., Varadi, A., et al. (2004). High-affinity interaction of tyrosine kinase inhibitors with the ABCG2 multidrug transporter. *Molecular Pharmacology, 65*(6), 1485–1495. http://dx.doi.org/10.1124/mol.65.6.1485.

Pavlos, R., Mallal, S., & Phillips, E. (2012). HLA and pharmacogenetics of drug hypersensitivity. *Pharmacogenomics, 13*(11), 1285–1306. http://dx.doi.org/10.2217/pgs.12.108.

Peeters, M., Siena, S., Van Cutsem, E., Sobrero, A., Hendlisz, A., Cascinu, S., et al. (2009). Association of progression-free survival, overall survival, and patient-reported outcomes by skin toxicity and KRAS status in patients receiving panitumumab monotherapy. *Cancer, 115*(7), 1544–1554. http://dx.doi.org/10.1002/cncr.24088.

Pichler, M., & Calin, G. A. (2015). MicroRNAs in cancer: From developmental genes in worms to their clinical application in patients. *British Journal of Cancer, 113*(4), 569–573. http://dx.doi.org/10.1038/bjc.2015.253.

Pujol, A., Mosca, R., Farres, J., & Aloy, P. (2010). Unveiling the role of network and systems biology in drug discovery. *Trends in Pharmacological Sciences, 31*(3), 115–123. http://dx.doi.org/10.1016/j.tips.2009.11.006.

Quintas-Cardama, A., & Cortes, J. (2009). Molecular biology of bcr-abl1-positive chronic myeloid leukemia. *Blood, 113*(8), 1619–1630. http://dx.doi.org/10.1182/blood-2008-03-144790.

Raison, C. L., Rutherford, R. E., Woolwine, B. J., Shuo, C., Schettler, P., Drake, D. F., et al. (2013). A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: The role of baseline inflammatory biomarkers. *JAMA Psychiatry, 70*(1), 31–41. http://dx.doi.org/10.1001/2013.jamapsychiatry.4.

Rajtik, T., Carnicka, S., Szobi, A., Mesarosova, L., Matus, M., Svec, P., et al. (2012). Pleiotropic effects of simvastatin are associated with mitigation of apoptotic component of cell death upon lethal myocardial reperfusion–induced injury. *Physiological Research, 61*(Suppl. 2), S33–41.

Ramanan, S., & Grampp, G. (2014). Drift, evolution, and divergence in biologics and biosimilars manufacturing. *BioDrugs, 28*(4), 363–372. http://dx.doi.org/10.1007/s40259-014-0088-z.
Rha, B., Tate, J. E., Weintraub, E., Haber, P., Yen, C., Patel, M., et al. (2014). Intussusception following rotavirus vaccination: An updated review of the available evidence. *Expert Review of Vaccines, 13*(11), 1339–1348. http://dx.doi.org/10.1586/14760584.2014.942223.

Riley, M. F. (2015). An unfulfilled promise: Changes needed to the drug approval process to make personalized medicine a reality. *Food and Drug Law Journal, 70*(2), 289–314. ii–iii.

Roche, P. C., & Ingle, J. N. (1999). Increased HER2 with U.S. Food and Drug Administration–approved antibody. *Journal of Clinical Oncology, 17*(1), 434.

Sattar, N., Preiss, D., Murray, H. M., Welsh, P., Buckley, B. M., de Craen, A. J., et al. (2010). Statins and risk of incident diabetes: A collaborative meta-analysis of randomised statin trials. *Lancet, 375*(9716), 735–742. http://dx.doi.org/10.1016/S0140-6736(09)61965-6.

Schmidt, A. F., Klungel, O. H., & Groenwold, R. H. (2016). GetReal Consortium. Adjusting for confounding in early postlaunch settings: Going beyond logistic regression models. *Epidemiology, 27*(1), 133–142. http://dx.doi.org/10.1097/EDE.0000000000000388.

Schott, J. M., Reiniger, L., Thom, M., Holton, J. L., Grieve, J., Brandner, S., et al. (2010). Brain biopsy in dementia: Clinical indications and diagnostic approach. *Acta Neuropathologica, 120*(3), 327–341. http://dx.doi.org/10.1007/s00401-010-0721-y.

Schulthess, D., Chlebus, M., Bergström, R., & Baelen, K. V. (2014). Medicine adaptive pathways to patients (MAPPs): Using regulatory innovation to defeat Eroom’s law. *Chinese Clinical Oncology, 3*(2), 21. http://dx.doi.org/10.3978/j.issn.2304-3865.2014.05.07.

Sebat, J., Lakshmi, B., Troge, J., Alexander, J., Young, J., Lundin, P., et al. (2004). Large-scale copy number polymorphism in the human genome. *Science, 305*(5683), 525–528. http://dx.doi.org/10.1126/science.1098918.

Shah, N. P., Guilhot, F., Cortes, J. E., Schiffer, C. A., le Coutre, P., Brummendorf, T. H., et al. (2014). Long-term outcome with dasatinib after imatinib failure in chronic-phase chronic myeloid leukemia: Follow-up of a phase 3 study. *Blood, 123*(15), 2317–2324. http://dx.doi.org/10.1182/blood-2013-10-532341.

Shan, G., Wilding, G. E., Hutson, A. D., & Gerstenberger, S. (2015). Optimal adaptive two-stage designs for early phase II clinical trials. *Statistics in Medicine. http://dx.doi.org/10.1002/sim.6794.

Shi, Z., Peng, X. X., Kim, I. W., Shukla, S., Si, Q. S., Robey, R. W., et al. (2007). Erlotinib (Tarceva, OSI-774) antagonizes ATP-binding cassette subfamily B member 1 and ATP-binding cassette subfamily G member 2-mediated drug resistance. *Cancer Research, 67*(22), 11012–11020. http://dx.doi.org/10.1158/0008-5472.CAN-07-2686.

Shimoni, A., Volchek, Y., Koren-Michowitz, M., Varda-Bloom, N., Somech, R., Shem-Tov, N., et al. (2015). Phase 1/2 study of nilotinib prophylaxis after allogeneic stem cell transplantation in patients with advanced chronic myeloid leukemia or Philadelphia chromosome-positive acute lymphoblastic leukemia. *Cancer, 121*(6), 863–871. http://dx.doi.org/10.1002/cncr.29141.

Singer, D. R. J., & Watkins, J. (2012). Using companion and coupled diagnostics within strategy to personalize targeted medicines. *Personalized Medicine, 9*, 751–761.

Slamon, D., Eiermann, W., Robert, N., Pienkowski, T., Martin, M., Press, M., et al. (2011). Adjuvant trastuzumab in HER2-positive breast cancer. *The New England Journal of Medicine, 365*(14), 1273–1283. http://dx.doi.org/10.1056/NEJMoa0910383.

Southworth, M. R., Reichman, M. E., & Unger, E. F. (2013). Dabigatran and postmarketing reports of bleeding. *The New England Journal of Medicine, 368*(14), 1272–1274. http://dx.doi.org/10.1056/NEJMep1302834.

Soverini, S., Hochhaus, A., Nicolini, F. E., Gruber, F., Lange, T., Saglio, G., et al. (2011). BCR-ABL kinase domain mutation analysis in chronic myeloid leukemia patients treated with tyrosine kinase inhibitors: Recommendations from an expert panel on behalf of European LeukemiaNet. *Blood, 118*(5), 1208–1215. http://dx.doi.org/10.1182/blood-2010-12-326405.
Stallard, N., Hamborg, T., Parsons, N., & Friede, T. (2014). Adaptive designs for confirmatory clinical trials with subgroup selection. *Journal of Biopharmaceutical Statistics, 24*(1), 168–187. http://dx.doi.org/10.1080/10543406.2013.857238.

Stern, H. M., Gardner, H., Burzykowski, T., Elatre, W., O’Brien, C., Lackner, M. R., et al. (2015). PTEN loss is associated with worse outcome in HER2-amplified breast cancer patients but is not associated with trastuzumab resistance. *Clinical Cancer Research, 21*(9), 2065–2074. http://dx.doi.org/10.1158/1078-0432.ccr-14-2993.

Sugimoto, Y., Tsukahara, S., Ishikawa, E., & Mitsuhashi, J. (2005). Breast cancer resistance protein: Molecular target for anticancer drug resistance and pharmacokinetics/pharmacodynamics. *Cancer Science, 96*(8), 457–465. http://dx.doi.org/10.1111/j.1349-7006.2005.00081.x.

Sun, H., Depaetere, K., De Roo, J., Mels, G., De Vloed, B., Twagirumukiza, M., et al. (2015). Semantic processing of EHR Data for clinical research. *Journal of Biomedical Informatics. http://dx.doi.org/10.1016/j.jbi.2015.10.009.*

Svoboda, M., Wlcek, K., Taferner, B., Hering, S., Steiger, B., Tong, D., et al. (2011). Expression of organic anion-transporting polypeptides 1B1 and 1B3 in ovarian cancer cells: Relevance for paclitaxel transport. *Biomedicine & Pharmacotherapy, 65*(6), 417–426. http://dx.doi.org/10.1016/j.biopharm.2011.04.031.

Taylor, P. C., Clark, A. J., Marsh, A., Singer, D. R., & Dilly, S. J. (2013). A chemical genomics approach to identification of interactions between bioactive molecules and alternative reading frame proteins. *Chemical Communications (Cambridge, England), 49*(83), 9588–9590. http://dx.doi.org/10.1039/c3cc44647f.

Thue, L. C., Teshima, Y., Takahashi, N., Nagano-Torigoe, Y., Ezaki, K., Yufu, K., et al. (2010). Mitochondrial K(ATP) channels-derived reactive oxygen species activate pro-survival pathway in pravastatin-induced cardioprotection. *Apoptosis, 15*(6), 669–679. http://dx.doi.org/10.1007/s10495-010-0473-0.

Van Cutsem, E., Kohne, C. H., Lang, I., Folprecht, G., Nowacki, M. P., Cascinu, S., et al. (2011). Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: Updated analysis of overall survival according to tumor KRAS and BRAF mutation status. *Journal of Clinical Oncology, 29*(15), 2011–2019. http://dx.doi.org/10.1200/jco.2010.33.5091.

Vincent, A., Buckley, C., Schott, J. M., Baker, I., Dewar, B. K., Detert, N., et al. (2004). Potassium channel antibody-associated encephalopathy: A potentially immunotherapy-responsive form of limbic encephalitis. *Brain, 127*(Pt. 3), 701–712. http://dx.doi.org/10.1093/brain/awh077.

Wainwright, C. E., Elborn, J. S., Ramsey, B. W., Marigowda, G., Huang, X., Cipolli, M., et al. (2015). Lumacaftor-ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. *The New England Journal of Medicine, 373*(3), 220–231. http://dx.doi.org/10.1056/NEJMoA1409547.

Watkins, J., Marsh, A., Taylor, P. C., & Singer, D. R. (2010). Personalized medicine: The impact on chemistry. *Therapeutic Delivery, 1*(5), 651–665.

Welzen, M. E., Dezentje, V. O., van Schaik, R. H., Colbers, A. P., Guchelaar, H. J., van Erp, N. P., et al. (2015). The effect of tamoxifen dose increment in patients with impaired CYP2D6 activity. *Therapeutic Drug Monitoring, 37*(4), 501–507. http://dx.doi.org/10.1097/dfd.0000000000000195.

Wen, J., Luo, J., Huang, W., Tang, J., Zhou, H., & Zhang, W. (2015). The pharmacological and physiological role of multidrug-resistant protein 4. *The Journal of Pharmacology and Experimental Therapeutics, 354*(3), 358–375. http://dx.doi.org/10.1124/jpet.115.225656.

Williamson, B., Soars, A. C., Owen, A., White, P., Riley, R. J., & Soars, M. G. (2013). Dissecting the relative contribution of OATP1B1-mediated uptake of xenobiotics into human hepatocytes using siRNA. *Xenobiotica, 43*(10), 920–931. http://dx.doi.org/10.3109/00498254.2013.776194.
Wright, S., Hashemi, K., Stasiak, L., Bartram, J., Lang, B., Vincent, A., et al. (2015). Epileptogenic effects of NMDAR antibodies in a passive transfer mouse model. *Brain*, 138(Pt. 11), 3159–3167. http://dx.doi.org/10.1093/brain/awv257.

Yang, H., Higgins, B., Kolinsky, K., Packman, K., Bradley, W. D., Lee, R. J., et al. (2012). Antitumor activity of BRAF inhibitor vemurafenib in preclinical models of BRAF-mutant colorectal cancer. *Cancer Research*, 72(3), 779–789. http://dx.doi.org/10.1158/0008-5472.can-11-2941.

Zair, Z. M., Eloranta, J. J., Stieger, B., & Kullak-Ublick, G. A. (2008). Pharmacogenetics of OATP (SLC21/SLOC), OAT and OCT (SLC22) and PEPT (SLC15) transporters in the intestine, liver and kidney. *Pharmacogenomics*, 9(5), 597–624. http://dx.doi.org/10.2217/14622416.9.5.597.

Zheng, X., & Hu, S. J. (2005). Effects of simvastatin on cardiac performance and expression of sarcoplasmic reticular calcium regulatory proteins in rat heart. *Acta Pharmacologica Sinica*, 26(6), 696–704. http://dx.doi.org/10.1111/j.1745-7254.2005.00105.x.

Zhu, A. X., Park, J. O., Ryoo, B. Y., Yen, C. J., Poon, R., Pastorelli, D., et al. (2015). Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): A randomised, double-blind, multicentre, phase 3 trial. *The Lancet Oncology*, 16(7), 859–870. http://dx.doi.org/10.1016/s1470-2045(15)00050-9.