# Translational strategies to implement personalized medicine: rheumatoid arthritis examples

Advances in the molecular definition of disease, biomarker technologies and informatics have brought us to the threshold of a new way to individualize treatment for patients – personalized medicine. However, while the clinical translation of drug metabolism and cancer-related genomics data has resulted in accepted individualized treatment paradigms, this has not occurred as frequently or efficiently for patients with common chronic diseases such as rheumatoid arthritis. This gap between the rapidly increasing amount of disease-related genomic information and its clinical translation can be addressed through the creation and testing of personalized medicine treatment hypotheses using the same strategies that translational medicine scientists utilize to achieve proof-of-concept for drugs with novel targets. This is illustrated with three testable personalized medicine hypotheses for rheumatoid arthritis where known genetic markers in patients can potentially be used to select the most appropriate treatments and dose. Incentives resulting from changes in government and regulatory agency policies, investments in sample and data repositories, acceptance of new economic models by pharmaceutical companies and third party payers as well as more training, research support and academic opportunities for translational medicine scientists are all needed to speed up the implementation of personalized medicine for patients with rheumatoid arthritis and other common chronic diseases.

**KEYWORDS: ADME ■ biomarkers ■ individualized therapy ■ personalized medicine ■ SNP ■ translational medicine**

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Whose job is it to implement personalized medicine? This is a key question for healthcare in the early 21st Century. Advances in informatics and molecular technologies, disease understanding, pharmacogenetics, systems biology and translational medicine, along with the reduced costs of biomarker and genetic/genomic testing, have taken us to the threshold of a new way to practice medicine that has the potential to optimize individualized treatment and improve patient outcomes. Swen *et al.* recently reviewed the necessary steps, progress and hurdles along the path leading to the integration of personalized medicine into clinical practice but did not dwell on the initial requirement for the creation and testing of viable individualized treatment hypotheses [1]. In addition, most reviews dealing with the clinical translation of pharmacogenomic testing have primarily dealt with variation in drug exposure and resultant efficacy and safety issues, although the potential clinical and drug-development applications of other types of pharmacogenomic data are mentioned [1,2]. Outside of oncology there is little evidence for the efficient translation of disease-specific pharmacogenomic data into the clinic. In fact, there is a growing gap between our knowledge of genetic and biomarker-related individual differences that relate to disease-relevant biological processes, disease predisposition and expression, and the application of this knowledge in clinical practice. Who will create, test and clinically validate disease-related personalized medicine hypotheses as a first step towards closing this gap? Who will support these activities? What strategies and incentives will governments, regulatory agencies, professional organizations, academic institutions and third party payers adopt to help translate these types of personalized medicine clinical paradigms into standard practice? These questions are addressed in this article and are illustrated using personalized medicine hypotheses for rheumatoid arthritis (RA).

Translational medicine clinical scientists are well equipped to create and test disease-specific personalized medicine hypotheses as a first step towards validating individualized treatment paradigms. The strategies used to develop personalized medicine paradigms are the same as those addressed by translational medicine groups in the pharmaceutical industry when developing drugs with novel targets and mechanisms, but the starting points are reversed. Translational medicine scientists in the pharmaceutical industry begin with novel drug targets and mechanisms

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based on the molecular understanding of abnormal pathway expression in disease, they test molecules that modulate those targets and have specific absorption, distribution, metabolism and excretion (ADME) characteristics that determine the drug's pharmacokinetic profile and then use biomarkers to select 'molecularly correct' human populations that optimize efficacy and safety signals in early proof-of-concept (POC) studies [3]. As illustrated in FIGURE 1, when developing personalized medicine paradigms, the strategy is the same but the order of the steps is reversed. Clinical translational medicine scientists begin with patient characteristics (disease subpopulations/biomarkers and pharmacogenetics) and select the best drug mechanism, drug molecule and dose based on these.

Translational medicine strategies for creating and testing disease-related personalized medicine hypotheses are built around some basic concepts. Disease definition has traditionally relied on clinical and pathological descriptions, for example, non-small-cell lung cancer, a disease phenotype. Traditional disease definitions are now being replaced by molecular disease definitions. Again, cancer is a good example where oncogene mutations (e.g., *K-RAS* [4]), gene overexpression (e.g., *HER-2* [5]) and specific biomarkers (e.g., estrogen receptor positivity [6]) are all used to describe the disease and have treatment implications. Thus, a disease phenotype may be further defined molecularly into subpopulations based on various types of biomarkers. This is just as relevant to common chronic diseases as it is to cancer.

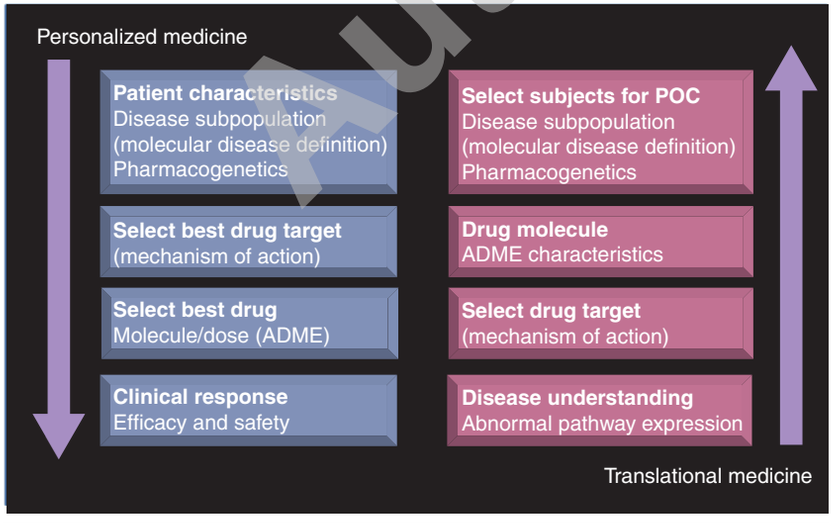


**Figure 1. Shared logic with opposite starting points: personalized medicine paradigms and translational medicine drug-development strategies.**
ADME: Absorption, distribution, metabolism and excretion drug characteristics; POC: Proof of concept.

Drugs are developed based on knowledge of specific molecular targets thought to be important in disease expression. FIGURE 2 illustrates two other concepts that are important for personalized medicine paradigms when considering selection of the best drug target for an individual [7]. The first, illustrated by the black solid curve, is that the level of abnormal activity expression (lower or higher) of a biochemical pathway that is responsible for any specific aspect of a disease phenotype is related to the severity of that aspect of the disease. A drug targeting that abnormality will be most effective in patients with the most abnormal expression of that pathway. The second is that patients with the same disease phenotype do not all have the same level of abnormal activity of a biochemical pathway or expression of a drug target; there is a distribution of patients with differing degrees of abnormal pathway expression and the distribution is specific to each disease-relevant pathway. Therefore, the shape of this distribution determines the percentage of patients with that disease who will have a significant therapeutic response to a drug whose target modulates the expression of the pathway. In FIGURE 2, the population with the highest (upper 25%) abnormal pathway expression was arbitrarily selected to illustrate this, since this population would be expected to have a much greater than average response to a drug targeting this pathway. A very efficacious personalized medicine treatment paradigm could be a prerequisite for rapid acceptance and could also be more easily confirmed in small clinical trials where large differences between a subpopulation's response and the response of an unselected disease population are needed. With this level of abnormal pathway expression, the proportion of patients who are very responsive to a drug targeting this pathway is highly dependent on the distribution of pathway expression in the overall disease population. The three hypothetical distributions illustrated here result in anywhere from a very small population of patients (approximately 5%) who are very good responders to almost half of the patients being good clinical responders.

Oncology is leading the way with multiple examples of the clinical translation of molecular disease knowledge into personalized medicine treatment strategies that are becoming the standard of care. This makes sense given the trend towards the molecular rather than the pathological definition of cancers, clinically validated biomarkers and diagnostics that help in this process and guide therapeutic decisions and specific targeted biologics and small molecules.

For example, *K-RAS* wild-type is required for good clinical responses to anti-EGF receptor (EGFR) antibodies in colon cancer [4], *HER2* overexpression is required for good clinical responses to trastuzumab in breast cancer [5], estrogen receptor expression in breast cancer predicts responsiveness to selective estrogen antagonists such as tamoxifen [6] and *EGFR* mutations determine the sensitivity or resistance to EGFR tyrosine kinase inhibitors in lung cancer, since these mutations can modulate expression of the actual drug target (binding site) [8,9]. Here, the relationship between oncogene and biomarker expression, the neoplastic phenotype and response to targeted agents has been demonstrated in clinical trials and has become part of the standard of care for cancer patients. Likewise, individual differences that influence drug exposure are very important in cancer patients receiving traditional chemotherapeutic agents with a narrow therapeutic index. Clear differences in efficacy and safety can become apparent when the same dose of these drugs is used in different patients without considering their individual drug metabolism capabilities. In a classic study, Petros *et al.* demonstrated important differences in survival between genetically defined subpopulations of breast cancer patients receiving the same treatment protocol [10]. In this study, retrospective Kaplan–Meier analyses of overall long-term survival in breast cancer patients following standard-dose chemotherapy and high-dose cyclophosphamide, cisplatin and carmustine were performed for patients segregated based on the presence of genetic polymorphisms in *CYP3A4*1B*, *CYP3A5*1*, *MET1F G-7T* and glutathione-*S*-transferase M1. Survival differences between the optimal genetically defined subpopulations and unselected populations at 8 years after restaging ranged from 15–30%. Other examples of the acceptance of pharmacogenetic testing to guide dosing are rare outside of oncology unless, like cancer chemotherapeutic agents, the drug has a narrow therapeutic index. One example where such testing is also becoming standard of care is warfarin [11]. Clinical translation of pharmacogenetic differences influencing drug exposure in these situations is an important consideration for personalized medicine and has been largely accepted by physicians and regulatory agencies, especially when the safety or efficacy of the drug is clearly improved. However, the clinical translation of disease-related genetic differences into personalized medicine treatment paradigms deserves more focus and can be approached using the translational medicine strategies described above.

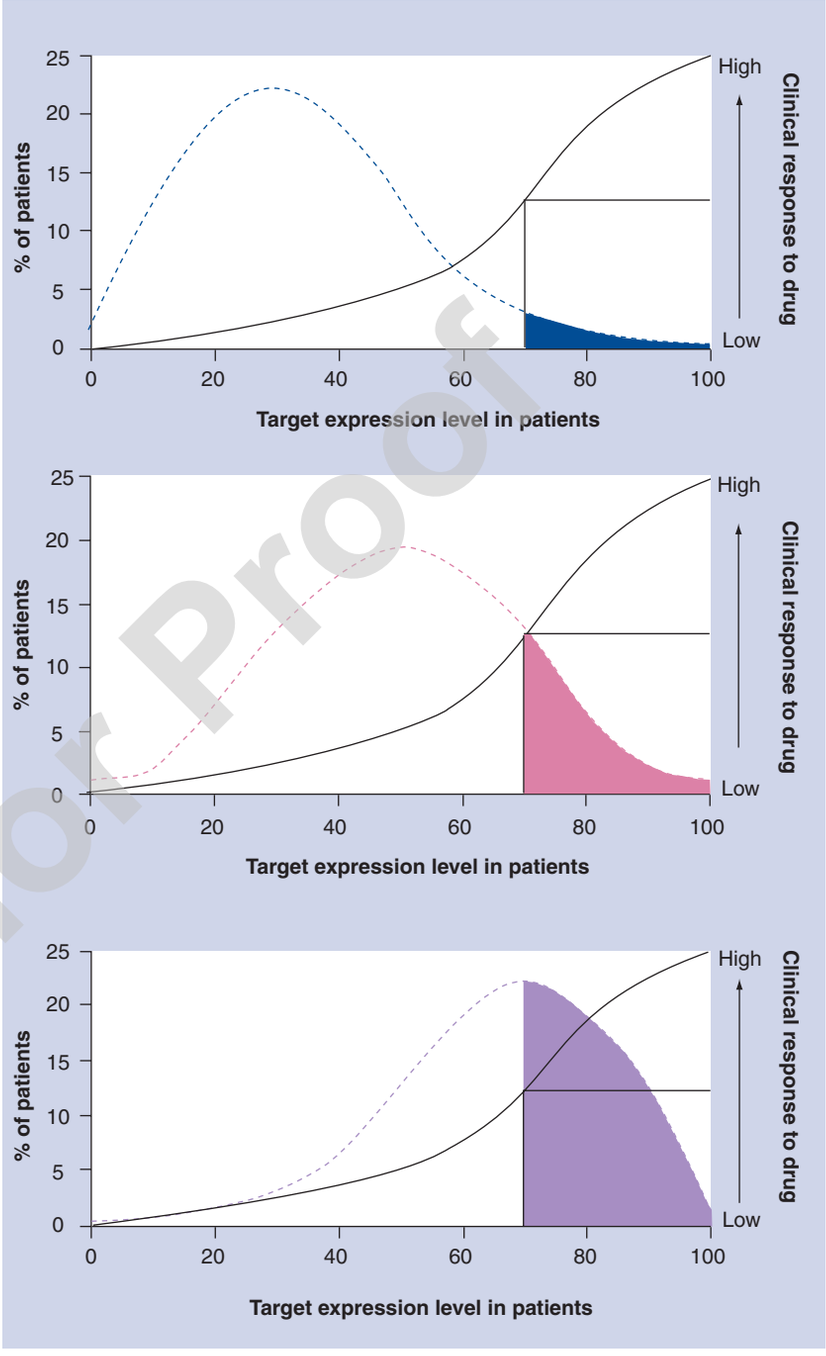


**Figure 2. Three distributions of pathway expression for different drug targets demonstrating sizes of disease subpopulations with good clinical responses to drugs targeting each pathway.**
The dark solid black curve illustrates the clinical response to a drug that targets the pathway and the response increases with the degree of abnormal expression of that pathway. The dashed line represents the distribution of pathway expression for a specific target pathway in patients with a disease. The shaded area represents patients that will have the best response to a drug targeting that pathway.
Data from [7].

Oncologists rapidly adopt individualized treatment paradigms owing to the urgency felt when treating patients with a life-threatening disease. As a result, these personalized medicine regimens for cancer patients are becoming the standard of care in almost real time, from the initial scientific observations to the creation, testing and confirmation of personalized medicine hypotheses. On the other hand, there is a large body of knowledge that could be used to create similar personalized medicine hypotheses for patients with common chronic diseases and as yet, this is not happening on a large scale and it is certainly not happening quickly. This gap between the knowledge of individual genetic differences associated with disease pathogenesis, progression and severity and the translation of that knowledge into testable personalized medicine hypotheses can be addressed by translational medicine scientists.

The best way to illustrate how translational medicine scientists can efficiently translate disease-related genomic data and other types of biomarker information into personalized medicine treatment paradigms is with specific examples. RA is one such chronic disease that is ripe for the creation and testing of personalized medicine hypotheses. RA is a heterogeneous phenotype, associated with multiple molecular differences and inflammatory pathway abnormities that differ between patients. Here, the development of effective targeted biological and small molecule drugs [12], advances in the understanding of the molecular biology of immunologic and inflammatory pathways including the role of cytokines in RA [13] and the functional significance of SNPs in relevant genes can lead to testable individualized treatment hypotheses. At least 19 specific genes are significantly associated with RA susceptibility, severity or response to therapy and have been associated with differences in T-lymphocyte activation, macrophage function, specific cytokine and inflammatory signaling pathways and/or inflammatory pathway dysregulation [101]. While these same pathways are targeted by biological drugs, rheumatologists treat their patients without considering these individual differences and instead they use a 'try it and see' paradigm. These agents were approved because they are safe and effective for the 'average patient'. In other words, in each study, the mean efficacy for the drug group was statistically better than that of the control group. Yet for biologics targeting TNF, approximately 29–54% of patients do not achieve clinically important efficacy (American College of Rheumatology Criteria 20 [ACR20] response [**Box 1**]) [12] and the per patient cost of a 6-month treatment trial is in the range of US$5000–US$7000 [14]. In addition, for the nonresponders, more effective treatment is delayed by 6 months. Similarly, for tocilizumab, an anti-IL-6 receptor antibody, 30–40% of patients do not achieve an ACR20 response [15–17]. With abatacept, a CTLA-4-Ig construct, only 60% of patients achieve an ACR20 response when administered with methotrexate compared with 30% on methotrexate alone [18]. For each of these treatments, testable personalized medicine hypotheses can be evaluated in either new prospective clinical trials or retrospectively by using stored samples from completed dose-ranging clinical studies.

## Dose selection for TNF-α-targeted agents

TNF-α production is influenced by SNPs in the promoter region of the gene and is associated with outcomes in malaria and other infectious diseases. For example, the -308 G→A SNP has a gene frequency of 0.23 (in a Swedish study) [19] and probably has clinical significance since it is associated with a number of infectious, allergic and autoimmune diseases [102]. It has functional significance since *in vitro* cells from subjects with A/A and A/G genotypes produce significantly more TNF-α in response to inflammatory stimuli and there are clear differences in transcription rates [20,21]. In RA, this SNP may have clinical significance as well. In a RA study with infliximab, clinically significant improvement occurred in 81% of G/G patients compared with 42% of A/A and A/G patients [22]. This suggests that a standard infliximab treatment regimen during disease flares may not be sufficient to neutralize increased levels of TNF-α. This hypothesis can be tested and, if confirmed, may lead to a more rational approach to dose selection in RA patients. Currently, G/G patients (approximately 60% of the population) may be receiving more anti-TNF-α than they need while A/G and A/A patients may require higher doses or more frequent treatment to prevent disease flares. Individualized dosing from the beginning of therapy could reduce infectious adverse events and improve efficacy.

## Patient & dose selection for tocilizumab

Tocilizumab is an anti-IL-6 receptor antibody that is approved for RA treatment in Europe [103] and is expected to be approved in the near future in the USA. A third of patients treated with

tocilizumab in Phase II and Phase III clinical trials did not achieve an ACR20 clinical response [15–17]. A common SNP at position -174 of the *IL-6* gene changes the amount of IL-6 produced upon stimulation with IL-1 and other inflammatory stimuli [23,24]. The C allele frequency is relatively high – 0.403 in the general population of London, UK – but is significantly reduced in patients with juvenile RA [23]. C/C constructs do not increase IL-6 production after stimulation with IL-1 or lipopolysaccharide compared with the 2.35- and 3.6-fold increase by G/C and G/G constructs, respectively [23]. Could the nonresponders to tocilizumab be patients whose disease is less dependent on IL-6 (i.e., C/C genotype) or patients who produce more IL-6 (i.e., G/C and G/G genotypes)? Again, these are testable hypotheses with the potential to improve patient outcomes by identifying those patients who are most likely to respond or those patients requiring a higher dose of tocilizumab.

## Patient selection for abatacept

Abatacept is a fusion molecule of CTLA4 and an Fc fragment of IgG. It blocks interaction between CD28 and CD80/86 (B7–1 and B7–2), mimicking the natural CTLA4-mediated downregulation of T-lymphocyte immune responses by inhibiting the co-stimulation pathway [25]. Approximately 40% of patients who receive abatacept on methotrexate background therapy do not achieve an ACR20 response [18]. PTPN22 is a lymphoid-specific phosphatase that downregulates T-lymphocyte activation mediated by CD28 co-stimulation and ligation of the T-cell receptor [26]. A SNP (1858 C→T) in the *PTPN22* gene results in an amino acid change from arginine to tryptophan at position 620 and reduces phosphatase function [27]. This SNP is present in 17% of the general population and in 28% of RA patients [27]. It is reasonable to assume that abatacept may be more active in patients with a *PTPN22* SNP that results in decreased phosphatase function and a more active co-stimulation pathway. Abatacept directly targets this co-stimulation pathway. It is currently prescribed in RA patients who have first failed a disease-modifying antirheumatic drug (DMARD), but it may make sense to use abatacept first in patients with this 1858 C→T SNP if it can be demonstrated that this subpopulation of patients has a much higher response rate than the general RA population. Again, this is a testable hypothesis with the potential to improve patient outcomes and reduce the cost of medical care.

**Box 1. ACR20 definition.**

**American College of Rheumatology (ACR) 20% improvement in tender and swollen joint counts and 20% improvement in at least three of the following five ACR core set measures: pain, patient and physician global assessments, self-assessed physical disability and acute phase reactant (C-reactive protein or erythrocyte sedimentation rate).**

What can be done to move these types of hypotheses forward into medically acceptable and reimbursable individualized treatment paradigms more rapidly? First, investments in infrastructure such as electronic medical records (EMRs) linked to sample repositories and support of training programs in translational medicine will facilitate the creation and testing of hypotheses concerning individualized treatment paradigms and the clinical validation of associated biomarkers. These investments by academic centers, hospitals, clinics and third party payers could also become a source of revenue for these institutions since others could pay for access to test their own hypotheses or share in the intellectual property discoveries (biomarkers, diagnostics, drug targets and treatment indications) that have commercial value. These types of investments have also been identified by others as being critical to the future implementation of personalized medicine treatment paradigms [1,2]. For pharmaceutical companies, these investments could also reduce the cost and time of drug development as well as increase research productivity [28,104]. In addition, using their own data and samples, pharmaceutical and biotech companies could retrospectively evaluate personalized medicine hypotheses during the course of drug development at little additional cost, preferentially in early development but even after Phase II and III trials are complete, to potentially reduce late-phase attrition.

If translational medicine clinical scientists are successful and more personalized medicine hypotheses are created, tested and clinically validated, what else is needed to implement these treatment paradigms in medical practice? First, there must be some demonstration of more favorable outcomes (cost–benefit) over conventional treatment paradigms and pharmaceutical companies should be allowed to alter pricing to reflect this improved cost–benefit. Second, if the opinion expressed here, analyses by the Boston Consulting Group [104] and the views of other academic and industry experts [2,28], are correct, the cost and time to develop drugs linked to pharmacogenomic tests and/or diagnostics

will be reduced compared with drugs that have 'blockbuster' marketing targets, and pharmaceutical companies will consider personalized medicine paradigms for new drugs, especially with the active involvement of regulatory authorities. However, it is unlikely that pharmaceutical companies will adopt label changes for successfully marketed drugs without financial incentives or new regulatory requirements. In some of the RA examples presented above, the difference in revenue between the current 'try it for 6 months' paradigm and a personalized medicine paradigm where potential nonresponders never receive an expensive biological drug is approximately US$250,000 for every new 100,000 RA patients. For drugs in development, it is also unlikely that Phase III programs will be tailored towards personalized medicine paradigms rather than more inclusive labeling claims unless marketing approval is at stake or other financial incentives exist. For example, Roche (Basel, Switzerland) has not published any data on the efficacy of tocilizumab in RA subpopulations identified by the IL-6 promoter SNPs discussed above, despite the availability of the samples and the data to test this personalized medicine hypothesis [Littman BH, Translational Medicine Associates, CT, USA & Woodworth T, Roche Products Ltd and Hoffmann-La Roche, Basel, Switzerland. Pers. Commun.]. Their Phase II and III studies included patients who failed to respond to other DMARDs so it is likely that this is the indication they are seeking in the USA [15–17]. It is also the approved indication in Europe [103]. Again, the demonstration of superior clinical outcomes and cost–benefit advantages are required if these treatment paradigms are to be adopted by clinicians, payers and regulators.

Given these considerations, after the successful validation of personalized medicine hypotheses, clinical implementation of the treatment paradigm requires not only the demonstration of improved clinical outcomes but also a cost–benefit advantage in disease populations. In RA, such studies have been conducted to justify the high cost of biological DMARDs (often supported by pharmaceutical and biotechnology companies) but they have not been conducted to test the cost–effectiveness of specific personalized medicine treatment paradigms. In a review of eight studies [29], the authors found that the cost of a quality adjusted life year (QALY) for RA patients who are resistant to methotrexate and receiving biological therapy ranged from US$3580 to US$119,578 with 13 of 22 different treatment comparisons in those eight studies showing the incremental cost of a QALY for biologics to be over US$50,000. Since some of this high cost includes the cost of treating nonresponders, it would be considerably lower for these same drugs if personalized medicine treatment paradigms were adopted, where the probability of a significant clinical response with acceptable safety would be much higher and where patients who are less likely to respond will not be treated. Future studies in RA will also have to better quantitate the 'opportunity cost' of ineffective or less effective treatments that allow joint damage to progress until a more effective treatment is received.

The responsibility for creating, testing and implementing personalized medicine treatment hypotheses should belong to academic medical institutions, hospitals, pharmaceutical companies, government agencies, physicians and third party medical payers who all have a significant stake in the success, cost–effectiveness and clinical validity of a widely accepted personalized medicine future scenario. As noted above, infrastructure investments in universal EMR systems and repositories for clinical data and samples for research purposes will facilitate hypothesis generation and testing, but universal EMRs will also enable quality of care and cost–effectiveness comparisons to be made between conventional and personalized treatment regimens. In fact, the ability of universal EMRs to facilitate quality of care and drug effectiveness comparisons is one of the reasons why the Obama administration has made universal EMRs in the USA such a high priority for both economic recovery and improved healthcare [30]. They will also help to better define phenotypes for subjects in clinical trials and reduce the cost of pharmacogenomics in general [28,31]. Clinical and outcomes research studies that evaluate specific personalized medicine treatment paradigms should be conducted and/or funded by those institutions that will benefit by using the data to make decisions that improve the cost–effectiveness of healthcare delivery; third party payers (government and private) have the greatest financial incentives while academic institutions, regulatory agencies, physicians and patients have the greatest clinical incentives to further evaluate and implement clinically validated personalized medicine treatment paradigms.

Hypothetical models, such as the one proposed by Garrison and Finley [32], can be used to predict the general economic impact of personalized medicine, but it is unlikely that they will provide the necessary motivation and incentives that will result in the acceptance of specific

personalized treatment paradigms. Adopting these one at a time once their benefit is demonstrated in studies grounded in the reality of a comparison of outcomes data is the more likely future scenario. Personalized medicine clinical grants from government agencies and third party payers as well as new outcomes research regulatory requirements during the development of drugs with testable personalized medicine hypotheses will also provide an incentive to conduct this type of research. Finally, academic medical institutions and professional organizations should reward translational medicine and personalized medicine outcomes research successes, much as they do the more traditional laboratory-based research successes.

Training and education in translational medicine is the last piece of the puzzle that is needed to help implement personalized medicine. In the pharmaceutical company environment, translational medicine clinical scientists have generally been trained internally and have backgrounds in early clinical research, clinical pharmacology, pharmacogenomics and biology. There is a great need for new translational medicine training programs and this could be facilitated by collaborations between industry, government and academic institutions [33]. The US FDA and the NIH have recognized the need to advance this area with their 'Critical Path' [105,106] and 'Clinical and Translational Science Awards' [107] initiatives, but again, progress has been slow outside of oncology. Some universities have recently set up translational medicine departments or spin-off institutions to address this need [34]. Currently, many educational programs focused on pharmacogenomics are found in pharmacology departments and pharmacy schools with more of a focus on how genetic factors influence drug exposure [35]. More investment is needed in educational programs that focus on the clinical translation of new knowledge regarding the molecular definition of chronic diseases, molecularly defined disease subpopulations and responsiveness to drugs targeting their specific molecular and pathway abnormalities.

In summary, the concepts presented here for translating the molecular definition of disease phenotypes, particularly of functionally important genetic associations, into testable personalized medicine hypotheses is within the expertise of translational medicine scientists and apply to all chronic diseases. This process has much in common with the way translational medicine experts in the pharmaceutical industry approach the demonstration of POC for drugs with novel targets. However, the real world is quite different from the pharmaceutical company environment. There is no question regarding who is responsible for demonstrating the activity of novel drugs within a company while the responsibility for creating and testing personalized medicine hypotheses in the real world remains to be defined. Clearly, new academic opportunities, educational programs and rewards for translational medicine researchers, financial and regulatory incentives for drug companies and developers, EMR and sample repository infrastructure investments and the demonstration of improved clinical outcomes and cost–benefit advantages are all required to make personalized medicine a reality.

## Future perspective

Personalized medicine has the potential to satisfy the need to reduce drug-development costs and time, reduce healthcare costs and improve health outcomes. This will be the driver towards implementing personalized medicine treatment paradigms for patients with common chronic diseases over the next 5–10 years. As we are seeing with the clinical translation of molecular disease knowledge in cancer into personalized medicine treatment practices, this will occur one by one for patients with common chronic diseases. We will begin to see such examples and the demonstration of their cost–effectiveness over the next 5 years. The clinical and regulatory acceptance of these examples along with their reimbursement by payers will provide motivation for pharmaceutical companies, regulators, third party payers and translational medicine scientists to further advance personalized medicine and develop new drugs specifically targeting molecularly-defined patient subpopulations. Academic institutions, third party payers (including governments), hospitals and clinics will help to develop the infrastructure to facilitate personalized medicine research and its acceptance into clinical practice, but it will be the payers who will eventually insist on its implementation based on cost–effectiveness.

## Financial & competing interests disclosure

*Bruce H Littman owns Pfizer Inc. stock options and is a member of the Board of Directors of BioFortis, a bioinformatics company with tools for translational research. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.*

*No writing assistance was utilized in the production of this manuscript.*

**Executive summary**

- Personalized medicine treatment paradigms are rapidly being adopted for cancer patients.
- Like cancer, common chronic diseases are being better defined on a molecular basis but there is still a huge gap between this basic disease knowledge and the implementation of individualized treatment paradigms.
- The generation and testing of personalized medicine treatment hypotheses parallels the way translational medicine scientists approach the demonstration of proof-of-concept for drugs with novel targets.
- The degree of abnormal pathway expression in disease is related directly to the level of disease activity and the potential for clinical response to a drug that targets that pathway.
- The distribution of patients with various levels of abnormal pathway expression determines the proportion of patients that will respond well to a drug targeting that pathway.
- Three examples of rheumatoid arthritis personalized medicine hypotheses are used to illustrate how individualized treatment paradigms can be created and tested, and can potentially replace the current 'try it and see' strategy used for expensive biological drugs.
- Closing the gap between the molecular definition of disease and the implementation of personalized medicine treatment paradigms will probably occur gradually, one paradigm at a time, but it can be accelerated by the demonstration of improved outcomes (cost–benefit), appropriate educational programs and rewards for translational medicine researchers, incentives for pharmaceutical companies and investments in electronic medical records and sample repositories by hospitals, clinics and third party payers.


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