New approaches to personalized medicine for asthma: Where are we?

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Access to an electronic medical record is essential for personalized medicine. Currently, only 40% of US physicians have such access, but this is rapidly changing. It is expected that 100,000 Americans will have their whole genome sequenced in 2012. The cost of such sequencing is rapidly dropping, and is estimated to be $1000 by 2013. These technological advances will make interpretation of whole genome sequence data a major clinical challenge for the foreseeable future. At present, a relatively small number of genes have been identified to determine drug treatment response phenotypes for asthma. It is anticipated that this will dramatically increase over the next 10 years as personalized medicine becomes more of a reality for asthma patients. (J Allergy Clin Immunol 2012;129:327-34.)

Key words: *Personalized medicine, asthma, genomics, pharmacogenomics, drug treatment, whole genome sequencing*

Abbreviations used
ED: Emergency department
5-LO: 5-Lipoxygenase
GWAS: Genome-wide association study
ICS: Inhaled corticosteroid
LABA: Long-acting β_2-agonist
NAEPP: National Asthma Education and Prevention Program
SABA: Short-acting β_2-agonist
SNP: Single nucleotide polymorphism

One of the most important parts of asthma care that physicians oversee is the use of medication to relieve asthma symptoms and prevent morbidity and mortality from the disease. Asthma medication cannot cure, nor can it alter the natural history of lung function growth and decline. However, it can dramatically improve physical functioning, quality of life, morbidity, and mortality and thus significantly reduce health care costs if applied appropriately to the right patient at the right time. The goal of providing personalized care to each patient with asthma is difficult to achieve. In most clinical care settings, even in the absence of genomic data, asthma medications are imperfectly used by both clinicians and patients alike, resulting in needless excess morbidity and cost.

This review will address the question of personalized medicine for asthma care and the promise of genomics to advance more personalized care for the asthmatic patient. We will begin by addressing the question of what a health care system needs to be able to do to institute personalized medicine for asthma. We will then consider the health care burden related to asthma care and the role of medication in addressing that health care burden. We will then briefly review modern pharmacotherapy for asthma, how effective it actually is, and where there is room for improvement. We will then review the genes identified for asthma drug treatment response. We will conclude with what we need to get from genomics to improve our ability to predict asthma drug treatment response.

Table I[1] depicts the 6 defining elements that a health care system needs to enable it to institute personalized medicine. The vast majority of American health care settings fall far short of these goals. For example, as of 2 years ago, only 5% of all physicians in the United States used an electronic medical record in their routine clinical care of patients. With recent initiatives in Washington, DC, this has dramatically increased to 40% (David Blumenthal, personal communication, 2011). Many of these electronic medical records systems are in a small number of major academic health centers and the Veterans Administration. Even these systems, for the most part, do not have access to the full range of decision support tools to minimize drug interaction errors, to identify patients' allergies, or to ensure the right drug for the right patient at the right time. Furthermore, when audited, only a minority of patients have a personalized identifiable health plan in their charts or electronic medical records, and only a very few health systems have the capability of delivering personal genomic data to clinicians on their desktop terminals. The number of health care systems that can deliver on most of the essentials for personalized health care, as outlined by the Secretary of Health and Human Services (Table I), is so few that they can be explicitly named: Partners Health Care, Mayo Clinic, Vanderbilt Health System, Geisinger Clinic, Marshfield Clinic, and perhaps a few others.

Currently, genomic diagnostics and prognostics is a $1 billion a year industry and growing at the rate of 25% per year. With this veritable explosion in genomic knowledge and the inevitable exponential growth in clinically relevant data that will result from it, the American health care system seems ill equipped to enter the era of personalized medicine for asthma or any other condition. For example, whole-genome sequencing and its interpretation are now clinically available, and use of this technology will increase exponentially as the cost of such sequencing decreases over the

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TABLE I. What do we need to institute personalized medicine?

Essentials of personalized medicine
- An electronic medical record
- A personalized health plan
- Physician access to decision support tools
- Personalized treatments
- Personal genomic data available for clinical use
- Personal clinical information available for research

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next 5 years. More than 100,000 Americans will have their whole genome sequenced in 2012, and it is estimated that whole-genome sequencing will cost less than $1000 dollars per person by 2013, a cost well below what is being charged now for most specific disease genetic tests (Scott Weiss, personal communication, Harvard Partners Personalized Medicine Conference, 2011). The number of patients with whole-genome sequencing data will rapidly increase as the American public demands these data be used to guide their treatment. This growing demand will place the burden not on the technology of doing the sequencing but on delivery of high-quality interpretation of the whole-genome data at the point of care. As one geneticist put it: "It may be the $1000 genome but it will be the $100,000 interpretation" (Bruce Korff, personal communication, 2011). Although the interpretation of whole-genome sequencing data entering clinical medicine will place immense pressure on providers to change our health care delivery system, an additional issue that needs to be addressed is whether the conversion to such an electronically based health care system, with genomic data available to providers and patients alike, will result both in more personalized service and ultimately decrease the cost of care. This hypothesis remains unproved.

MAGNITUDE OF THE HEALTH CARE BURDEN RELATED TO ASTHMA CARE

There are more than 300 million subjects with doctor-diagnosed current asthma worldwide, with more than 24.6 million in the United States alone.[2] These 24.6 million asthmatic patients incur $56 billion in direct health care costs related to the disease on a yearly basis.[3] The greatest costs relate to 4 areas: the cost of the medications themselves and the costs of office visits, hospitalizations, and emergency department (ED) visits. Roughly half of all asthma costs are related to medication use, with the remainder related to health care use. It is clear that use of inhaled corticosteroid (ICS) controller medication can decrease these health care use events (hospitalizations and ED visits) by 50% if the medications are taken with even modest regularity.[4,5] It is clearly established that drug treatment response for at least 2 of the major classes of asthma drugs, short-acting bronchodilators and ICSs, are genetically determined and that about 50% of subjects who take these medications do not benefit because they are not responding to the drug because of their genetic constitution.[6,7] Another major inefficiency issue is noncompliance. Asthma is similar to high blood pressure or high cholesterol in that the penalty for not regularly taking the medication is rarely immediate death but more commonly poor control of the disease and resultant increased morbidity and health care costs. In usual clinical circumstances asthmatic patients take their controller medications about half of the time, and even at that rate, they achieve about a 50% reduction in morbidity (eg, reduced hospitalizations and ED visits).[4,5] An additional inefficiency results from a segment of the patient population with moderate-to-severe persistent disease that is unusually compliant with medication use but does not seem to benefit from this compliant use because of drug resistance from genetic or environmental causes.[8] In an ideal world we could identify both the noncompliant patients and the highly compliant patients who are not benefiting from asthma medication and modify their treatment to improve health outcomes. This might increase costs in the short-term, but if patients were easily identified by means of genetic testing, costs would ultimately go down if we got the correct medications to the responsive patients. Although examples of this for asthma are lacking, in patients with cancer, the use of targeted therapies for breast and lung cancer is now commonplace and routine care.

MODERN PHARMACOTHERAPY FOR ASTHMA: ISSUES COMPLICATING PERSONALIZED CARE

The most recent version of the National Asthma Education and Prevention Program (NAEPP) guidelines had several innovations, the most important being the distinction between severity and control.[9] Clinicians traditionally divide asthma into 4 severity groups: mild, mild persistent, moderate, and severe. Severity is defined as the symptoms that occur off all medication and that reflect the natural intrinsic intensity of the disease process. Control is the degree to which the manifestations of disease are minimized by medication. Two other domains of severity and control, namely impairment and risk, might not correlate with each other and might respond differently to treatment. The level of complexity of the current guidelines makes it difficult for even asthma experts to completely follow the guidelines as currently written.[10] When the implementation of the NAEPP guidelines has been examined in clinical practice, they have routinely fallen short of the ideal.[11]

Most recently, the recurrent nature of exacerbations despite adequate therapy[11] and the heterogeneity of severity phenotypes[12] have added to the complexity of personalized care for asthma. An additional challenge is that combination treatment with long-acting β_2-agonists (LABAs) plus an ICS has become the standard of care for asthmatic patients with mild persistent and moderate persistent disease. This combination treatment makes it difficult to separate the genetics of ICS use from that of LABA use. These concepts, now firmly enshrined as the standard of care, complicate the search for personalized therapy for asthma. Another factor complicating a search for personalized medicine for asthma is that most asthma clinical trials are small in size and lack the large numbers needed to find genomic determinants of drug response.

ORGANIZATION TO FIND GENES FOR ASTHMA DRUG TREATMENT RESPONSE

Given all of the difficulties in advancing personalized care for asthma, what is the best approach to finding genes that predict drug treatment response, and how can this search be accelerated? Fig 1 outlines the basic approach.[13] Complexity resides at every step of the process. Initial approaches have used first candidate genes and then genome-wide association studies (GWASs) for step 1. However, most pharmacogenomic studies have populations an order of magnitude smaller than those for other complex traits, thus making power a major problem in pharmacogenomic

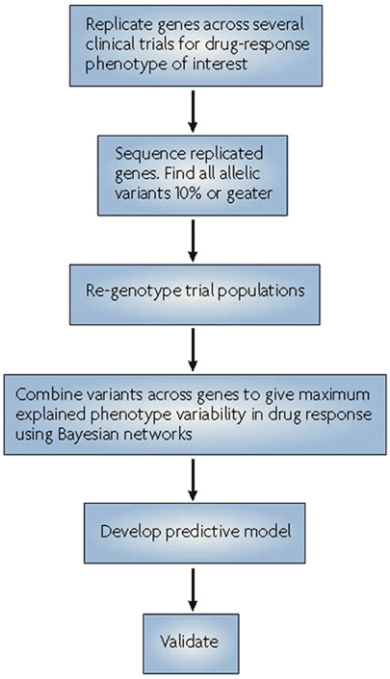

FIG 1. Proposed methodology for developing pharmacogenetic predictive tests. This flow diagram describes the steps to take in the development of a hypothetical predictive pharmacogenetic test. The cutoff of 10% in set 2 is arbitrary. The methodology for combining variants in step 4 could be any multivariate approach and not just Bayesian networks. Validation (set 6) will probably occur in samples from the general population rather than in randomized controlled trials. Used with permission from Weiss et al.[13]

GWASs. An additional issue is that rare variants, insertion deletion polymorphisms, and some noncoding functional variants might be missed in GWASs. A third issue is that most GWASs only explain a small portion of the variation in clinical phenotype. Integrative genomics studies are now being used to enhance the first step of Fig 1 to address all of these problems.[14] By using RNA to determine transcript levels in response to a drug administered to a relevant cell line and relating this to the GWAS single nucleotide polymorphism (SNP) data in which the SNP is regressed on transcript, investigators can identify e-SNPs, which are SNPs that explain a significant amount of the variation in transcript abundance. If these cell lines come from the participants in the clinical trial, there is a direct link between the *in vitro* and *in vivo* experiments, further strengthening this approach (Fig 2).[14]

PROMISE OF GENETICS AND GENOMICS IN IMPROVING AND PREDICTING ASTHMA CARE RESPONSE

What specific genes have been identified that significantly predict response to β-agonists, ICSs, leukotriene antagonists, and anti-IgE therapy? Table II[15-42] provides a summary of the variants and phenotypes for the genes identified as associated with the various classes of asthma medications. In these studies one is looking for replication of results from at least 2 genetic association studies and, if possible, some functional data linking the polymorphism to the drug response phenotype. Many of these studies do not meet this standard. An additional problem is that because many asthma drug trials are small, the power of these studies is limited. Many studies do not identify an actual functional variant but one in linkage disequilibrium with it. Finally, to control for population stratification, most studies are limited to white subjects.

β-AGONISTS

β-Agonists are the most common medication for asthma. Short-acting β_2-agonists (SABAs) are the preferred treatment for acute asthma attacks. LABAs are only used in combination with ICS therapy to provide long-term asthma control. This is because of concern about the long-term adverse effects of unopposed LABA use, especially in African American patients.

The β_2-adrenergic receptor is a G protein–coupled receptor the activation of which leads to an increase in levels of adenylyl cyclase, an enzyme that catalyzes the conversion of ATP to cyclic AMP. Cyclic AMP in turn binds to protein kinase A, which activates a downstream cascade of target proteins as a result of phosphorylation. Adrenergic receptors on bronchial smooth muscle function to counter the parasympathetic innervation that controls bronchoconstriction by providing bronchodilatation. Receptor activation also increases translocation of the glucocorticoid receptor from the cytoplasm to the nucleus, thus demonstrating molecular cross-talk between these 2 pharmacogenetic pathways. This cross-talk suggests that genes identified as being part of one pathway might actually function to influence drug response in the other pathway.

The *ADRB2* gene is located on chromosome 5q31-33 close to the cytokine cluster, a region linked to asthma. On the basis of deep resequencing, the gene is moderately polymorphic, with 49 SNPs identified.[43] Three SNPs result in amino acid changes at positions 16, 27, and 164 of the encoded protein, and these have been the most extensively studied. These are at positions 46G>A, 79C>T, and 491C>T. Additional functional variation occurs in the 3′ untranslated region.

Pharmacogenetic studies have primarily looked at the Arg/16 Gly polymorphism at position 46 of the gene in relationship to both SABA and LABA response (Table II).[15-23] Although this gene is the most studied gene in asthma pharmacogenetics, no clear conclusion as to its functional effects has been reached. Although the Arg/16 Gly polymorphism has been linked to the level of lung function, it has not clearly been linked to change in lung function with either SABAs or LABAs. These data are more consistent, with this variant being correlated with another functional variant in the gene through linkage disequilibrium rather than a functional relationship between this polymorphism and β-agonist response. Most likely, that variant is a regulatory variant in the 3′ untranslated region of the gene that controls gene activity.

Two other genes have been associated with β-agonist response: *ARG1* and *GSNOR*. Of these 2 genes, the evidence is most extensive for *ARG1*. Nitric oxide is a natural bronchodilator the activity of which is controlled by the enzyme nitric oxide synthase. The substrate for nitric oxide synthase is L-arginine. In turn, the *ARG1* gene encodes arginase, which controls L-arginine synthesis and homeostasis.[44] Increased *ARG1* expression has been shown in bronchoalveolar epithelial and inflammatory cells from human asthmatic subjects, thus supporting a role of *ARG1* in airway function.[45] Three separate pharmacogenetic studies with replication have linked *ARG1* to bronchodilator response (Table II).[24-26]

Bronchoalveolar lavage fluid of adults with mild asthma shows increased S-nitrosoglutathione reductase *GSNOR* expression, and *GSNOR* expression was positively correlated with airway

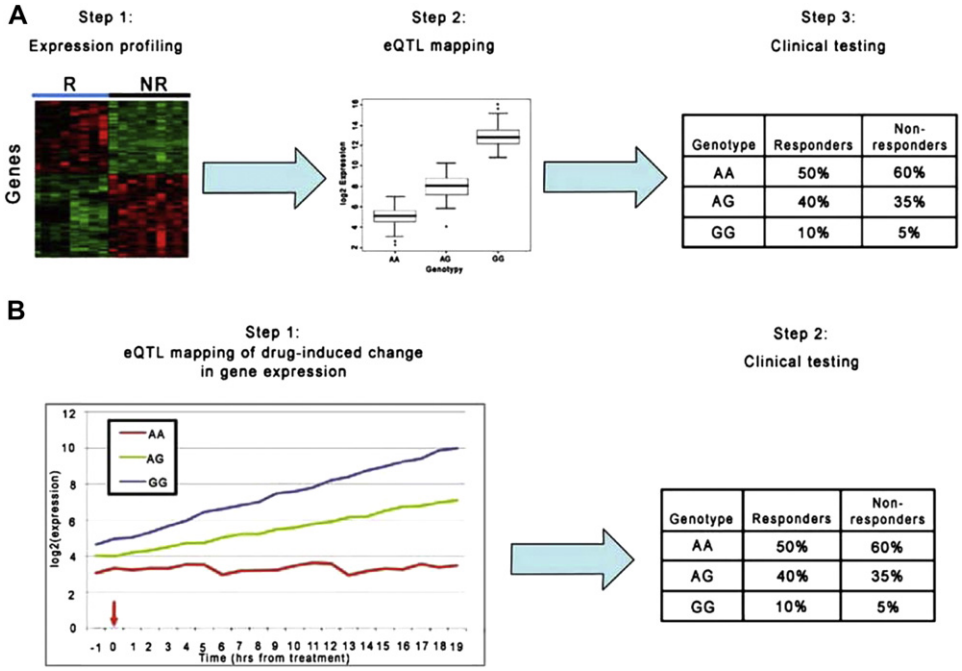

FIG 2. Pharmacogenetic expression quantitative trait loci *(eQTL)* study designs. **A,** Sequential design. Comparison of microarray expression profiles of responders *(R)* with nonresponders *(NR)* for identification of pharmacogenetic candidates *(step 1)*, followed by eQTL mapping of candidate gene expression levels in the larger samples *(step 2)*. Significant eQTLs are subsequently carried to clinical cohorts for classical pharmacogenetic testing *(step 3)*. **B,** Perturbation design. Time-series experiments measuring global gene expression in response to drug administration *(arrow)* testing for SNP-specific differences in response phenotype *(step 1)*, which can then be carried forward to clinical testing in *step 2*. These designs are not mutually exclusive. Used with permission from Raby.[14]

TABLE II. Variants and phenotypes for the genes identified as associated with the various classes of asthma medications

Drug pathway	Gene	SNP	Phenotype	Replication	Reference no.
β-Agonist	*ADRB2*	Arg16/Gly	Lung function	No	15-23
β-Agonist	*ARG1*	Rs2781659	Lung function	Yes	24-26
β-Agonist	*GSNOR*	+17059	Lung function	No	27
ICS	*CRHR1*	Inversion	Change in lung function with ICS	Yes	28,29
ICS	*GLCCI1*	Rs37973	Change in lung function with ICS	Yes	30
ICS	*TBX21*	rs2240017	Airway responsiveness	No	32
ICS	*FCER2*	T2206C	Exacerbations	Yes	33, 34
ICS	*STIP1*	rs4980524, rs6591838	Change in lung function with ICS	No	31
Leukotriene	*ALOX5*	rs4986832, rs2115819	Change in lung function with leukotrienes, exacerbations	Yes	35-38
Leukotriene	*LTC4S*	C444A	Change in lung function with leukotrienes	No	39-41
Leukotriene	*SCCo2B1*	Rs12422149	Concentration montelukast	No	42

hyperresponsiveness in these same subjects.[27] *GSNOR* catabolizes the endogenous bronchodilator S-nitrosothiol. One genetic association study has linked *GSNOR* polymorphisms to an interaction with *ADRB2* (Table II).[27]

To date, no GWAS of bronchodilator response has been published.

INHALED STEROIDS

ICSs are the most common and most effective anti-inflammatory controller medications for the treatment of asthma of all severity classes.[9] Glucocorticoids act by first forming a complex with the intracellular glucocorticoid α receptor. This complex translocates to the nucleus and acts as a transcription factor for genes involved in stress responses through directly binding with DNA or indirectly by interacting with other transcription factors.[46]

Three pharmacogenomic phenotypes have been examined: lung function response defined as change in FEV_1 after 8 weeks on ICSs, airway responsiveness to methacholine, and exacerbations defined as hospitalizations and ED visits.

LUNG FUNCTION

A candidate gene study of 14 corticosteroid pathway genes identified the corticotropin-releasing hormone receptor 1 *(CRHR1)*

genotype (homozygous for the minor allele of rs242941) as a significant predictor of FEV_1 after 8 weeks of ICS treatment in clinical trials of both adult and childhood asthma.[28] *CRHRI* is one of the receptors for corticotropin-releasing hormone. Corticotropin-releasing hormone is secreted by the pituitary gland and controls the release of adrenocorticotropic hormone from the adrenal gland that in turn controls cortisol production.[28] The functional variant responsible for this effect is unknown because *CRHR1* is part of a large gene inversion on chromosome 17. This inversion is thought to have multiple phenotypic effects.[29]

A recent GWAS of ICSs has been published, implicating an SNP in the promoter of *GLCCI1* as the functional variant determining lung function change while taking ICSs. Investigators studied 935 subjects and replicated their findings in both adults and children.[30] Using luciferase assays, they were able to identify a transcription factor binding site in the promoter as the functional site for this effect. The gene appears to be important in immune response and might control apoptosis.

AIRWAY HYPERRESPONSIVENESS

Relatively few studies have looked at the change in airway responsiveness with ICS medication. The one gene that has been examined for this phenotype is *TBX21*. *TBX21* is a T-cell transcription factor responsible for T-cell differentiation, maturity, and lineage commitment. An increase in T-box transcription factor expression leads to differentiation of naive T lymphocytes into T_H1 cells while simultaneously repressing T_H2 cells.[31] *TBX21* is directly related to the immune aspects of the asthma phenotype by virtue of its role in CD4 cell development. Asthmatic subjects have decreased expression of T-box transcription factor expression in their peribronchial $CD4^+$ lymphocytes compared with that seen in healthy subjects.[47] Rs2240017, a rare nonsynonymous variation coding for replacement of histidine 33 with glutamine (*H33Q*; minor allele frequency of 4.5% in white subjects), has been associated with marked improvement in airway hyperresponsiveness (PC_{20}) in children receiving ICS therapy.[32,48] On the other hand, subjects receiving ICSs who were homozygous for histidine (H33H) demonstrated only a slight improvement in PC_{20} compared with the placebo group.[49]

ASTHMA EXACERBATIONS

Increased total serum IgE levels are associated with asthma exacerbations. The *FCER2* gene encodes for CD23, a low-affinity IgE receptor. Although glucocorticoids have been shown to decrease *FCER2* expression and CD23 production,[50] an SNP variant in *FCER2*, T2206C, has been associated with increased IgE levels and severe asthma exacerbations in asthmatic children despite ICS use.[50] White children homozygous for the T2206C mutant allele were more likely (odds ratio, 3.95; 95% CI, 1.64-0.51) to have a severe asthma exacerbation compared with those homozygous for all other T2206C genotypes.[33] This finding has recently been replicated.[34]

LEUKOTRIENE ANTAGONISTS

The leukotrienes are a potent class of inflammatory mediators that derive from arachidonic acid. Leukotriene antagonists block key steps in the inflammatory cascade and are used for the treatment of asthma. There are 2 biochemical types of antagonists: cysteinyl leukotriene receptor blockers (eg, montelukast, zafirlukast, and pranlukast) and inhibitors of 5-lipoxygenase (5-LO; eg, zileuton). Because leukotriene antagonists are less effective than ICSs, they are mostly used as adjunctive therapy in patients with more severe symptoms.[7] As with all drug treatment for asthma, the response to treatment with leukotriene modifiers among asthmatic patients is heterogeneous.[51]

Arachidonic acid is metabolized to both prostaglandins and leukotrienes. The leukotriene pathway, which is proinflammatory, begins with the conversion of arachidonic acid to leukotriene A_4. This reaction is catalyzed by the enzyme 5-LO.[52] Leukotriene A_4 is subsequently converted to leukotriene C_4 under the influence of leukotriene C_4 synthase. Sequential cleavage of glutamate and glycine residues results in the formation of leukotriene metabolites E_4 and D_4. Leukotrienes bind to receptors present on leukocytes and airway smooth muscle cells to cause smooth muscle contraction and mucus secretion and are highly proinflammatory.[53]

LUNG FUNCTION

ALOX5, the gene coding for the enzyme 5-LO, has a tandem repeat polymorphism (factor Sp1-binding motif) within its promoter region that has been associated with diminished promoter-reporter activity.[35] This polymorphism is associated with improvement in FEV_1 in subjects taking the 5-LO inhibitor, ABT-761, who were homozygous or heterozygous for the wild-type allele (5 repeats).[36] A more recent study of montelukast also showed improvement of FEV_1 in asthmatic patients with at least 1 wild-type allele.[37]

Lima et al[38] examined montelukast pharmacogenetics in a candidate gene study in a small clinical trial. Variants in *ALOX5* (rs4986832) were associated with an improvement in peak expiratory flow rates in subjects with the wild-type alleles.[38]

In another small candidate gene study of leukotriene pathway variants, Klotsman et al investigated a group of asthmatic patients randomized to montelukast for 12 weeks.[37] They were able to confirm the finding of Lima et al[38] that an SNP in *ALOX5* (rs2115819) was associated with change in FEV_1. Although this was not the same SNP found by Lima et al, it does lend credibility to the importance of *ALOX5* as a pharmacogenetic locus for leukotriene response. Additional replication for lung function of *ALOX5* comes from a study using zileuton, a different leukotriene antagonist.[54]

Another polymorphism in the leukotriene pathway associated with lung function response to leukotriene modifiers is the *LTC4S* C-444A locus.[39] Several studies have shown that asthmatic patients with at least 1 variant allele (C/C or C/A) had a significantly better response to a variety of leukotriene antagonists compared with patients with the 2 wild-type alleles, as evidenced by increased FEV_1, forced vital capacity, and peak expiratory flow values.[39-41]

EXACERBATIONS

A study of montelukast reported decreased number of asthma exacerbations and decreased use of β_2-agonists after treatment with montelukast in asthmatic patients with at least 1 wild-type allele of the promotor polymorphism of *ALOX5*.[37]

In the previously cited study of Klotsman et al, when looking at montelukast, the authors found variants in *ALOX5* (rs4986832) associated with reduced asthma exacerbations.[37]

Lima et al's previously cited study of montelukast[38] found a variant in *LTA4H* (rs2660845) associated with a 4-fold increase in the risk of asthma exacerbation over the treatment period, whereas *LTC4S* rs730012 and the mutant *ALOX5* repeat polymorphisms were associated with a greater than 70% reduction in exacerbations. This finding is in the opposite direction of all previously reported *ALOX5* results.

DRUG LEVELS

Leukotriene modifiers are not endogenously produced compounds, such as β-agonists and corticosteroids, and because they are administered orally and the drugs are metabolized in the liver, they are subject to first-pass kinetics. Variants in *SLCO2B1*, a gene that encodes the organic anion transporter OATP2B1, might partly mediate this effect. A nonsynonymous SNP in *SLCO2B1* has been associated with plasma concentrations of montelukast after 1 and 6 months of treatment.[42] Heterozygotes for the mutant allele demonstrated an up to 30% reduction in their plasma montelukast levels compared with homozygotes for the wild-type alleles.

ANTI-IgE

To date, no pharmacogenomics studies of omalizumab have been performed.

VITAMIN D

Sometimes genomic discovery has unusual applications. The identification of the *VDR* gene as a gene associated with asthma first identified by means of positional cloning[55,56] began to stimulate interest in the role of vitamin D in influencing steroid resistance in asthmatic patients already taking ICSs. The theoretic basis for this idea comes from *in vitro* studies. Vitamin D is associated with reduced airway smooth muscle proliferation.[57,58] In addition, vitamin D enhanced IL-10 levels at the airway epithelium and thus increased the transduction of inhaled steroid across the airway epithelial cell.[59] At least 4 human studies, one observational[60] and the others retrospective analysis of 3 existing clinical trials,[61-63] all suggest that asthmatic patients taking ICSs with low vitamin D levels have more exacerbations and lower lung function compared with those who do not. To date, no one has examined *VDR* polymorphisms as potential modifiers of this response. Because both ICS use and vitamin D deficiency are very common, the hypothesis has been offered that many patients with asthma who are unresponsive to ICSs can be treated by improving their vitamin D status and hence their steroid responsiveness. This unusual application of a genomic discovery is currently the subject of at least 7 ongoing prospective clinical trials (see clinicaltrials.gov for details).

SUMMARY

In summary, the number of genes identified for the various asthma drug response phenotypes remains small. In addition, there remain a number of barriers to personalized asthma care. The most important of these are greater dissemination of the electronic medical record, appropriate application of the NAEPP guidelines, a greater number of genes identified for each asthma drug response pathway, and the ability to use this genomic information for predicting drug treatment response in individual patients. Additional methodological factors hinder scientific advancement noted here: small clinical trials, the phenotypic and genotypic heterogeneity of asthma, and difficulty in determining functional effects of associated variants. Despite these formidable challenges, we seem poised to rapidly expand the number of genes involved in all categories of the drug treatment response for asthma. The novel discovery of a potential role of vitamin D in modulating steroid treatment response could be an important finding if confirmed by prospective clinical trials. Although prediction of asthma drug response based on genetic tests still seems distant, when this does occur, we will have a better chance of focusing our therapy on those who will respond rather than treating all of those who have the disease in the same way. This increased complexity will result in the need for more careful adherence to guideline-prescribed treatments.

CONCLUSIONS

In 1950, before the discovery of DNA, there were only 1 type of leukemia and 3 types of lymphoma described based on pathologic classification. By 1990, 40 years later but still before the human genome project, there were 31 types of leukemia and 51 types of lymphoma, all of which had specific treatments. Today, cancer genomics leads the revolution in personalized medicine. It seems likely that such a revolution as occurred for leukemia and lymphoma will not take 40 years for asthma. Increasing the number of genes and their functional effects will increase the ability to predict drug treatment response, and nonlinear discoveries like the vitamin D story might reveal other novel treatments. The use of integrative genomics and systems biology approaches will speed discovery and enhance prediction. The goal of the right drug for the right patient is something that is an achievable translational scientific goal over the next 10 to 20 years provided that investigators address the cost issues that remain at the forefront of any advances in health care.

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