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Drug Allergy (L Mayorga, Section Editor)

Pharmacogenomics as a Tool for Management of Drug Hypersensitivity Reactions

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Abstract

Purpose of review Drug hypersensitivity reactions constitute an unpredictable, serious problem for health care systems as they interfere with drug treatment, limit therapeutic options, and may be life-threatening. In addition to specific patient factors, they are also

influenced by a genetic component. Indeed, a considerable body of knowledge supports the participation of genetic variants in their underlying mechanisms.
Recent findings Latest research on this topic confirms the involvement of specific HLA alleles in non-immediate reactions. Two well-known examples are the HLA-B*58:01 allele in severe allopurinol-triggered reactions, and the HLA-B*15:02 allele in carbamazepine-induced Stevens-Johnson syndrome/toxic epidermal necrolysis. However, there is a lack of reliable genetic markers for immediate reactions and for hypersensitivity to NSAIDs.
Summary We summarize available information on the genetics of drug hypersensitivity reactions, highlighting regulatory agencies recommendations when available. We include some comments about new technological tools that should be implemented in the study of these reactions.

Introduction

The WHO defined an adverse drug reaction as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function" [1]. Edwards and Aronson further classified these reactions in several categories, which include predictable and dose-dependent (type A, augmented) reactions, and unpredictable, not dose-dependent (type B, bizarre) reactions [2]. Drug hypersensitivity reactions (DHRs) belong to the second group, and encompass a set of pathologies triggered by immunological (allergic reactions) or non-immunological mechanisms (non-allergic reactions) [3, 4].

DHRs also may be labeled as immediate (IRs) and non-immediate reactions (NIRs) when considering the interval elapsed between last drug intake and the elicitation of clinically observable symptoms [5, 6].

IRs can be triggered by immunological or non-immunological (pharmacological) mechanisms. The prototype of immunological IRs is represented by specific IgE antibody-mediated reactions to betalactam (BLs) antibiotics [7], which appear within the first hour, and with clinical entities including urticaria and/or angioedema, and anaphylaxis/anaphylactic shock. Non-immunological IRs are represented by cross-reactive hypersensitivity (CRH) to nonsteroidal anti-inflammatory drugs (NSAIDs), in which the underlying mechanism has been linked to inflammatory mediators release subsequent to cyclooxygenase (COX)-1 inhibition without immunological recognition (pharmacological mechanism) [8]. However, NSAIDs are also responsible for IgE-mediated IRs (selective reactions) [8].

NIRs, which are mediated by T cells, appear more than 1 h after last drug intake and comprise a clinically heterogeneous set of conditions that, in addition to mild reactions, include severe and potentially life-threatening entities such as Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) [5, 6].

DHRs represent a serious problem in health care practice as they may difficult drug treatment, limit therapeutic options, and cause complications during hospital stay [9, 10]. In addition to specific patient factors such as sex, age, ethnicity, concomitant drug treatments, and environmental factors [11], the risk of developing DHRs is also modulated by individual genetic background [12, 13]. Consequently, the identification of genetic variants associated with drug response could be used in genetic testing to prevent DHRs and to avoid its potential effects on therapy, leading to a personalized treatment. In fact, personalized medicine has become the great promise of pharmacogenomics.

Here we will summarize the main aspects of the pharmacogenomics of most frequent types of DHRs, including CRH to NSAIDs. We will also include some recommendations for genetic testing, and comments on new technological approaches that may shed light on the underlying mechanisms or have a potential role in prevention/diagnosis. We think this manuscript will be of interest not only for professionals in the allergy field who deal daily with these reactions, but also for those who develop their activity in related settings, and for general practitioners.

Immediate reactions

Due to their low molecular weight, drugs or drug metabolites need to conjugate with proteins to trigger an immunological reaction mediated by specific IgE antibodies (immune-mediated IRs) or T cells (NIRs), a process which requires a previous exposition to the culprit drug (sensitization). During sensitization, dendritic cells process drug-protein adducts, which are presented to a Th2 phenotype lymphocytes. Th2 cells induce the production of drug-specific IgE antibodies (sIgE) by plasma cells, which are finally bind to basophils and mast cells specific receptors. In a subsequent contact, the drug-protein complex may be recognized by at least two adjacent sIgE, triggering an intracellular signaling pathway that culminates with basophil/mast cell degranulation. Consequently, these cells release a number of pro-inflammatory preformed (histamine, chymase, and tryptase) and de novo synthesized mediators (prostaglandin D2 and cysteinyl leukotrienes) which are responsible of the clinical symptoms [14].

A recently published PRISMA-compliant systematic review identified a total of 19 studies dealing with the genetics of IRs to BLs, with only four of them replicating the discovery findings in a different, independent population [15••]. Of particular interest is the association of IRs to BLs with atopy, as it has been shown by the associations between *IL4RA* Q551R and I50V variants and total and specific IgE to prevalent allergens, respectively [16]. In addition, the rs11125 variant in *LGALS3*, which encodes a β-galactoside-binding lectin that binds to IgE, has been reported to predict IRs to BLs in two populations from Spain and Italy [17•]. The major allele of the rs2066845 variant in nucleotide-binding oligomerization domain containing 2 gene (*NOD2*) was associated with a higher IgE level in an Italian population [18]. Another study found significant associations between variants in *IL13* (-1055C>T and R130Q) and in the α-chain of the IL4 receptor variants (*IL4RA* I50V and Q551R) with IRs to BLs [19]; and the same group also described higher specific IgE levels in carriers of the minor allele of the promotor *TNFA* polymorphism -308G>A [20]. Other associations with pro-inflammatory cytokines and related genes (IL4, IL13, IL4RA, IL10, IL18, IFNγ, and STAT6) have been described in different populations [21–28].

To the best of our knowledge, only one genome-wide association study (GWAS) has been conducted on immediate BL allergy, which found an association with polymorphisms in the *HLA-DRA* (rs7192 and rs8084) and *C5* (rs17612) genes in Spanish and Italian populations [29•].

There are few studies on the genetics of potentially IgE-mediated reactions to NSAIDs. However, we have reported that two intronic variants (rs2241160 and rs2241161) in centrosomal protein of 68 kDa (*CEP68*) were significantly associated with an increased risk of immediate selective reactions to these drugs [30]. Interestingly, variants in this gene were previously associated with two different clinical entities induced by CRH to NSAIDs in Korea and Spain [31, 32]. However, further research is needed to shed light on the reasons of this association.

Non-immediate reactions

In addition to T lymphocytes, other cells from the immune system are also involved in NIRs. Thus, NIRs may be grouped at least into four categories: (1) Type IVa, with T cells producing interferon (IFN)-γ-activated macrophages, being eczema the typical clinical manifestation; (2) Type IVb, mediated by T

cells producing Th2 cytokines (mainly IL 4 and IL 5), which in turn induce B cells to produce antibodies, and mast cell and eosinophil responses, mainly in DRESS, maculopapular exanthema (MPE), and bullous exanthema; (3) Type IVc, induced by CD4+ and CD8+ T lymphocytes, which produce cytotoxic mediators that lead to keratinocyte apoptosis in MPE and massive apoptosis in SJS/TEN; and (4) Type IVd, characterized by neutrophil activation and recruitment induced by T cells through the production of the chemokine CXCL8, being AGEP the typical clinical entity [33].

Most genetic associations between NIRs have been found with HLA alleles [34••]. In this section we will focus on main genetic findings in DHRs induced by allopurinol, antiepileptics, and antiretrovirals, the most frequently involved drugs in NIRs. The Clinical Pharmacogenetics Implementation Consortium (CPIC) published several guidelines that are periodically updated and try to incorporate pharmacogenetics information into clinical decisions (https://cpicpgx.org/).

Allopurinol

The anti-hyperuricemic xanthine oxidase inhibitor allopurinol is the most frequent medicine triggering SJS/TEN [35]. The *HLA-B*58:01* allele has been consistently associated with SJS/TEN mostly in Asian populations [36], although data on European patients are also available [37, 38]. In fact, in a recent meta-analysis of 21 studies in *HLA-B*58:01* carriers suffering from allopurinol-induced severe cutaneous NIRs, a summary OR of 82 was found, rising to 100 in matched and population-based studies [39••].

The robustness of these associations supports that this marker takes a central role in allopurinol-induced SSJ/TEN pathogenesis, with different hypothesis aiming to explain how the T cell receptor and the HLA system interact with peptides and drugs, and elicit an immunological reaction [40–42].

Several studies have proposed the screening of the *HLA-B*58:01* allele to reduce the incidence of severe cutaneous allopurinol-triggered NIRs [43•, 44•, 45, 46]. However, currently their routine testing in patients being prescribed allopurinol does not appear to be cost-effective in Europe [47•], although different results have been found in a retrospective, population-based cohort study in Taiwan [48]. In fact, the authors found that HLA-B*58:01 genetic screening showed an adequate cost-effectiveness ratio prior to therapy with urate-lowering which also included lifetime saved and quality-adjusted life-years gained [48].

The CIPC guideline concerning HLA-B genotyping and allopurinol dosing, initially published in 2013 [49], has been recently updated [50]. According to Han Chinese and Thai populations data, the positive predictive value for *HLA-B*58:01* testing is around 1.5% and the negative predictive value is 100% [51], which implies that a substantial number of individuals will not develop NIRs subsequent to allopurinol treatment. More research is needed to improve the positive predictive value in order to differentiate the carriers of the *HLA-B*58:01* allele that will present a reaction from those that will not.

Finally, the *HLA-B*58:01* allele has also been proposed as a risk factor for other severe and mild NIRs in Han Chinese individuals [52].

Antiepileptics

Most NIRs to aromatic antiepileptic drugs have been reported for carbamazepine (CBZ), phenytoin (PHT), and lamotrigine (LTG).

Carbamazepine

NIRs to CBZ appear in up to 10% of patients, with skin being the most commonly affected organ [53]. In addition to mild entities such as MPE, these reactions also include SJS/TEN and DRESS [53]. The HLA-*B*15:02* allele has been strongly associated with CBZ-induced SJS/TEN in different Asian populations, in which this allele is frequent. Thus, the US Food and Drug Administration (FDA) recommend genetic testing for *HLA-B*15:02* before initiating treatment in subjects with Asian origin [54, 55]. It has been proposed that the interaction of the drug with T cell receptors and three specific residues on the peptide-binding groove of *HLA-B*15:02* directly participates in the pathogenesis of CBZ-induced SJS/TEN [41, 56].

In the first study reporting the strong association between *HLA-B*15:02* and CBZ-triggered SJS/TEN, this allele was present in 100% of Han Chinese patients suffering from the reaction, and only in 3% of CBZ-tolerant patients and in 8.6% of the general population [57]. This association has been further replicated in the same ethnic group [58, 59] as well as in other Asian countries [60–62], with the exception of Japan [63, 64]. However, this association has not been found in two European studies [37, 65]. Recently, *HLA-B*15:02* has been also associated with CBZ-induced SJS/TEN and MPE (OR = 70.91 and OR = 7.27, respectively) in a Thai population [66]. Interestingly, the *HLA-B*58:01* was significantly linked to CBZ-induced MPE and DRESS in this study [66].

In addition to *HLA-B*15:02*, it has been also proposed to test the *HLA-B*31:01* allele in patients at risk of developing DHRs to CBZ [67•]. In fact, this allele has been associated with CBZ-induced MPE in Han Chinese patients from Taiwan [58], with MPE and DRESS in Europeans [68], and with DRESS in Japanese [69]. A recent meta-analysis concluded that the *HLA-B*31:01* allele is a specific predictor for CBZ-induced DRESS but not for CBZ-induced SJS/TEN [70]. This allele has been recently linked to oxcarbamazepine-induced DRESS [71].

Phenytoin

*HLA-B*15:02* has also been associated with PHT-induced SJS/TEN in Han Chinese [72] and in a Malay population [73], and in a lesser extent with LTG-induced SJS/TEN in Han Chinese [72]. The missense rs1057910 variant in *CYP2C19*3* has been linked to an accumulation of PHT in patients suffering from severe cutaneous DHRs to this drug in a study comprising patients from Taiwan, Japan, and Malaysia [74].

A recent manuscript has found a strong association between the intronic variant rs78239784 of the complement factor H-related 4 gene (*CFHR4*) with PHT-induced MPE in Europeans [75].

Another interesting point is how allele combination may help to predict NIRs. Thus, in a study on PHT-induced severe cutaneous reactions, the *HLA-B*13:01*, *HLA-B*56:02/04*, and *CYP2C19*3* alleles were found to be strong risk factors for DRESS [76]. Carriers of the allele *CYP2C9*3* were also at risk of developing SJS/TEN only if they had Chinese ancestry [76]. However, in Thai patients this variant was not found to be associated with PHT-induced DRESS but with SJS/TEN [77]. Recently, concurrent testing of the *CYP2C9*3*/*HLA-B*13:01*/*HLA-B*15:02*/*HLA-B*51:01* alleles has shown an appropriate sensitivity and specificity to be potentially used as a predictive tool to prevent PHT-associated DHRs in East Asian populations [78].

Information concerning the interpretation of genetic testing and available tests for CBZ and PHT can be found in the CPIC guidelines [79, 80].

Lamotrigine

In contrast to CBZ-induced severe cutaneous DHRs, the allele *HLA-B*15:02* was not found to be associated with LTG-induced SJS/TEN and MPE in two independent studies carried out in Han Chinese populations [81, 82]. However, in a recent meta-analysis, *HLA-B*15:02* was associated with LTG-induced SJS/TEN in Chinese patients, whereas the variant *HLA-B*24:02* was associated with the risk of both SJS/TEN and MPE [83••]. In addition, *HLA-B*33:03* was protective in Chinese and Korean populations [83••], contrary to the findings of a Thai study that associated it with MPE [84]. Finally, the *HLA-A*02:01:01/HLA-B*35:01:01/HLA-C*04:01:01* haplotype has been linked to LTG-induced MPE in Mexican Mestizo patients [85].

Antiretrovirals

Abacavir, a nucleoside reverse transcriptase inhibitor used in combination therapies for the treatment of HIV-1 infections, is usually well tolerated; however, 5–7% of exposed patients developed DHRs within the first 6 weeks after initiation of abacavir [86]. The first links between abacavir-triggered DHRs and the *HLA-B*57:01* allele were reported in 2002 on Australian and North American patients [87, 88], and the first study showing that the pre-prescription of pharmacogenetic testing for this allele could be cost-effective was published in 2004 [89]. Thus, the FDA recommended in 2008 a *HLA-B*57:01* screening test for all patients prior to starting abacavir [90••]. In fact, the associations of this allele with DHRs to abacavir have been also described in other populations [91–95]. As *HLA-B*57:01* is significantly less common in HIV-infected Koreans than in other populations, testing this allele may be a less useful tool for screening in Asians patients, who have a low prevalence of this variant [96].

A guideline on HLA-B genotyping and abacavir dosing is available [97], and has been recently updated [98].

SJS/TEN has been associated with the administration of nevirapine, another reverse transcriptase inhibitor used in HIV-1 infections. The *CYP2B6* c.983T>C polymorphism has been associated with nevirapine-induced SJS/TEN in Africans, and considered an ethnic-specific predisposing factor [99]. The intronic variant rs76228616 in the TRAF3 interacting protein 2 gene (*TRAF3IP2*), which encodes for a protein involved in regulating responses to cytokines by members of the Rel/NF-κB transcription factor family, has also been recently linked to nevirapine-triggered SJS/TEN susceptibility [100].

Cross-reactive hypersensitivity to NSAIDs

According to the timing of the reaction, CRH may have an immediate outcome or appear several hours after the last drug intake [101].

As COX-1 inhibition and subsequent cysteinil-leukotrienes (CysLTs) release have been proposed as key players in CRH to NSAIDs [102], most genetics studies have evaluated SNPs related to the arachidonic acid (AA) metabolic pathway following a candidate gene strategy [103]. NSAIDs-induced acute urticaria/angioedema (NIUA) is the most frequent entity induced by NSAIDs

hypersensitivity [104–106]; however, most available genetic information refers to NSAIDs-exacerbated respiratory disease (NERD) [103]. Another drawback for most genetic studies on CRH to NSAIDs is that a second population to replicate potential findings had not been usually included [103].

Concerning the AA pathway, two variants (rs5789 and rs10306135) in the prostaglandin-endoperoxide synthase gene, which encodes COX-1, were found to be associated with NERD [107]. Increased eosinophil expression levels of the leukotriene C4 synthase gene (*LTC4S*) were found in two studies in bronchial biopsies from NERD patients [108, 109]. These findings were further replicated in another NERD population and associated with the minor allele of the *LTC4S* promotor polymorphism rs730012 [110]. However, this association was not found in other NERD populations [111–114] or in NIUA patients [115]. Regarding lipoxigenases, we found an association between NIUA and the rs1132340 variant in arachidonate 5-lipoxygenase (*ALOX5*) activating protein [115], which was not found in a previous Korean study in NERD patients [113]. The promotor polymorphism rs7220870 (-272C>A) in *ALOX15* was associated with NIUA in two independent populations from Spain [115]; however, this variant was not linked to NERD in Korea [94]. Another variant in *ALOX15* (rs3892408) was also associated with NERD in a Spanish population [107]. Other associations have reported between NIUA and thromboxane A (TBXA) synthase 1 gene (*TBXAS1*, rs6962291) [116], and in the prostaglandin receptors genes *PGE1R* (rs3810253 and rs3810255), *PGER2* (rs1254598), and *PGDR* (rs8004654) [115].

Several associations with SNPs in *PGR1-4* and *PGGIR* have also been reported for NERD [117, 118]. Concerning CysLTs receptors, three SNPs in the *CYSLTR1* promotor (-634C>T, -475A>C, and -336A>G) have been associated with NERD [117, 118], whereas the synonymous rs320995 variant has been linked to NIUA [115]. SNPs in *CYSLTR2* affecting gene expression have been associated with NERD [119]. The minor allele of the 795T>C *TBXA2R* polymorphism was found to be higher in NERD than in ASA-tolerant asthmatics [120], and the *TBXA2R* variant -4684T>C was associated with NIUA [121].

Apart from candidate genes, other associations have been reported between NERD and NIUA and the missense SNP rs10156191 (Thr16Met) in the diamine oxidase gene (*DAO*) [122], and the 8956 C>G variant has been recently linked to NIUA in Brazilian patients [123]. We have also found in a Spanish population some associations between NIUA and SNPs in genes involved in mast cell activation such as phospholipase A2 group IV A (*PLA2G4A*, rs12746200), phospholipase C gamma 1 (*PLCG1*, rs2228246), and TNF receptor superfamily member 11a (*TNFRS11A*, rs1805034) [124]. Two intronic polymorphisms in the epithelial cell apoptosis-related gene gasdermin B (*GSDMB*, rs870830 and rs7216389) were statistically associated with FEV1 in a Korean NERD population [125]. Other associations have been described between NERD and *IL4* (-589T>C) [126], and with CCTTT repeats in nitric oxide synthase 2 gene (*NOS2A*) [127]. As non-immunological mechanisms have been demonstrated to take part in the pathogenesis of CRH to NSAIDs, it is intriguing that some studies have linked NERD to some alleles from the HLA system [128, 129].

Up to now three GWAS on CHR to NSAIDs are available. The first one was published in 2010 in a Korean population of NERD patients, and found an interesting association between the non-synonymous SNP rs7572857 (Gly74Ser) in *CEP68* and the decline in FEV1 [31]. We

further evaluated the genetic variability in this gene and found evidence of association between 17 SNPs and NIUA, including the Gly74Ser variant, whereas 8 of these polymorphisms were marginally associated with NERD [32]. As stated before, we have also found variants in this gene associated with selective reactions to NSAIDs [30]. *CEP68* participates in centrosomal cohesion and epidermal growth factor signaling mechanisms [130, 131]; however, the cause of this association needs to be clarified at the molecular level. The second GWAS was also performed in NERD in Korea, and found the most significant association with *HLA-DPB1* rs1042151 (Met105Val) [132]. In addition, this variant also showed a gene dose effect for the decline of FEV1 after aspirin challenge, supporting a potential role for HLA-DPB1 in the etiology of NERD [132]. We have performed the last available GWAS on CRH to NSAIDs, focusing on NIUA and including two independent populations from Spain and Taiwan [32]. The most interesting finding was a suggestive association in Spanish patients with *RIMS1*, which encodes a protein from the RAS gene superfamily member that regulates synaptic vesicle exocytosis; whereas in the Han Chinese group from Taiwan, it was with *ABI3BP* [32]. Most of suggestively associated regions are linked to Ca^{2+}, cAMP, and/or P53 signaling pathways [32].

New available technological approaches

Personalized medicine aim should not be confounded with the hypothetical design of an individual specific treatment for every patient to maximize drug effectiveness and to minimize unwanted responses. In fact, the US National Research Council has proposed the term "precision medicine," defined as the "ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease, in the biology and/or prognosis of those diseases they may develop, or in their response to a specific treatment" [133].

Outstanding advances achieved in molecular biology techniques over recent years are making it possible to begin to elucidate the genetic mechanisms leading to the development of DHRs in some individuals but not in others; however, as our knowledge of individual disease-predisposing factors is still sparse, precision medicine is not currently in clinical use for most pathologies, including DHRs.

As stated, genetic studies on DHRs have been usually performed following a candidate gene strategy without including replication populations. Concerning GWAS, although they have been successful in elucidating genomic regions influencing some pathologies [134••], they do not assess rare variants that need sequencing to be identified and are widely thought to influence complex diseases [135–137]. The need of high-throughput, faster, and cheaper sequencing methods was evidenced with the completion of the human genome project [138, 139], which finally guided the development of parallel or next-generation sequencing (NGS) and bioinformatics tools [140]. The description of fundamentals of NGS is beyond the aims of this manuscript although comprehensive revisions about this topic are available [141••, 142].

As for other pathologies, genomic sequencing in DHRs patients would improve not only our understanding of the association between genetic

variability and individual drug response, but also its interpretation and translation to diagnosis and clinical decisions. NGS technologies, including whole exome and whole genome sequencing (WES and WGS, respectively), are transforming biomedical research and have shown their potentiality in a variety of human diseases; however, they have not yet been applied to the discovery of variants involved in DHRs.

In addition to genotype changes (WES and WGS, and targeted sequencing), other NGS techniques could evaluate phenotypic changes induced by DNA methylations (Methyl-Seq) or by histone modifications affecting the interactions DNA-proteins such as transcription factor binding (chromatin immunoprecipitation sequencing, ChIP-Seq). These phenotypic changes may affect gene expression-related processes or RNA expression, which can be assessed through RNA sequencing (RNAseq) [143••]. Changes in gene expression during the acute phase of different types of DHRs have been described [144].

Finally, an interesting clinical application of NGS in DHRs refers to HLA typing, which could be a powerful clinical predictive tool [145, 146••] especially in severe, life-threatening diseases.

Conclusion

The identification of reliable genetic markers to predict DHRs is a crucial issue for healthcare professionals and represents an important goal for the pharmaceutical industry.

Up to now most of them have been identified for NIRs, with a central place for alleles from the HLA system [146••]. In fact, FDA recommendations for genetic testing to prevent DHRs are mainly related to these alleles, and pharmacogenomic biomarkers are increasingly included in drug labeling. An exhaustive table of such biomarkers has been updated in June 2018 and is available in PDF format (https://www.fda.gov/downloads/drugs/scienceresearch/ucm578588.pdf).

Although substantial information exists for IRs and for CRH to NSAIDs, genetic variants with a clinical utility to identify or prevent DHRs have not been identified yet, even if some of these reactions can also be life-threatening.

Two main approaches have been used in the study of the genetic basis of DHRs, i.e., candidate gene and GWAS. Both have shown to be of utility in pharmacogenetics/pharmacogenomics but they also have important limitations, mainly related to statistical power and their inability to detect rare variants, which is widely accepted to play a substantial role.

NGS technologies are increasingly used in the study of several human diseases for diagnostic purposes and for identifying potential therapeutic targets. With the reduction of sequencing costs, it is expected that these approaches could be generally used in other clinical settings, including the field of DHRs. The implementation of NGS in the clinics may lead to simultaneous, quick testing of many genes at relatively low costs. International collaboration efforts will be needed to circumvent difficulties related to sample size when evaluating rare variants and ethnic/ancestry influence.

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Compliance with Ethical Standards

Conflict of Interest
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Papers of particular interest, published recently, have been highlighted as:
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