REVIEW ARTICLE

Precision medicine in allergic disease—food allergy, drug allergy, and anaphylaxis—PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma and Immunology

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Abstract

This consensus document summarizes the current knowledge on the potential for precision medicine in food allergy, drug allergy, and anaphylaxis under the auspices of the PRACTALL collaboration platform. PRACTALL is a joint effort of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma and Immunology, which aims to synchronize the European and American approaches to allergy care. Precision medicine is an emerging approach for disease treatment based on disease endotypes, which are phenotypic subclasses associated with specific mechanisms underlying the disease. Although significant progress has been made in defining endotypes for asthma, definitions of endotypes for food and drug allergy or for anaphylaxis lag behind. Progress has been made in discovery of biomarkers to guide a precision medicine approach to treatment of food and drug allergy, but further validation and quantification of these biomarkers are needed to allow their translation into practice in the clinical management of allergic disease.

Abbreviations
AAAAI, American Academy of Allergy, Asthma & Immunology; AERD, aspirin-exacerbated respiratory disease; AGEP, acute generalized exanthematous pustulosis; BAT, basophil activation test; COX-1, cyclooxygenase-1; CRD, component-resolved diagnostics; CyTOF, time-of-flight mass cytometry; DIHS, drug-induced hypersensitivity syndrome; DRESS, drug reaction with eosinophilia and systemic symptoms; EAACI, European Academy of Allergy and Clinical Immunology; EoE, eosinophilic esophagitis; FA, food allergy; FPIES, food protein-induced enterocolitis syndrome; HLA, human leukocyte antigen; HRF, histamine-releasing factor; IT, immunotherapy; LTC4, leukotriene C4; LTE4, leukotriene E4; LTT, lymphocyte transformation tests; mAb, monoclonal antibody; NGS, next-generation sequencing; OIT, oral immunotherapy; PAF, platelet-activating factor; PGD2, prostaglandin D2; PRACTALL, practical allergy; SCAR, severe cutaneous adverse reactions; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis; TSLP, thymic stromal lymphopoietin.

Observed variations in treatment response in patients with similar clinical characteristics (termed phenotype) reinforce the concept that for treatment, 'one size does not fit all', and encourage the scientific community to determine pathophysiological mechanisms. To this end, classifying disease phenotypes into subclasses termed endotypes (i.e., identifying characteristics defined by specific mechanisms) takes into consideration associated variations in genetic, pharmacologic, physiologic, biologic, and/or immunologic pathways with each phenotype. Treatment that is targeted to an individual based on endotypic profile, rather than phenotypic profile, has now been termed by consensus as precision or personalized medicine (among other terms) (1, 2).

European Academy of Allergy and Clinical Immunology and AAAAI conducted a project focused on evaluating the latest findings in precisely defining the endotype of the allergic and/or asthmatic patient, and the potential for the specialty of allergy/immunology to utilize this precision medicine approach. The PRACTALL approach was utilized to conduct these analyses, in which a panel of experts from these two geographic regions reviewed the relevant literature and harmonized the supporting evidence. PRACTALL examined the potential benefits of applying precision medicine to airway and skin allergic diseases (3), and to food allergy (FA), drug allergy, and anaphylaxis. Although several terms have been used to define this approach, we employ the term 'precision medicine' here. Precision medicine is an emerging approach for disease prevention and treatment that takes into account the individual variability in genes, environment, and lifestyle of each person (1).

Precision medicine in food allergy

There is marked heterogeneity of clinical presentations for FA, which poses a challenge to successful management and treatment; therefore, precision medicine and its goals are highly relevant to the field of FA to improve prevention and therapy. Avoidance of allergenic foods and the use of epinephrine in case of a severe reaction triggered by accidental ingestion remain the standard of care, as there are currently no approved treatments for FA (4–6). Recent technological advances and big data analytics have now made possible further insights into the molecular mechanisms underlying FA giving us new opportunities to further classify FA into phenotypes and endotypes with the end goal of using precision medicine to safely and efficaciously treat individual FA endotypes. Sensitive and specific biomarkers for determination of FA endotypes, risk of developing allergies, reaction severity, and prognosis with treatment are essential components in the path toward precision medicine (7).

Phenotypes in food allergy

Clinical presentation of FA differs with respect to offending allergens, age at presentation, timing of reaction, presence of comorbid atopic diseases, resolution with time, and response to immunotherapy. The following FA phenotypes can be considered in possible approaches toward improving precision medicine in FA.

Age of onset and spontaneous resolution

Food allergies may present in infancy, toddlerhood, childhood, or in adulthood. Certain genetic mutations, genetic variations, gene associations (as determined by GWAS), copy number variations, and epigenetic changes in several genes or gene loci such as *SPINK5*, *FOXP3*, *HLA-DR*, or *HLA-DQ* are associated with early onset of food allergies (8). Other biomarkers such as T regulatory cells and Th1 activity may predict resolution of disease (9). In a study by Lack et al., children who had spontaneous resolution of peanut allergy had high levels of IFN-γ and TNF-α and low levels of IL-4, IL-5, and IL-13 indicating a Th1-type skewing. In contrast, children with peanut allergy showed a Th2-type profile with low levels of IFN-γ and TNF-α and high levels of IL-4, IL-5, and IL-13 (10). A longitudinal study by Ho et al. (11) demonstrated that peanut-specific IgE and SPT wheal size are lower initially in infants with natural resolution of their peanut allergy. In addition, component-resolved diagnostic (CRD) testing show trends for association of IgE to Ara h 1 and Ara h 8 with persistence of peanut allergy (12).

Allergen type and disease severity

More than 170 foods have been associated with food allergies, the most common of which are milk, egg, wheat, fish, shellfish, peanuts, soy, and tree nuts, although regional variations occur. Symptom severity can vary and precision medicine can be used to assist with prediction of severity (13). For example, using CRD, severe reactions during oral food challenges have been shown to be associated with high sIgE to Ara h 2 peanut allergies (14, 15). Absence of IgE to specific components such as Ara h 2 in peanut allergy or Cor a 14 or Cor a 9 in hazelnut allergy may predict absence of or less severe clinical reactivity (16, 17). A study by Vadas et al. found that serum platelet-activating factor (PAF) levels were positively correlated, while serum PAF acetylhydrolase activity was inversely correlated with the severity of anaphylaxis. The study found that 20% of patients with allergic reactions (cutaneous only) had elevated PAF, compared with 100% of those with severe anaphylactic signs with hypotension or serious respiratory involvement. Low levels of PAF acetylhydrolase have been reported in fatal anaphylaxis, and failure of this enzyme to inactivate PAF may help identify individuals at risk of severe or even fatal anaphylaxis (18). In addition, Brough et al. (19) recently showed that patients with peanut allergy had higher levels of IL-9 compared with children who had peanut sensitization or those without atopic disease indicating that IL-9 could potentially be a valuable biomarker for diagnosis.

Comorbid atopic disease

The atopic march (20, 21) suggests an increased risk of atopic dermatitis and FA in children who carry the filaggrin mutation (22, 23), although this mutation alone is not sufficient for the clinical presence of atopic disease.

Endotypes in food allergy

Increased understanding of the cells involved (e.g., epithelial cells, ILC2s, T helper cells, mast cells, eosinophilic cells), cytokines (e.g., IL-4, IL-5, IL-9, IL-13, IL-25, IL-33), antibodies (e.g., IgE, IgG), and other pro-inflammatory molecules (e.g., histamine, tryptase) in allergic mechanisms has led to the development of many drugs that are currently being tested in clinical trials. A well-defined classification based on molecular characteristics can assist with identification of those that may be more likely to see positive outcomes from therapy. Characterization of FA into the following preliminary endotypes can be considered to enable precision medicine (24).

IgE-mediated endotype

IgE-mediated allergies are typically immediate onset with reactions ranging from mild to severe to life-threatening anaphylactic reactions involving single or multiple organs. However, two variants of typical IgE endotypes have been observed:

- *Alpha-gal allergy*: These allergies result in a delayed allergic reaction that occurs 3–8 h after the consumption of red meat and diagnosed by IgE to α-gal (25). Reactions may be mild to life-threatening anaphylactic reactions. Open food challenge with red meat in individuals with sIgE to α-gal resulted in increased tryptase levels and increased expression of CD63 on basophils, indicating their potential use as biomarkers (26).
- *Oral allergy syndrome (pollen-food syndrome)*: Those who have developed allergies to pollen can have symptoms on eating uncooked fruits, raw vegetables, spices, and nuts that have allergens very similar to the offending pollen allergen. Consumption of apples and hazelnuts, in those with birch-pollen allergy, often leads to oral allergy syndrome. Symptoms are generally mild and confined to the oral cavity, but more severe reactions can occur in rare cases. A recent study showed that specific IgG4/IgE ratios to either apple (Mal d 1) or hazelnut (Cor a 1) were higher in those associated with allergy than those associated with tolerance (27).

Non-IgE and mixed endotypes

- *Food protein-induced gastrointestinal endotype:* Food protein-induced enterocolitis syndrome (FPIES) is an example of this endotype. FPIES, diagnosed in infants and toddlers (with spontaneous resolution within 1–5 years), includes reactions with vomiting and diarrhea primarily due to FA to cow's milk or soy. However, FPIES also occurs following ingestion of other foods such as cereal grains, fish, and shellfish (28, 29). Gonzalez-Delgado et al. (30) recently demonstrated that TNF-α and HLA-DR were both increased in patients with FPIES to fish compared with controls.
- *Eosinophilic endotype:* This endotype is best exemplified by eosinophilic esophagitis (EoE). High levels of thymic stromal lymphopoietin (TSLP) have been shown to be increased in patients with EoE and could be helpful for the diagnosis of the disease (31). Anti-TSLP monoclonal antibodies for EoE are being tested in clinical trials. Recently, it has been shown that desmoglein-1, an intracellular adhesion molecule, is downregulated by IL-13 leading to impaired barrier function. Tracking of desmoglein-1 in individuals with EoE can aid in diagnosis and management, leading to improved precision medicine (32). Recent studies have shown that children with EoE have high or very high titers of IgG4 and low, but detectable IgE (24). Moreover, an EoE-like disease has been described that can be distinguished from EoE by *eotaxin-3*, *MUC4*, and *CDH26* expression levels (33).

Biomarkers in food allergy

More specific and sensitive *in vitro* tests for determination of reaction severity, prognosis with immunotherapy, and evaluation of treatment efficacy are under investigation. Basophil activation tests (BAT) and CRD are novel methods that have shown promise (34). Genetic mutations and epigenetic modifications have been associated with FA and may assist with assessing risk of developing allergies as well as diagnosis and prognosis with treatment.

Skin prick tests

Associations between SPT wheal size and severity of reaction on food challenge have been observed in a few studies, but these findings have not been consistent among studies (35, 36). An analysis of a subset of infants from the longitudinal HealthNuts Study found peanut SPT and sIgE levels were significantly associated with persistent peanut allergy. Thresholds for SPT and sIgE were determined to be ≥8 mm and ≥2.1 kU/l, respectively, in children aged 4 years (37). Analysis of over 5000 infants from the HealthNuts Study found that SPTs and sIgEs had a 95% positive predictive value for challenge-proven allergy to peanuts and eggs (38). Results from the LEAP study indicates that increasing SPT wheal sizes (0 mm, 1–4 mm, and >4 mm) are predictive of increased risk of peanut allergy. Along with other markers, SPT wheal size may enable determination of long-term efficacy of early introduction of peanuts (39).

Allergen-specific IgE (sIgE)

Allergen-specific IgE is commonly used, in conjunction with clinical history and SPTs, for diagnosis of FA, thus reducing the need for food challenge. Although correlation between sIgE and severity of reaction has been observed in some studies, the clinical utility of sIgE for assessing risk of severe reactions has not been established (35). In a small clinical study, Vickery et al. (40) demonstrated that high IgE to peanut at baseline was associated with less sustained unresponsiveness in oral immunotherapy (OIT); other groups have not found similar predictive features of IgE and instead are using other biomarkers for potential prediction of outcome for precision medicine practices (41, 42).

CRD

Component-resolved diagnostics may be helpful in the management toward precision medicine care of allergy patients. For example, sIgE to Ara h 2 and Ara h 8 was associated with high and low risk of severe and persistent peanut allergies, respectively (14). A study of children with wheat allergy found that children with severe symptoms had significantly higher IgE antibody levels to ω-5 gliadin, gliadin, and high and low molecular weight glutenin (43). CRD before immunotherapy for milk allergy may also help to identify children with lower probability of a successful outcome, as high IgE levels to α-lactalbumin, β-lactoglobulin, and casein have been associated with lower maintenance dose reached (44). Further refinement of CRD and high-resolution epitope microarrays could allow for improved accuracy in the future.

BAT

In basophils obtained from peanut-allergic children who were challenged with peanuts, increased levels of activation markers, such as CD63 or CD203c, were observed (45). Santos et al. found that when basophils were sensitized with plasma from peanut-allergic (but not from peanut-sensitized) children were exposed to peanuts, dose-dependent activation occurred. The ratio of the percentage of $CD63^+$ basophils after stimulation with peanut and after stimulation with anti-IgE was found to be correlated with disease severity (46). Mukai et al. (47) found that blood stored in heparin tubes at 4°C for 24 h can be used for BATs to measure upregulation of basophil CD203c and induction of a $CD63^{hi}$ basophil populations, which should help with ease and standardization of protocols.

IgG4

Increases in IgG4 with immunotherapy are associated with successful clinical outcomes. A study found that an increase in the IgG4 concentration to milk components during treatment indicated effective desensitization (44). In another study, it appears that mast cells became activated on exposure to peanuts and IgG4 depleted plasma from peanut-sensitized children, suggesting a role for IgG4 in tolerance. Further, addition of post-OIT sera containing specific IgG antibodies inhibited IgE-mediated allergic reactions (46). The ratio of IgG4 : IgE has found promise in several studies of immunotherapy. An early introduction of peanuts to infants decreased the incidence of peanut allergy and was associated with higher peanut-specific IgG4 : IgE ratio (48). Monitoring these ratios may therefore have some value in precision medicine applications to the natural history of FA.

Genetic markers

Genetic predispositions in the following loci have been found to be associated with FA and atopy: *Filaggrin*, *FOXP3*, *STAT6*, *SPINK 5*, *IL-10*, and *IL-13* (49). A GWAS of patient-reported FA in a large cohort of children from the Chicago Allergy Study identified peanut allergy-specific loci in the human leukocyte antigen (HLA) DR and DQ regions at 6p21.32, tagged by rs7192 and rs9275596. Both significantly affected DNAm in the *HLA-DRB1* and *HLA-DQB1* genes and increased population attributable risk by 19- 21% (50).

Epigenetic markers

Studies of peanut-allergic individuals undergoing OIT have found increases in FOXP3 T regulatory cells and decreases in FOXP3 methylation in patients who attained desensitization (41). Epigenetic modification of *FOXP3* and other gene loci have been shown to alter Treg function (41, 51) and could be associated with FA and response to therapy (52). A genome-wide DNA methylation study by Martino et al. (53) used blood mononuclear cells obtained from individuals undergoing oral food challenge and found a DNAm signature of 96 CpG sites that predicted oral food challenge outcomes with increased predictability compared with SPTs and sIgE. An epigenome-wide association study of cow's milk allergy in a subset of children from the Chicago Food Allergy Study and from the Boston Birth Cohort indicates that specific gene loci are associated with cow's milk allergy (54). Another study found that tolerance in children with IgE-mediated cow's milk allergy was characterized by a distinct Th1 (IL-10 and INF-γ) and Th2 (IL-4 and IL-5) cytokine gene DNA methylation pattern (52).

Mediators

Elevated serum tryptase and histamine have been found in some, but not the majority of cases of FA anaphylactic reactions and cannot be considered a reliable marker of FA-related anaphylaxis (55–57). Urinary metabolites of histamine are more stable than plasma histamine and are being explored as a diagnostic tool for FA reactions (56, 58). In one study by Sato et al. (59), threshold of histamine release (defined as the minimum concentration of food antigen to induce a 10% net histamine release) was proposed to predict egg white, milk, and wheat FA.

Summary

Food allergy classification systems that take into account the heterogeneity of FAs are a crucial first step to enable precision medicine. With greater understanding of the key immune cells and molecules involved in FA, we are making progress in developing a composite set of biomarkers that could serve to predict, manage, and monitor prevention and treatment strategies in FA. Changes in immune cells (e.g., basophils from peripheral blood and T cells), cytokine profiles, effector molecules (e.g., histamine, tryptase), and DNA methylation of key loci are being evaluated to determine their roles in allergy and desensitization with immunotherapy. The key genetic and environmental risks of developing FA are being identified and biomarkers to determine treatment prognosis and efficacy can assist to further refine the options for immunotherapy.

Precision medicine in drug allergy

Several facets of precision medicine apply directly to the field of drug allergy. At a pharmacogenetics level, patients can be

identified to be at high risk of developing severe drug hypersensitivities. From a diagnostics perspective, patients who are inappropriately labeled as being allergic to certain medications can be proven to be tolerant of these medications primarily via drug skin testing and drug challenge, thus sparing the expense and side-effects of alternative therapies. Finally, from a therapeutic perspective, patients who are hypersensitive to specific medications may actually have conferred benefits from treatment with these medications via desensitization procedures. The use of molecular and pharmacogenetics tools can assist in the delivery of precision medicine for drug allergies.

Phenotypes in drug allergy

Hypersensitivity reactions to drugs may vary extensively in presentation. While clinical characteristics of many drug allergic reactions have been well defined, no agreed-upon system to organize these reactions into phenotypes has been developed. Nevertheless, utilizing clinical characteristics and timing of reactions to drugs, the following phenotypes can be considered.

Immediate-onset drug allergy

Immediate-onset drug allergic reactions manifest within 1–6 h of exposure to a drug, and present with cutaneous (e.g., flushing, pruritus, urticaria, angioedema), respiratory, and/or gastrointestinal symptoms, and anaphylaxis. Immediate drug allergic reactions may be due to several mechanisms including but not limited to IgE-mediated reactions, direct mast cell/basophil activation, and cyclooxygenase-1 (COX-1) inhibition. Two distinct presentations of IgE-mediated drug allergy reactions have emerged: (1) reactions that occur after multiple doses of the drug; and (2) reactions that occur with exposure to the first dose. IgE-mediated reactions to penicillin or carboplatin present after several exposures, whereas allergy to the monoclonal antibody (mAb) cetuximab manifests on the first dose in patients with pre-existing IgE antibodies to the carbohydrate determinant, galactose-alpha-1,3-galactose, present on the humanized antibody. Taxane reactions can occur at first exposure in atopic cancer patients, and sensitization is thought to occur through prior environmental exposure (60). Direct mast cell/basophil activation can present clinically identical symptoms to those of IgE-mediated reactions, via IgE-independent mechanisms. Complement activation and generation of anaphylatoxins C3a and C5a, which activate mast cells through complement receptors, can occur in contrast media reactions, and in reactions to over-sulfated chondroitin sulfate contaminated heparin (61). Recently, the human G protein-coupled receptor MRGPRX2 has been identified as a mast cell receptor capable of causing histamine release in response to drugs containing THIQ motifs such as quinolones (ciprofloxacin and levofloxacin), neuromuscular blocking agents, and icatibant (62). Finally, patients with various forms of NSAID hypersensitivity can have immediate reactions induced by mediators generated by COX-1 inhibition (63).

Delayed-onset drug allergy

In delayed-onset drug allergy, reaction usually occurs days to weeks after allergen exposure. These reactions have heterogeneous clinical manifestations, but may be subdivided into those with isolated, single-organ involvement or systemic, multi-organ involvement.

Cutaneous reactions are the most common manifestation of drug allergy. Numerous clinical phenotypes exist, with the most common being maculopapular exanthems, fixed drug eruption, urticaria, angioedema, and acneiform reactions (64). Delayed drug reactions may also affect a single-organ system including the hepatic, pulmonary, renal, and hematologic systems (65). Numerous mechanisms exist for these single-organ delayed drug reactions, ranging from T cell-specific delayed hypersensitivity responses to idiosyncratic reactions or those due to toxic metabolites, some of them determined by genetic specificity.

The most severe drug reactions are referred to as severe cutaneous adverse reactions (SCAR) and include three major syndromes: drug reaction with eosinophilia and systemic symptoms (DRESS or DIHS for drug-induced hypersensitivity syndrome), acute generalized exanthematous pustulosis (AGEP), and Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN). SCAR commonly have multi-organ involvement including but not limited to mucosal, hepatic, hematologic, and renal systems. The risk of SJS/TEN is higher in persons expressing certain HLA haplotypes, and patients with HIV, cancer, or systemic lupus erythematosus; mortality rates for SJS/TEN can be up to 90% and may be predicted by a validated measure of disease severity, the SCORETEN (66). Persistent sequelae occur in 50–90% of survivors, involving scarring of the conjunctiva and eyelids, and dermatologic, dental, urogenital, and pulmonary complications as well as psychological impact (67). The immunopathogenesis of SCAR is not completely understood, but may involve T cell-mediated drug hypersensitivity and heterologous immunity (e.g., molecular mimicry between prior virus and current drug exposure) in predisposed hosts (68).

Endotypes in drug allergy

Multiple endotypes exist for drug allergic reactions, including IgE-mediated reactions, T cell-mediated reactions, pharmacologic interactions, and genetic predispositions. Well-defined endotypes are discussed below.

IgE-mediated endotype

IgE-mediated reactions depend on sensitization to the culprit drug or a cross-reactive substance, with resultant production of drug and epitope-specific IgE. The phenotype is an immediate reaction and may be diagnosed via skin testing most commonly, or in some cases, through *in vitro* specific IgE or BATs (69).

Aspirin-exacerbated respiratory disease (AERD) endotype

Aspirin-exacerbated respiratory disease patients are characterized phenotypically by the classic triad of asthma, nasal

polyposis, and immediate respiratory reactions to aspirin and NSAIDs. This syndrome is characterized by eosinophilic tissue infiltration and excessive production of cysteinyl leukotrienes. Recently, platelet-adherent granulocytes in peripheral blood and nasal polyp tissue of AERD patients have been shown to contribute to the over production of cysteinyl leukotrienes (70).

HLA-associated drug-hypersensitivity reactions

Associations between HLA haplotypes and specific drug reactions have been recognized for several years. Recently, several specific HLA alleles have been associated with specific drug reactions, and screening for certain alleles has been recommended prior to specific drug therapy (71). One of the earliest examples of the specificity of pharmacogenetics in drug allergy was a report in 2004 on the strong association of the HLA-B*15:02 allele and carbamazepine-induced SJS (72). The HLA-B*15:02 allele was present in 100% (44/44) of Han Chinese patients with carbamazepine-induced SJS compared with only 3% (3/101) of carbamazepine-tolerant patients yielding an odds ratio of 2504 with a p-value of 3.13×10^{-27}! While the HLA-B*15:02 allele is predictive in other Asian populations, it is uncommon in those of European descent. Although the HLA-A*31:01 allele was initially reported to be associated with carbamazepine-induced hypersensitivity reactions in subjects of Northern European descent, this association was not consistently seen in subsequent studies (68).

The best example of utilizing a pharmacogenomics approach to reduce drug allergy relates to the association of HLA-B*57:01 and the development of the abacavir hypersensitivity syndrome, which was discovered in 2002 (73, 74). Abacavir is a nucleoside reverse transcriptase inhibitor that has been associated with a multi-organ hypersensitivity reaction in 2–7% of patients. Abacavir hypersensitivity presents with a phenotypic reaction of a delayed drug reaction with symptoms of fever, rash, malaise, and gastrointestinal and respiratory symptoms. Susceptible patients may be identified by carriage of the HLA-B*57:01 allele and by positive patch testing before exposure to the drug. The altered peptide repertoire model has been proposed to explain this reaction in which abacavir sits in the HLA-B*57:01 pocket resulting in a conformational change allowing self-peptides to bind resulting in activation of abacavir-specific T cells (75).

Biomarkers in drug allergy

SPT and sIgE

The most widely used *in vivo* biomarker for IgE/mast cell/basophil drug-hypersensitivity reactions is immediate skin testing. For most antibiotics, skin testing lacks well-defined predictive values. Positive skin tests with nonirritant concentrations are suggestive of drug-specific IgE; however, negative skin tests are less helpful due to unclear negative predictive values (76). In contrast, penicillin skin testing has well-defined negative predictive values with some reports having negative predictive values over 97%, indicating that patients with a history of penicillin allergy and negative skin test have a 3% risk of reaction when challenged with penicillin (77). Anaphylaxis or severe adverse outcomes after negative skin tests are rare (78). Over 85% of patients with carboplatin hypersensitivity reactions have a positive skin test, indicating a strong correlation between skin testing and clinical symptoms in the population of cancer patients with chemotherapy allergy (79, 80).

Because most drug allergens are not captured by skin testing, it is important to develop new and more specific reagents to address drug allergy and hypersensitivity, which is thought to affect close to 10% of the general population and is affecting new target populations exposed to chemotherapy and mAbs (81). Specific IgE to platins have recently been reported, revealing the high cross-reactivity between oxaliplatin and both cisplatin and carboplatin. This provides a rationale for the observation of oxaliplatin IgE-sensitized patients presenting with high rates of cisplatin and carboplatin sensitization without prior exposure (69).

BAT and basophil histamine release assay

Basophil activation test has been used *in vitro* to provide evidence of IgE sensitization. Cell activation has been demonstrated by the expression of CD63 and CD203 markers in the presence of the implicated drug (82). BAT has been used for multiple drugs, including antibiotics and general anesthetics, as well as to identify chemotherapy drug reactions, and may be a useful tool to identify sensitized patients before reactions occur (83). A review of electronic records found that positive serum basophil histamine release assay is a useful marker for cyclosporine responsiveness in patients with chronic spontaneous urticaria (84).

Mediators

Tryptase, the more abundant of the mast cell proteases, is released during mast cell activation and its blood levels correlate with the extent of hypersensitivity drug reactions, with patients presenting higher levels during drug anaphylaxis (85).

Cells

T cell-mediated drug reactions have been investigated through patch testing, lymphocyte transformation tests (LTT) and, more recently, with markers of inflammation such as granzyme B and granulysin. These later biomarkers have also been identified in severe hypersensitivity reactions such as SJS. A recent report indicates that granulysin expression in $CD3^+CD4^+$ T cells, in association with granzyme B and IFN- γ expression, may provide a high sensitivity and specificity for patients with SJS (86).

Patch testing

Patch testing is a useful biomarker of maculopapular rashes, flexural exanthems, fixed drug eruptions, and AGEP. Drug patch testing has been found frequently to be positive in patients with recent histories of DRESS and SJS, due to carbamazepine. Standardization is still lacking and the predictive value is different according to the implicated drug. In TEN, only up to 23% of the cases are positive (87).

HLA markers

International guidelines and the U.S. Food and Drug Administration have recommended prospective screening for HLA-B*57:01 prior to initiation of abacavir (88). A double-blind prospective randomized study assigned patients to undergo HLA-B*57:01 screening and excluded HLA-B*57:01 positive patients from abacavir (89). HLA screening eliminated immunologically confirmed (i.e., patch test positive) patients with a negative predictive value of 100%. In addition, international guidelines and the U.S. Food and Drug Administration have also recommended prospective screening for HLA-B*15:02 prior to initiation of carbamazepine in high risk populations (those of Han Chinese descent and patients in Vietnam, Cambodia, the Reunion Islands, Thailand, India (specifically Hindus), Malaysia, and Hong Kong) (90, 91). Future research using prospective pharmacogenomics screening should help reduce severe, potentially fatal reactions to other drugs.

Summary

In summary, drug allergy is increasing in the 21st century and we are faced with numerous challenges when treating patients with reported drug allergy. These challenges include the lack of standardized drug allergens, the paucity of diagnostic methods with reliable positive and negative predictive values, and the limited treatment options. Specifically, skin testing and other *in vitro* tests including specific IgE, BATs, and lymphocyte activation tests need to be developed for the majority of drugs including not only antibiotics, but chemotherapy drugs, new monoclonal antibodies, and targeted therapies. Measurable mediators of acute and delayed reactions will need to be developed including new mast cell/basophil mediators and soluble chemokines, cytokines, and other molecular targets of inflammation. We anticipate genotyping of patients not only at the time of the reactions but also when exposed to new medications that could carry a potential risk. Desensitization protocols that can provide increased quality of life and increased life expectancy such as in cancer patients will need to be tailored to each patient reaction phenotype/endotype and genotype. We envision that, with these advances of precision medicine, patients with drug allergy will be diagnosed and classified according to the expression of their reactions into different endotypes/phenotypes. In the future, appropriate tools will be used for the management of their symptoms, and treatments will be aimed at reversing the inflammatory reactions. Whether acute reactions will continue to necessitate epinephrine and other mast cell mediator-targeted therapies, and whether delayed reactions such as SJS/TEN will target cytokines, chemokines, and activation pathway molecules for therapeutic intervention will be defined in the next few years.

Precision medicine in anaphylaxis

There is an unmet need for precision medicine in predicting, preventing, and managing anaphylaxis, a life-threatening systemic allergic reaction. In contrast to the disease entities food and drug allergy, anaphylaxis is a syndrome that can be caused by a number of conditions.

Phenotypes in anaphylaxis

Anaphylaxis can be classified based on the eliciting factor, such as foods (e.g., peanuts, tree nuts, and shellfish), hymenoptera venom (e.g., bees and wasps), natural latex rubber, and medications (e.g., codeine, morphine, contrast media, fluoroquinolone antibiotics, and muscle relaxants), but also physical phenomena such as cold exposure. Each of these forms may be modulated by cofactors, such as exercise, medication, or alcohol intake, and comorbidities such as mastocytosis may also alter the clinical presentation (92).

Endotypes in anaphylaxis

Anaphylaxis is primarily IgE-mediated, but anaphylaxis can also be caused by alternate pathways involving mast cells/basophils, or complement. The mechanisms behind these alternate pathways are not well understood and have mainly been studied in animal models. The following endotypes can be considered part of precision medicine approaches in the field of anaphylaxis:

IgE-mediated endotype

This is the best characterized anaphylaxis endotype. In IgE-mediated endotypes, mast cells and basophils, upon cross-linking of sIgE bound to FcεRI, release preformed mediators such as histamine, tryptase, chymase, carboxypeptidase A, and tumor necrosis factor (93). Amplification and prolongation of allergic response occurs in the late phase with the synthesis of lipid-derived mediators such as PAF, prostaglandins, and leukotrienes (94). Currently, there are no tests that have been well established for reliably determining severity to reaction to allergens, but sIgEs, SPTs, BAT, and CRD have shown promise. Observed increases in levels of mediators such as tryptase and PAF are also being further evaluated as diagnostic and prognostic markers (95).

Non-IgE-mediated endotype

Substances such as radiopaque contrast media, antibiotics (e.g., penicillin, cephalosporin), opiates, latex, and others cause hypersensitivity by direct release of mast cell and basophil inflammatory mediators. Such reactions occur without prior sensitization to the allergen and occur in the absence of IgE. Anaphylactoid reactions are derived from the activation of complement or other mechanisms, such as via the bradykinin cascade or by direct activation of mast cells and/or basophils. Two classes of anaphylactoids can be considered:

- *Complement-activated endotype*: Anaphylatoxins such as C3a and C5a, small peptides derived from C3 and C5, respectively, have been associated with anaphylaxis. In a study of wasp-sting anaphylaxis, C3a was found to correlate with severity of reaction (96). PEGylated liposomes can also activate the complement system resulting in acute anaphylactic reactions (97).

- *Complement- and antibody-independent endotype*: Anaphylactic reactions also occur in the absence of complement or antibody production. Over-sulfated heparin has been shown to induce hypotension and anaphylaxis via the bradykinin type 2 receptors by increased production of bradykinin (98). The mechanisms underlying anaphylactic reactions to vancomycin appear to involve phospholipase C and phospholipase A2 pathways (99). Fluoroquinolone antibiotics with a tetrahydroisoquinoline motif activate mast cells directly by binding to MRGPRX2, a G protein-coupled receptor (100).

Table 1 Some Gene associations with food allergies, drug allergies, and/or anaphylaxis

Gene/Gene locus	Association
HLA	• Peanut allergy was associated with *HLA-DQB1*02* and *DQB1*06:03P* (130) • *HLA-B*57:01* is associated with increased risk of abacavir hypersensitivity (131) • *HLA-B*15:02* is associated with increased risk of carbamazepine hypersensitivity (71) • *HLA-B*58:01* is associated with increased risk of allopurinol hypersensitivity (132).
Filaggrin	• *Filaggrin* loss-of-function genetic variants were associated with food allergy (23)
STAT6	• *STAT6* gene polymerism was associated with risk of nut allergy (126)
IL-10	• Persistent form of cow's milk allergy was associated with *IL10-1082G/A* polymorphism (133). • In a Taiwanese population, single nucleotide polymorphisms at -1082A/G and -592A/C of *IL-10* were associated with food allergy (134).
IL-13	• Single nucleotide polymorphism of C-1055T in the *IL-13* gene is associated with increased risk of food sensitization (135)
SPINK5	• *SPINK5* polymorphism is associated with food allergy in children with atopic dermatitis (136)
FOXP3	• Severe food allergy as a variant of IPEX syndrome is caused by a deletion in a noncoding region of the *FOXP3* gene (137) • Oral immunotherapy for peanut allergy leads to desensitization and hypomethylation of FOXP3 (41)
GRIA1	• Polymorphisms in *GRIA1* gene are a risk factor for asparaginase hypersensitivity (125)
N567D STAT3	• Anaphylaxis and high IgE was observed in a patient carrying the *N567D STAT3* mutation (127)

This list is not an exhaustive list and represents highlights of those genes involved in food allergy, anaphylaxis, and drug allergy.

Biomarkers in anaphylaxis

Skin Prick Tests and sIgE

Along with clinical history, SPTs and sIgEs are valuable for diagnosing FA, but correlations with reaction severity or prediction of anaphylaxis have met with mixed results (35). A study found that neither SPT or sIgE were useful for predicting severity and combining SPT and sIgE improved specificity but did not help to achieve clinically useful sensitivity (101). In contradiction, a study of peanut-allergic children found that the mean peanut SPT wheal size and specific IgE level were associated with the severity of reactions on challenge (36).

CRD

Positive test results to both bee and vespid venom are frequently observed during diagnosis of hymenoptera venom allergy making it difficult to identify the causative insect to determine proper immunotherapy. In an analysis of studies of diagnostic methods, CRD showed lower rates of double sensitization to both bee and vespid venom, but inconsistent results were common (102). In peanut-sensitized individuals, sIgE to rAra h 2 was more often found in patients with peanut allergy and anaphylaxis and the ratio of rAra h 2 sIgE to peanut sIgE was found to predict those who will develop anaphylaxis (103).

BAT

The utility of BAT in identifying those with food, drug, and venom allergy has been established by many studies and, in some studies, has been correlated with severity of disease with those undergoing oral food challenge (104). The ability of BAT in identifying those with severe bee and wasp allergy have been demonstrated by studies (105, 106). In a case report, a positive BAT result was obtained 1 month after severe anaphylaxis caused by allergy to patent blue V (107). In a study of peanut-allergic children, BAT significantly correlated with severity of reaction. The study also found that a very low or negative BAT excludes peanut allergy. BAT was found to have a higher diagnostic specificity with comparable sensitivity than IgE for major peanut allergen components (108).

Mediators

The anaphylaxis markers generally measured in clinical laboratories are total tryptase and histamine, but others biomarkers are being explored. Tryptase elevation is usually more pronounced in drug-, anesthetic-, and insect sting-induced anaphylaxis than in food-induced anaphylaxis (18, 109). In a mouse model of allergy and asthma, histamine-releasing factor (HRF) was found to increase inflammation via binding to HRF-reactive IgE on mast cells. The use of peptide inhibitors to block HRF/IgE interaction inhibited HRF/IgE mast cell activation and cutaneous anaphylaxis and airway inflammation (110). In a study of 169 patients with hymenoptera venom anaphylaxis, basal PAF acetylhydrolase level was associated with clinical severity of anaphylaxis (111). In a small study, elevated chymase was associated with anaphylaxis-related death (112). Similarly, in a post-mortem study, tryptase and carboxypeptidase were found to

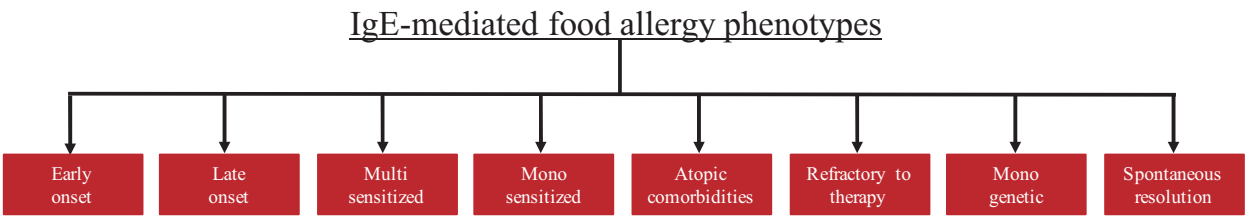

Figure 1 Possible phenotypes of food allergy.

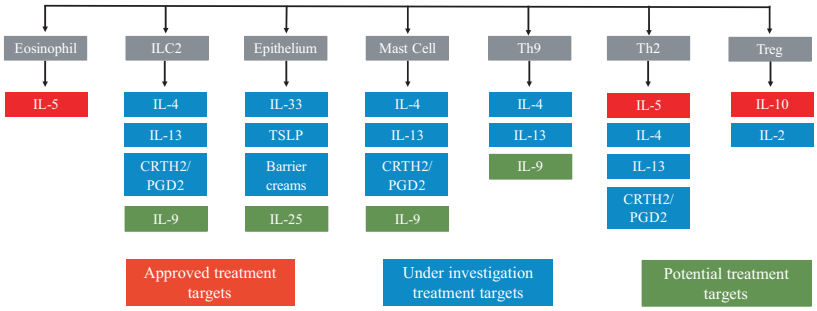

Figure 2 Possible endotypes of food allergy.

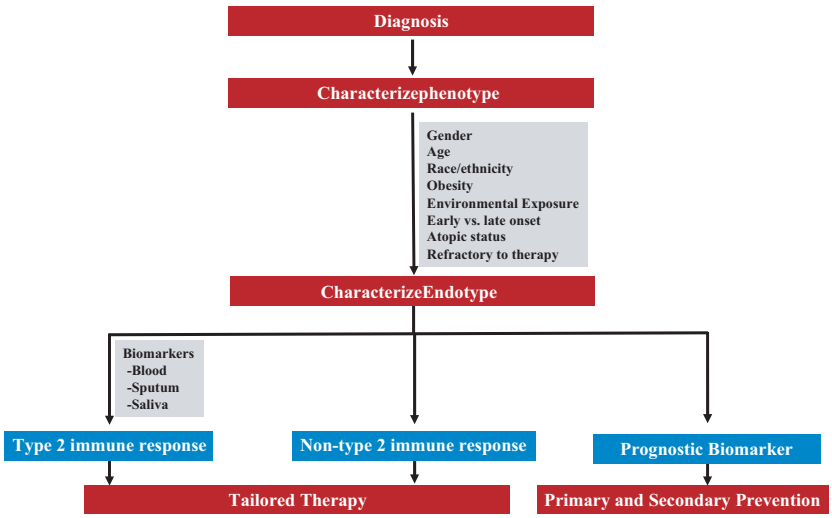

Figure 3 Approach to determining biomarker applications to atopic conditions.

be about eightfold and over twofold greater in those who died due to drug-related anaphylaxis than in nonanaphylactic deaths, respectively (113). Increased basophil histamine release was observed in a case study of exercise-induced anaphylactic shock after exposure to a sensitizing food allergen (114).

The generation of leukotrienes and prostaglandins occurs after inflammatory or allergic mast cell and basophil activation. The major arachidonic acid-derived mediators produced by mast cells leukotriene C4 (LTC4) and prostaglandin D2 (PGD2) are rapidly metabolized to leukotriene E4 (LTE4) and 9-α,11-β PGF2, respectively. These degradation products are relatively stable and can be measured in urine (115). Recently, the detection of 9-α,11-β PGF2 in serum after an anaphylactic episode has been reported and be able to diagnose acute anaphylaxis with better sensitivity and specificity than tryptase or histamine (116). Several cytokines, chemokines, and growth factors have been described to be increased during an anaphylactic episode. However, their sensitivity and specificity for the diagnosis of anaphylaxis are limited due to their production by many cells and their increase in other clinical conditions, such as general inflammation (117).

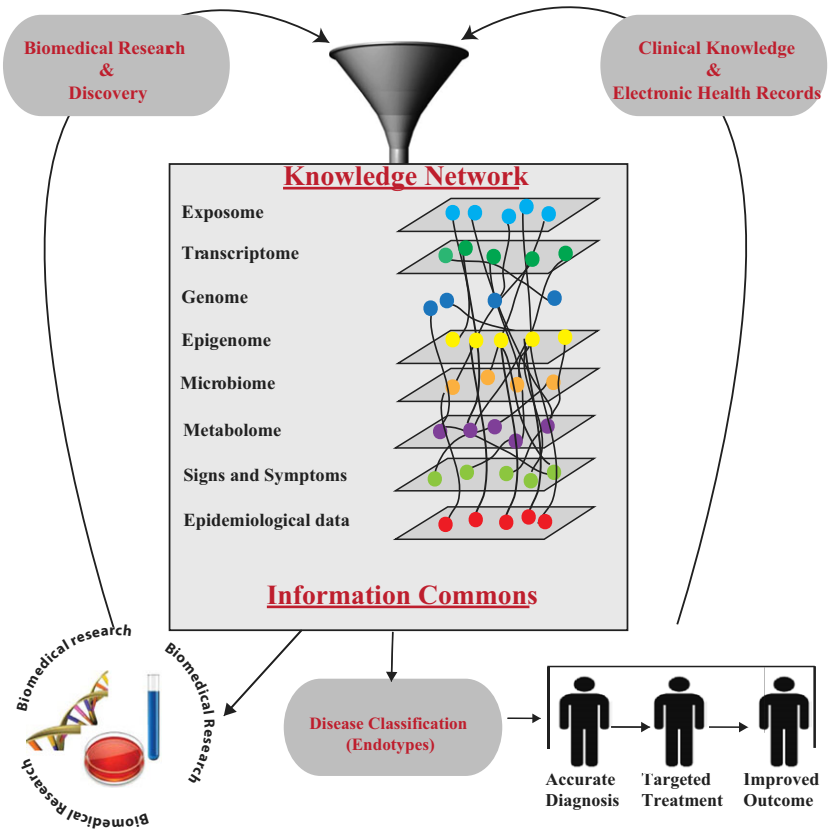

Figure 4 The future of precision medicine in food allergy, drug allergy, and anaphylaxis. By centralizing collection and analysis of vast amounts of data from biomedical research (i.e., 'omics' profiling, biomarkers, sequencing), clinical data from electronic health records, and clinical research, we can understand and differentiate the distinct endotypes of disease among individuals having a similar phenotype and assist with the ability to personalize treatment and prevention to improve health outcome (138).

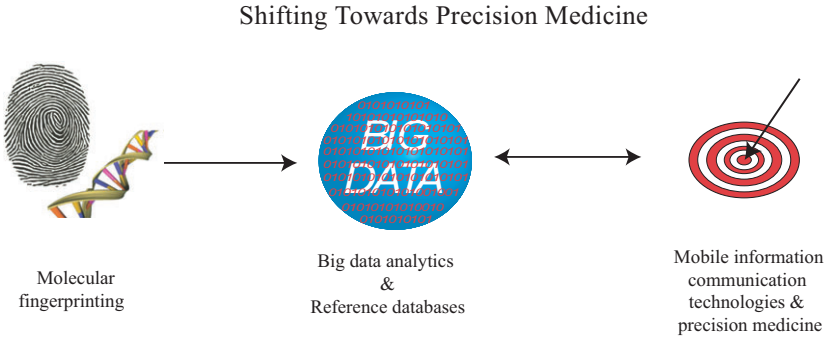

Figure 5 High-throughput specific and sensitive molecular fingerprinting techniques, big data analytics, and reference databases enable actionable clinical decision support for precision medicine.

Genetic markers

Patients at risk of anaphylaxis include patients with clonal (mastocytosis) and nonclonal (mast cell activation syndrome) mast cell disorders (118, 119). In mastocytosis, patients with mutation in the *KIT* gene experience anaphylaxis in 1 of 3 cases. The most common mutation, D816V, can now be established in a blood sample in addition to the bone marrow and the skin, but the allele burden does not correlate with the risk of anaphylaxis (120–122). CRD can also assist in depicting severity in patients with KIT mutation, or with elevated serum tryptase without KIT mutation, in venom allergy (123). Patients with hymenoptera-induced anaphylaxis

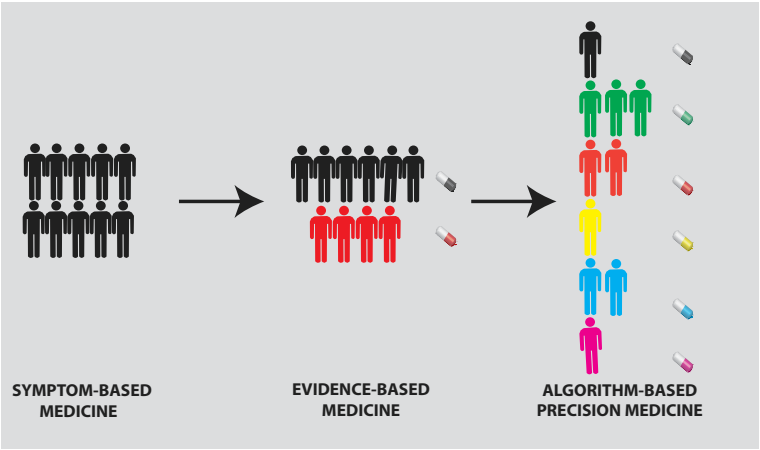

Figure 6 A paradigm shift toward precision medicine: From symptom-based medicine to evidence-based medicine to algorithm-based medicine.

presenting with hypotension are at increased risk of an underlying clonal mast cell disorder (systemic mastocytosis) (119, 124). Statistically significant association between SNPs in the *GRIA1* gene and the occurrence of asparaginase allergy (125) and *STAT6* 3'UTR polymorphism and severity in nut allergic patients (126) have been observed in separate studies. In a case study, an infant with a N567D STAT3 mutation and autosomal-dominant hyper-IgE syndrome (AD-HIES) presented with anaphylaxis (127).

Summary

Precision medicine in diagnosing and evaluating risk of anaphylaxis is important as reactions are immediate and life-threatening. Novel diagnostic and prognostic methods are being evaluated, some of which have shown great promise, in particular PAF acetyl hydrolase activity, BAT, and CRD. The role of complement and other mediators in anaphylaxis is poorly understood. There is still much to be done to identify genetic and epigenetic markers for determining risk of anaphylaxis to specific allergens. Other challenges include the role of cofactors, such as exercise, alcohol intake, and concomitant infection in increasing the severity of response.

The future of precision medicine in food allergy, drug allergy, and anaphylaxis

Present treatments for allergy immunotherapy provide an early approach toward precision medicine with allergens and dosing tailored to the patient. Identification of individual patients' allergen profiles is an ongoing area of research. We are gaining ground in our understanding of the underlying genetics that increase risk of allergies. Table 1 provides a list of some of the genes that have been associated with food and drug allergy and anaphylaxis. We are expanding our knowledge of the causative protein components that are responsible for FA, and CRD is being explored as a diagnostic tool for FA (128). Further, CRD may provide prognostic value and may enable physicians to predict severity of reactions to allergens based on knowledge of the antibodies specific to food-derived proteins. A possible approach to biomarker and phenotype studies is depicted in Figs 1–4. In recent years, there also have been technological advances in biology and bioinformatics, which enable a more detailed profile of an individual's genetic, epigenetic, cellular, and/or molecular characteristics (129). For example, recent advances in technologies such as next-generation sequencing (NGS) and time-of-flight mass cytometry (CyTOF), combined with functional testing *in vitro*, have greatly assisted with our understanding of the underlying mechanisms involved in atopy. Ongoing studies will determine the modifications in the immune profile of individuals before and after successful allergen immunotherapy, greatly advancing our understanding of immune regulation. Employing innovative and state-of-the-art tools will improve our definition of endotypes that connect specific immune cell signatures, genetic and epigenetic markers, plasma markers, tissue markers, 'omics' profiling (Fig. 4), and cell functional studies.

Our understanding of the role of immune regulators, such as T cell, B cells, antibodies, cytokines, complement, and others has vastly increased. In addition to immune biomarkers, future progress in defining endotypes in food and drug allergy will likely take into account allergen and cross-reacting allergen profiles, age of onset of disease symptoms, timing of onset of symptoms after exposure to allergens, history of other comorbid atopic diseases, and treatment outcome. By centralizing collection and analysis of vast amounts of data from biomedical research (i.e., 'omics' profiling, biomarkers, sequencing), clinical data from electronic health records, and clinical research (Figs 5 and 6), we will be able to understand and discern different endotypes of disease among individuals with the same phenotype and assist with the ability to personalize treatment and prevention to improve health outcomes.

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Author contributions

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Conflict of interest

The authors declare that they have no conflicts of interest.

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