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Roles of the immunoglobulin's in food allergy

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ABSTRACT

Food allergy refers to food allergen-induced and immunoglobulin (Ig)-mediated aberrant immune responses, and is a major cause of anaphylaxis across age groups. While IgE is the canonical effector that arms mast cells and basophils and triggers immediate hypersensitivity upon allergen re-encounter. Additionally, emerging evidence indicates that non-IgE subclasses, involving IgG, IgA, IgD and IgM, shape sensitization, clinical reactivity and the acquisition of tolerance in context-dependent ways, and even has diagnostic values on food allergy. In this review, we summarize current understanding of how each Ig subclass contributes to the pathogenesis, diagnosis and immunotherapeutic response evaluation of food allergy. We also highlight translational implications, including anti-IgE therapy, immunotherapy-driven subclass remodeling and the promise of multiplex immunoassays for personalized diagnosis and monitoring. Clarifying the coordinated and even contradictory functions of Ig subclass will refine risk stratification and accelerate precision immunotherapy for food allergy.

Keywords: food allergy; immunoglobulin subclass; role.

1. Introduction

Food allergy encompasses a spectrum of immunoglobulin (Ig)-mediated disorders triggered by specific dietary components, with IgE-dependent mechanism constituting pivotal pathogenesis[1]. The global prevalence of food allergy has been escalating over the past several decades[2], now affecting approximately 10% population in developed countries[3]. The well-characterized IgE-mediated type I hypersensitivity underlies acute-onset clinical manifestations ranging from urticaria, oral allergy syndrome to life-threatening anaphylaxis[4]. Notably, growing evidence highlights the involvement of other Ig subclasses like IgG, IgA, IgD and IgM in delayed or chronic inflammatory responses of food allergy. IgG subclasses display heterogeneous biology. At the mucosal frontier, IgA is not uniformly protective, allergen-specific or total IgA are elevated in certain food-induced conditions. IgD, an Ig implicated in mucosal immunity, can simultaneously enhance type-2 cytokines and dampen IgE-mediated effector cell degranulation. Finally, IgM has been associated with non-IgE-mediated reactions and with increased IgM^+ plasma cells in allergic tissues. In view of this, we synthesize the current evidence across IgE and non-IgE pathways in food allergy, highlight areas of consensus and controversy, and outline priorities for future research: mechanistic dissection of lesser-known subclasses, longitudinal profiling through natural tolerance, immunotherapy and clinical trials that incorporate composite Ig-based biomarkers for patient stratification. By clarifying how Ig subclasses cooperate and even counteract across tissues and time, we aim to inform the development of precise diagnostics and individualized immunotherapeutic strategies for patients with food allergy.

2. Ig subclasses in food allergy

2.1 IGE IN FOOD ALLERGY: MECHANISMS AND CLINICAL SIGNIFICANCE

The pathophysiology of IgE-mediated food allergy represents a complex cascade of immunological events that begins with the initial sensitization phase. During the first exposure to food allergen, antigen-presenting cells, such as dendritic cells located in the gastrointestinal mucosa and other tissues, stimulate naïve T cells to differentiate into Th2 cells, and thus activating naïve B cells to undergo Ig class-switching recombination, generating allergen-specific IgE-secreting plasma cells[5]. It is well known that these IgE bind to FcεRIα on mast cells and basophils with high affinity, establishing a sensitized state that persists for months despite the 2-3 days of serum half-life for IgE. This may result from that the half-life of IgE bound to FcεRIα on mast cells and basophils prolongs to several weeks[6], effectively creating a cellular memory of previous allergen exposure. The second allergen exposure induces the cross-linking of FcεRIα bound to IgE, triggering the rapid release of preformed mediators including histamine, tryptase, heparin and various chemotactic factors, and initiating *de novo* synthesis of lipid mediators, particularly leukotrienes and prostaglandins, primarily from mast cells and basophils[7]. These combined mediator effects manifest clinically as the characteristic symptoms of immediate hypersensitivity reactions, ranging from localized urticaria and gastrointestinal symptoms such as vomiting and diarrhea, to systemic anaphylaxis that can result in cardiovascular collapse and respiratory failure within minutes of exposure[8].

In clinical practice, apart from the *in vivo* oral food challenge test and skin prick test, the total free serum IgE level indicates individual allergic predisposition, and is widely used in IgE-mediated food allergy diagnosis[9]. However, the diagnostic utility of total IgE is inherently limited, as elevated levels may reflect various allergic conditions beyond food allergy, some food-allergic individuals may have normal total IgE level, and the predictive value of its clinical reactivity is also often suboptimal in sensitivity and specificity for certain food allergens[10]. These emphasize the critical need for more precise diagnostic approaches and complementary biomarkers.

Actually, the development of allergen-specific IgE test has revolutionized food allergy diagnosis by

enabling precise identification of causative foods through measurement of IgE directed against specific allergenic proteins[11]. This approach has been further refined through component-resolved diagnosis, a sophisticated methodology that differentiates between primary sensitization to major allergens versus cross-reactivity patterns, particularly among botanically related foods[12]. For example, component-resolved diagnosis can distinguish between genuine peanut allergy and cross-reactivity due to homologous proteins in tree nuts or birch pollen. Recent advances have introduced functional assays such as the basophil activation test, which measures the cellular response of basophils to allergen, combined with mass spectrometry techniques for enhanced allergen characterization, significantly improving the positive predictive value for food allergy diagnosis[13].

Notably, an emerging diagnostic consideration involves the measurement of total peripheral blood IgE, which encompasses both cell-bound IgE and free serum IgE, potentially providing a more comprehensive assessment of the individual allergic burden[14]. On the other hand, age represents another crucial factor in IgE-based diagnostics, as population studies have demonstrated that free serum IgE level for airborne allergens tends to increase with age, while allergen-specific IgE level may decrease over time[15]. However, these age-related patterns have not been thoroughly investigated for food allergens, representing an important area for future research that could refine age-specific diagnostic thresholds and interpretation guideline.

2.2 IGG IN FOOD ALLERGY: SUBCLASS DIVERSITY AND CLINICAL IMPLICATIONS

It is well known that the IgG comprises four distinct subclasses: IgG1, IgG2, IgG3 and IgG4, each with unique structural characteristics, functional properties and clinical significance in food allergic responses. These subclasses differ in their heavy chain constant regions, affecting their binding affinity to various Fc receptors, complement activation potential and overall biological functions. Understanding the differential roles of these IgG subclasses is increasingly important in food allergy research and clinical practice.

Research investigating the functional capabilities of different IgG subclasses has revealed important mechanistic insights. It is reported that IgG1, IgG3 and to a lesser extent IgG4, are capable of activating basophils to release histamine, whereas IgG2 is inactive in patients with chronic autoimmune urticaria[16]. This differential activation potential has significant implications for understanding the pathophysiology of food allergic reactions and the potential for IgG-mediated symptoms.

Additionally, clinical investigations in peanut-allergic children have yielded complex and even contradictory findings regarding IgG subclass patterns. Some studies report elevated levels of total and peanut-specifc IgG1, IgG2, IgG3 and IgG4 in affected children[17], suggesting a broad IgG response to peanut allergens. However, some evidence has indicated that peanut-specific IgG1, but not IgG2 or IgG3, serves as a reliable biomarker for peanut allergy, while elevated IgG4 level appear to correlate more closely with peanut exposure rather than clinical allergy[18]. These discrepancies may reflect differences in study populations, methodological approaches or the complex relationship between Ig levels and clinical reactivity.

In cow's milk allergy, the IgG subclass profile varies depending on the underlying mechanism of the allergic reaction. Children with IgE-mediated milk allergy typically demonstrate elevated levels of both total and milk-specific IgG1 and IgG4 [17]. In contrast, patients with non-IgE-mediated milk allergy show predominantly elevated milk-specific IgG4 level[19]. These suggest different immunological pathways in these distinct clinical phenotypes. Therefore, the diagnostic utility of component-specific IgG subclass in non-IgE-mediated milk allergy remains limited and controversial[20].

Egg allergy presents another complex pattern of IgG subclass involvement. Egg-allergic children typically exhibit elevated levels of total and egg-specific IgG1 and IgG4[17], but paradoxically show

decreased ovomucoid-specific IgG1 level[21]. This apparent contradiction highlights the complexity of the immune response to different allergenic components within the same food source and underscores the importance of component-resolved approaches in both research and clinical practice.

The involvement of IgG in shellfish allergy has also been documented, with elevated shrimp-specific IgG level observed in patients with shrimp hypersensitivity[22]. This suggests that IgG-mediated mechanisms may contribute to adverse reactions to shellfish, though the precise clinical significance requires further investigation.

Beyond their potential pathogenic roles, IgG serve crucial protective functions in food allergy. During early life, IgG plays a fundamental role in preventing allergic sensitization, likely through competitive inhibition and immune complex formation that promotes tolerance rather than sensitization[23]. Allergen-specific IgG functions as natural inhibitors of mast cell and basophil activation[24,25] through FcγRII-mediated mechanisms[26], providing a counterbalancing force against IgE-mediated activation. The protective role of IgG4 has been particularly well-characterized in the context of allergen immunotherapy. During successful immunotherapy, patients typically develop elevated IgG4 level specific to treated allergen, and these increases correlate strongly with the development of clinical immune tolerance[27]. Molecular studies have revealed that specific B cells from children who achieve remission from milk allergy show predominant expression of IgG2 genes during the desensitization phase and IgG1 and IgG4 genes during remission phase[28], providing mechanistic insights into the immunological basis of tolerance development. Consequently, the ratio of allergen-specific IgE to IgG4 has emerged as a particularly promising biomarker for evaluating both allergic sensitization and the effectiveness of immunotherapy interventions. A decreased IgE/IgG4 ratio typically indicates successful tolerance induction and reduced clinical reactivity[27]. However, clinical observations in eosinophilic esophagitis have revealed direct correlations between increased serum IgG4 level specific to milk and wheat proteins, suggesting that IgG4 may serve as both a biomarker and potential therapeutic target in this condition[29]. Therefore, these findings have also reinforced the concept that food-specific IgG4 often represent a bystander in food allergy rather than a primary diagnostic indicator, leading to recommendations against their routine use as standalone diagnostic tools in clinical practice.

2.3 IGA IN FOOD ALLERGY: MUCOSAL PROTECTION AND IMMUNE HOMEOSTASIS

IgA represents the most abundant Ig isotype in mucosal secretions and serves as the primary immunological barrier protecting mucosal surfaces throughout the gastrointestinal, respiratory and genitourinary tracts[30]. In the context of food allergy, IgA plays multifaceted roles that encompass both protective and potentially pathogenic functions, making it a critical component of the mucosal immune system response to food allergens.

Similarly to IgG, IgA in early life also prevents individual sensitization[23] and deliver oral tolerance signals[31]. Secretary IgA, the predominant form of IgA found in mucosal secretions, functions as a sophisticated molecular guardian at mucosal surfaces. This Ig binds directly to food antigens in intestinal lumen, facilitating their neutralization and exclusion from deeper tissue penetration. This binding prevents food allergen from accessing the systemic immune system, effectively maintaining the barrier function that separates the external environment from internal immune surveillance systems[32]. The secretory component of IgA provides additional protection against proteolytic degradation, ensuring sustained antibody function in the harsh chemical environment of the gastrointestinal tract[33].

Notably, clinical and experimental evidence strongly supports the protective role of adequate IgA responses in food allergy prevention. Deficiency or dysregulation of IgA responses have been correlated with increased susceptibility to

food allergy[34,35]. Hence, strategies to boost mucosal IgA by probiotic supplementation[36] or retinoic acid[37] are likely to reinforce gut barrier integrity and foster durable tolerance.

On the other hand, experimental studies in murine models have demonstrated that IgA can significantly attenuate anaphylaxis and subsequent inflammatory immune responses[38], providing direct evidence for its protective role in severe allergic reactions. Clinical observations in egg-allergic children have revealed specific patterns of IgA involvement that support its protective role. These children typically demonstrate lower level of ovomucoid-specific IgA1[21], suggesting that inadequate antigen-specific IgA responses may contribute to sustained allergic reactivity. Furthermore, during oral immunotherapy for egg allergy, increases in egg white-specific IgA and IgA2 are strongly associated with positive clinical responses and tolerance development[39], validating the concept that successful immunotherapy induces a beneficial shift from predominantly IgE-mediated responses toward IgA-mediated protective responses. Molecular studies have provided additional mechanistic insights into the role of IgA in tolerance development. Analysis of specific B cells from children who achieved remission from milk allergy has shown predominant expression of IgA1 and IgA2 genes[28], suggesting that the development of robust antigen-specific IgA responses is a hallmark of successful tolerance induction. Laboratory studies have further demonstrated that allergen-specific IgA can function as effective inhibitors of mast cell activation in food allergy[24], providing a mechanistic explanation for their protective effects.

On the contrary, the role of IgA in food allergy is not uniformly protective, and evidence suggests that under certain circumstances, IgA may actively participate in allergic processes. It is demonstrated that serum total IgA and milk-specific IgA levels are elevated in patients with atopic dermatitis[40] and chronic urticaria[41], respectively. Clinical studies in infants have revealed that those with positive challenge reactions to common food allergens including egg, soy and milk often demonstrate higher level of food-specific IgA[42]. Histopathological studies of intestinal mucosa from patients with food-induced eczema have shown increased numbers of IgA^+ plasma cells[43], indicating enhanced local IgA production in the context of food-allergic inflammation. These findings suggest that chronic exposure to food allergens in sensitized individuals may lead to dysregulated IgA responses that contribute to ongoing inflammation rather than resolution. Interestingly, studies of shrimp allergy have found no significant differences in shrimp-specific IgA level between allergic and non-allergic individuals[22], highlighting the complexity and food-specific nature of IgA involvement in allergic responses. These varied findings underscore the need for allergen-specific and context-dependent interpretation of IgA measurements in food allergy evaluation.

2.4 IGD IN FOOD ALLERGY: EMERGING ROLES IN MUCOSAL IMMUNITY

IgD, traditionally regarded primarily as a surface receptor on naïve B cells, has recently emerged as an important player in mucosal immunity and tolerance mechanisms, with significant implications for food allergy pathophysiology. This evolving understanding of IgD has revealed sophisticated regulatory mechanisms that extend far beyond its classical role as a B cell activation marker[44]. Recent research has demonstrated that secretory IgD possesses unique binding properties that enable it to interact with basophils through specific molecular partnerships involving Galectin-9 and CD44[44]. This binding interaction creates a novel pathway for immune activation that can significantly influence the downstream development of both IgE and IgG responses. Upon antigen-IgD engagement on basophil surfaces, these cells are stimulated to release IL-4 and B-cell activating factor (BAFF), two critical cytokines that shape subsequent adaptive immune responses. IL-4 promotes Th2 cell differentiation and IgE class-switching, while BAFF supports B cell survival and Ig production, creating a regulatory circuit that can amplify or modulate allergic sensitization.

Clinical investigations in egg-allergic children have revealed intriguing patterns of IgD involvement that suggest both protective and potentially pathogenic roles. Children with active egg allergy, as well as those who naturally outgrow egg allergy over time, demonstrate elevated level of ovomucoid-specific IgD[21,45]. This pattern suggests that IgD responses may represent a marker of immune system engagement with the allergen, regardless of whether the ultimate outcome is sustained allergy or natural tolerance development. Molecular analysis of antigen-specific B cells during the remission phase shows predominant expression of IgD genes[28], suggesting further that robust IgD responses may be associated with successful tolerance induction. Experimental studies using zebrafish models have corroborated these clinical observations, demonstrating that exposure to ovalbumin induces increases in IgD level. This animal model study provides valuable mechanistic insights and supports for the clinical relevance of IgD responses in food allergy[46].

Actually, the functional significance of basophil-bound IgD has been further elucidated through detailed mechanistic studies. Allergen-mediated cross-linking of IgD bound to basophil surfaces can trigger enhanced secretion of type 2 cytokines, which promote allergic sensitization and maintain Th2-skewed immune responses[47]. However, the IgD-allergen interactions can simultaneously interfere with IgE-mediated basophil degranulation[47]. These suggest the dual and opposing roles of IgD in allergen sensitization and the development of allergen tolerance. Therefore, the potential regulatory functions of IgD in food allergy are an emerging area of interest that warrants further investigation.

2.5 IGM IN FOOD ALLERGY: PRIMARY RESPONSES AND PATHOGENIC MECHANISMS

IgM, the first Ig secreted upon antigen exposure, is typically associated with early humoral responses and complement activation, and contributes to initial antigen clearance. In the context of food allergy, the involvement of IgM has been less extensively studied compared to other Ig subclasses, but emerging evidence suggests important and previously underappreciated roles in both allergic sensitization and ongoing allergic inflammation.

Clinical research examining shrimp-specific IgM in patients with shrimp allergy has found no significant changes[22], suggesting that IgM responses to shellfish proteins may not represent a major component of the allergic reaction in this context. Compelling evidence for the involvement of IgM in food allergy comes from studies of soy allergy in infants. Research has demonstrated distinct patterns of soy-specific IgM responses that correlate with clinical outcomes during food challenge test: infants who exhibit negative responses to soy challenge show increased level of soy-specific IgM, while those with positive challenge responses demonstrate decreased IgM level[42]. This inverse relationship suggests that adequate IgM responses to food antigens may actually be protective, potentially through mechanisms involving immune complex formation and enhanced antigen clearance that favor tolerance development over sensitization. The potential involvement of IgM in non-IgE-mediated food allergic reactions has been suggested through studies of immune complex-mediated pathology. Conditions such as food protein-induced enterocolitis syndrome[48,49] may involve IgM-containing immune complexes that contribute to intestinal inflammation and tissue damage. However, the underlying mechanisms require further investigation.

Experimental studies using zebrafish models have supported the clinical relevance of IgM responses to food proteins: ovalbumin exposure induces measurable IgM production in these experimental systems[46]. While zebrafish immunology differs from human immunology, these studies provide valuable comparative insights and suggest that IgM responses to food proteins represent a conserved feature of immune recognition across species.

Histopathological examination of intestinal tissues from food-allergic patients has revealed increased numbers of IgM^+ plasma cells in the mucosal compartment of both milk-allergic infants[50] and patients with food-induced eczema[43], suggesting that enhanced local IgM production represents a

common feature of food-allergic inflammation in the gastrointestinal tract. The accumulation of IgM-producing cells in affected tissues may reflect ongoing local immune activation and could contribute to chronic inflammatory processes that maintain allergic symptoms. Peripheral blood studies have corroborated these tissue-based findings, with research showing increased numbers of ovalbumin-specific IgM^+ plasma cells in the circulation of egg-allergic infants[51]. This systemic expansion of antigen-specific IgM-producing cells suggests that the immune response to food allergens involves both local mucosal and systemic compartments, with potential implications for both immediate and long-term allergic reactivity. Perhaps most intriguingly, functional studies in fish models have demonstrated that cross-linking of IgM bound to the surface of teleost basophils can directly induce basophil degranulation, releasing inflammatory mediators similar to those involved in IgE-mediated reactions[52]. While the direct applicability of these findings to human food allergy requires validation, they suggest that IgM may have more direct pathogenic potential than previously recognized.

These accumulated findings indicate that the role of IgM in food allergy is beyond a simple transitional Ig subclass produced early in immune responses. Instead, IgM appears to play substantive pathogenic roles in food allergic inflammation, with potential involvement in both immediate and delayed allergic reactions. Future research directions should focus on characterizing the specific mechanisms by which IgM contributes to food allergic pathogenesis, determining whether IgM-based diagnostics might provide additional clinical utility, and investigating whether therapeutic modulation of IgM responses could represent a novel treatment approach for certain types of food allergy.

3. Ig-based translational applications: therapeutic targets and clinical innovations

The comprehensive understanding of the involvement Ig subclasses in food allergy has opened multiple avenues for translational applications that encompass both therapeutic interventions and enhanced diagnostic capabilities. These applications represent the practical implementation of basic immunology research and hold significant promise for improving clinical outcomes in food-allergic patients.

3.1 THERAPEUTIC TARGETING OF IG SUBCLASSES

The development of anti-IgE monoclonal antibody therapy represents one of the most successful examples of Ig-targeted treatment in food allergy. Omalizumab, a humanized monoclonal antibody specifically designed to bind free circulating IgE, has demonstrated significant clinical efficacy in reducing the risk of severe allergic reactions to foods[53].

The action mechanism of omalizumab involves binding to the Fc region of IgE, preventing their interaction with FcεRIα on mast cells and basophils. This binding not only reduces the amount of free IgE available for allergen binding but also leads to downregulation of FcεRIα expression on effector cells, creating a sustained reduction in allergic reactivity potential[54]. Clinical trials of omalizumab in food allergy have demonstrated impressive results, with treated patients showing significantly increased threshold doses for allergic reactions during food challenges, reduced severity of accidental exposures and improved life quality[55]. This therapy has shown particular promise as an adjuvant treatment during oral immunotherapy, where it reduces the risk of severe reactions during the dose escalation phase and potentially improve the success rates of desensitization protocols[55].

3.2 ORAL IMMUNOTHERAPY AND IG MODULATION

Oral immunotherapy represents another major therapeutic approach that fundamentally relies on modulating Ig responses to achieve clinical benefits. Successful oral immunotherapy protocols consistently demonstrate characteristic changes in Ig profiles that correlate with clinical improvements. These changes include sustained increases in allergen-specific IgG4, which function as blocking antibodies that can compete with IgE for allergen binding, and enhanced production of allergen-

specific IgA, particularly in the mucosal compartment where they can provide local protection against allergen penetration[24,56].

The immunological mechanisms underlying successful oral immunotherapy appear to involve a complex reprogramming of the adaptive immune responses, shifting from predominantly Th2-driven IgE production toward a more balanced profile that includes robust Th1 and regulatory T cell responses[56]. This shift is reflected not only in Ig subclass changes but also in modifications of cytokine production patterns, T cell phenotypes and overall immune reactivity to the treated allergen[56].

3.3 BIOMARKER DEVELOPMENT AND DIAGNOSTIC INNOVATION

The differential expression patterns of various Ig subclasses in food allergy have provided a rich resource for biomarker development that could revolutionize both diagnostic accuracy and treatment monitoring capabilities. Current research efforts are focused on identifying specific combinations of Ig subclasses that can provide superior diagnostic performance compared to traditional single-Ig test[57].

The concept of Ig ratios has emerged as particularly promising, with the IgE/IgG4 ratio showing excellent potential for both diagnosing active allergy and monitoring treatment responses[56]. Decreasing ratios typically indicate successful tolerance development, while persistently elevated ratios may suggest ongoing allergic reactivity or treatment failure. Similar approaches using IgE/IgA ratio and other combination measurements are under active investigation[24].

Component-resolved diagnostics combined with Ig subclass analysis represents another frontier in precision food allergy diagnosis[58]. This approach involves measuring not only allergen-specific IgE to individual protein components within foods but also the corresponding IgG, IgA, and potentially IgD and IgM responses to these same components. Such comprehensive immunological profiling could provide unprecedented insights into individual reactivity patterns and treatment susceptibility.

3.4 MULTIPLEX IMMUNOASSAY DEVELOPMENT

The practical implementation of comprehensive Ig profiles requires sophisticated analytical platforms capable of simultaneous measurement of multiple Ig subclasses and specificities from small sample volumes. The development of multiplex immunoassays represents a critical technological advance that could enable routine clinical application of complex immunological assessments.

These advanced assay systems would allow simultaneous measurement of allergen-specific and component-specific antibodies across multiple Ig subclasses, providing comprehensive immunological profiles that could inform both diagnostic and therapeutic decisions. Such systems could also incorporate measurements of functional antibody activities, such as complement activation potential or basophil activation capacity, providing even more detailed insights into clinical relevance.

3.5 FUTURE THERAPEUTIC DIRECTIONS

Emerging therapeutic approaches continue to expand the applications of Ig-based interventions in food allergy. Novel monoclonal antibodies targeting different components of the allergic cascade are under development, including antibodies directed against IL-4, IL-13 and other critical cytokines that regulate Ig class-switching and allergic inflammation.

Passive immunization approaches using allergen-specific IgG are being investigated as potential treatments for high-risk patients or emergency situations. These approaches could provide immediate protection during accidental exposures while more definitive treatments take effect.

The integration of personalized medicine approaches with Ig-based therapies represents the ultimate goal of translational food allergy research. This would involve developing treatment algorithms that consider individual immunological profiles, genetic backgrounds, clinical histories, and treatment responses to optimize therapeutic outcomes while minimizing risks and adverse effects.

4. Conclusions

In conclusion, the Ig superfamily exhibits complex, context-dependent roles in food allergy, ranging from pro-allergy effects to protective functions. Elucidating their dynamic interplay will enhance diagnostic accuracy and immunotherapeutic response evaluation.

Conflict of Interest Statement:

The authors have no conflicts of interest to declare.

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