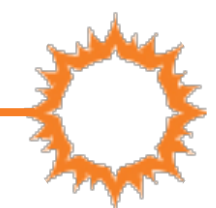


Harnessing Cross-Reactivity in OIT

David Fitzhugh, MD
06/23/2023

Goals

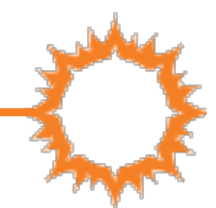
- Review cross-reactivity patterns among tree nuts, legumes, fish, and shellfish
- Distinguish molecular (in vitro) co-sensitization from clinical cross-reactivity (co-allergy)
- Discuss data for inclusion of specific allergens for co-desensitization (tree nuts in particular)



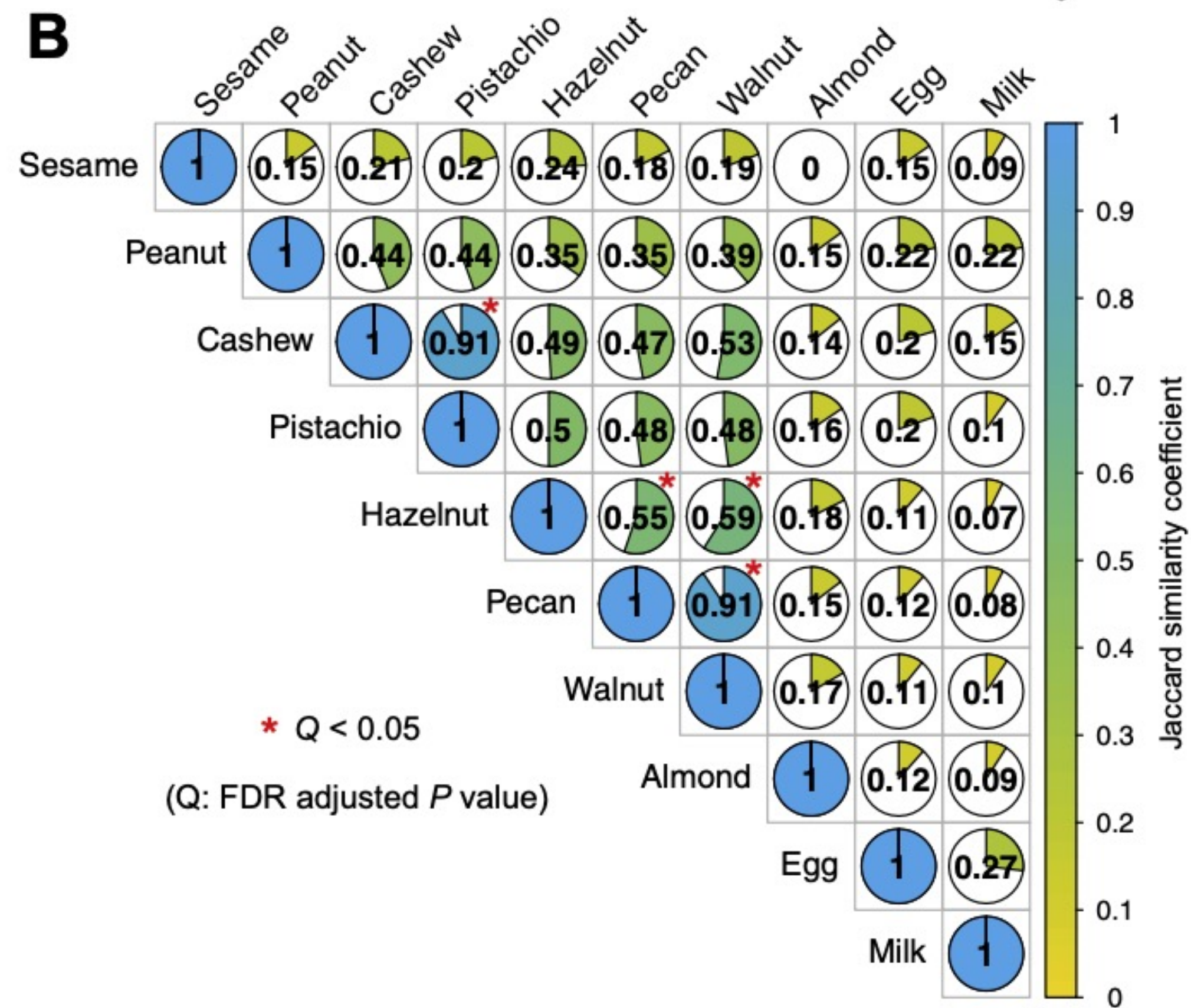
Basis of cross-reactivity: tree nuts

- There is a significant correlation at the protein sequence level between immunodominant components of related tree nuts
- This correlation translates both to sp IgE levels as well as to clinical allergy between these nuts
- Tree nut dyads:
 - Cashew / pistachio: Ana o3 level strongly correlates to pistachio sp IgE
 - Walnut / pecan: Jug r1 level strongly correlates to pecan sp IgE

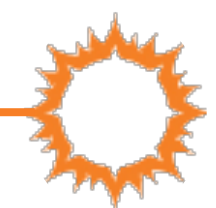
Nadeau et al, J Allergy Clin Immunol Pract 2017



Clinical cross-reactivity: tree nuts



Nadeau et al, J Allergy Clin Immunol Pract 2017



Clinical cross-reactivity: tree nuts

- Wasserman and Windom published their clinical experience in 2021:
- 94% of cashew-treated OIT patients passed a pistachio “cross-nut” challenge (83/88)
- 97% of walnut-treated OIT patients passed a pecan “cross-nut” challenge (30/31)
- Important to recognize the immundominant nuts in the dyads:
 - Cashew
 - Walnut

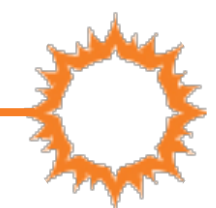
Wasserman et al, Letters / Ann Allergy Asthma Immunol 127 (2021)



Clinical cross-reactivity: tree nuts

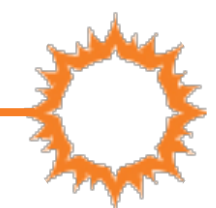
- Nut CRACKER study:
 - Assess co-desensitization to pecan, hazelnut, and cashew with walnut-only OIT
 - Pecan: 100% (46/46) of pecan-allergic patients were desensitized with walnut OIT (passed 4000 mg challenge)
 - Hazelnut: 53% (8/15) of patients with concomitant hazelnut allergy were fully desensitized with walnut OIT, though 93% (14/15) had a partial response (tolerance of 1000 mg protein or 10x increase from baseline)
 - No significant cross-desensitization observed to cashew with walnut OIT

Elizur et al, Lancet Child/Adolescent 2019



Tree nut: take homes

- Strong evidence to support that desensitization to walnut will co-desensitize to pecan
- Similarly, desensitization to cashew will desensitize to pistachio
- There is likely at least partial desensitization to hazelnut with walnut OIT
- Thus, you only need **cashew for cashew/pistachio** and **walnut for walnut/pecan.**



Legumes: peanut and everything else

- Peanut is not commonly associated with other clinical legume allergy
- Peanut allergy is commonly associated with soy sensitization but rarely with soy allergy
 - 10/32 peanut-allergic patients sensitized on SPT
 - 1/32 peanut-allergic patients clinically allergic to soy
- Legume “triad”:
 - Lentil, green pea, chickpea have a high rate of clinical cross-reactivity with each other
 - 64% of patients with at least one of the above reacted to the other two
 - By contrast, low rate of allergy in this group to green bean, white bean, or soy (or peanut)

Chan et al, J ALLERGY CLIN IMMUNOL PRACT 2019

Sicherer et al, J ALLERGY CLIN IMMUNOL PRACT 2020



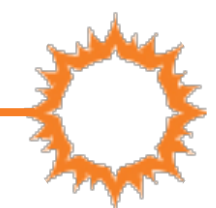
Lupin??

- Lupin is an emerging legume allergen in the US, though more recognized in Europe
- Lupine flour commonly found in pasta, baked goods, and as a “gluten replacer”
- Rate of peanut / lupin co-allergy appears higher than peanut and other legumes
 - 34-44% co-sensitization
 - True co-allergy estimates highly variable based on limited challenge data, but ranging 10 - > 80%.



Legume take-homes

- Peanut allergy is **not** highly associated with other legume allergy
- Chickpea, lentil, and pea have a fairly high degree of co-allergy (“**legume triad**”)
- Think about lupin
- It is not overall likely that peanut OIT would induce clinical desensitization of other legumes
- Reasonable to consider that among the chickpea, lentil, pea triad that OIT to one would help co-desensitize to others but no published data



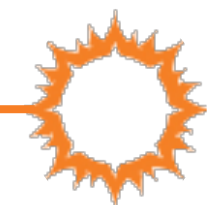
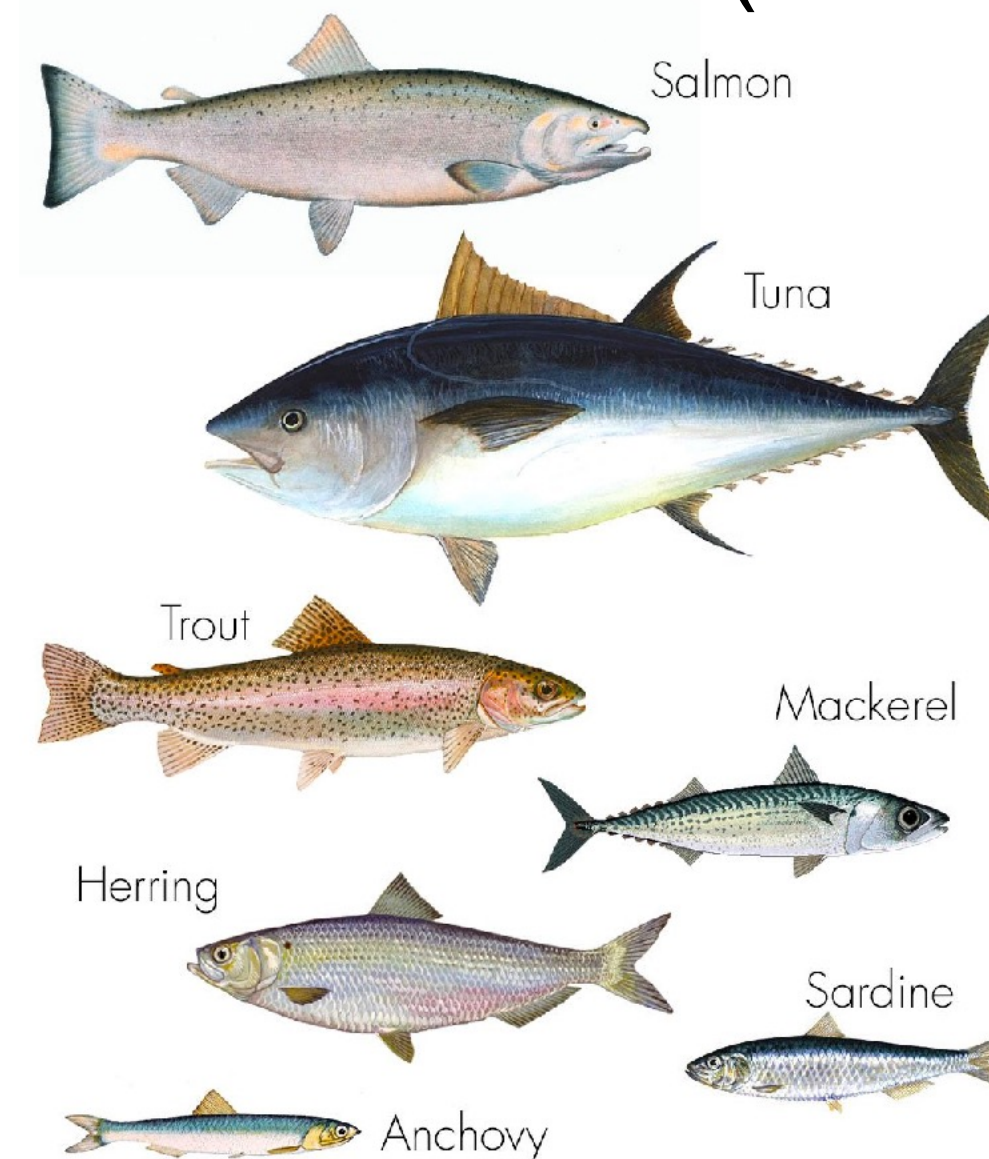
Fish and Shellfish

- No significant overlap between finned fish allergy and shellfish allergy on a molecular basis and relatively rare to see a patient allergic to both classes (2-7%).
- Two very distinct dominant allergens:

- Tropomysins (shellfish)



- Parvalbumins (finned fish)



Finned fish homology

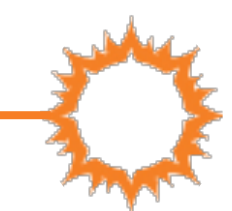
- Within finned fish, about 85% homology of parvalbumin among common fish (tuna, trout, salmon)
- However, there are some outliers with lesser homology: swordfish, sole, tilapia. Allergies to these fish may be more “isolated” and reflect minor, non-parvalbumin allergy
- **Tuna** tends to have the **lowest parvalbumin** content, so some patients who react even to multiple other finned fish might tolerate tuna
- Heating/canning fish can reduce parvalbumin allergenicity by 20-60%, and might result in clinical tolerance for some patients vs. fresh fish



Who's this guy? What's that fish?



TJ Ott. Tuna. Also, tuna is the most involved fish in scombroid reactions.



Finned Fish OIT

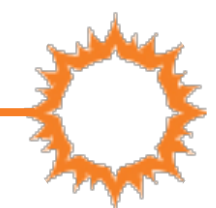
- Very limited data but a few case reports have been published
- 20 yo Japanese patient desensitized with 12 mg parvalbumin protein (mackerel)
- At the end of 2 years of OIT, she was able to tolerate a fillet with 66 mg parvalbumin protein
- Very different / low-slow protocol



Allergy care is different in Japan

This study was approved by the ethics committee of Tokyo Medical and Dental University (Approval number: M2017-100) and informed consent was obtained from the patient. Before initiation of OIT, an oral food challenge (OFC) test was performed for one-week with hospitalization to clarify the threshold. The loading dose of parvalbumin in the heated fillet was increased in a stepwise fashion (from 1 mg to 12 mg) and obvious symptoms were not observed. However, the actual threshold was not clarified because she would not remain in the hospital for more than 1 week due to her social life.

Rare to see inpatient food challenges even for 1 day in the US!



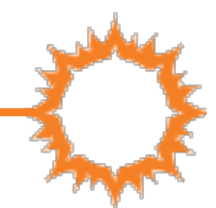
Shellfish homology

- Very high degree of homology among crustacean tropomyosin (95%), so most patients who are clinically allergic to one crustacean will react to all (crab, shrimp, lobster).
- Much lesser degree of homology between crustacean and mollusk tropomyosin (55-65%)
- Estimates vary, but only a minority of shellfish allergic patients are allergic to both crustacean and mollusk families (14%)
- Evolutionary conservation between arthropod tropomyosin (dust mite, roach) and shellfish tropomyosin, so sometimes see a variant of oral allergy syndrome with pts sensitized to these inhalants with shellfish ingestion



Shellfish OIT

- One very small study published:
 - 3 patients underwent desensitization to 300 mg shrimp protein
 - Notably, this was also in context of omalizumab
 - 2/3 tolerated 12 g shrimp challenge at 36 weeks
 - No cross-crustacean challenges performed



Hypoallergens for shrimp desensitization?

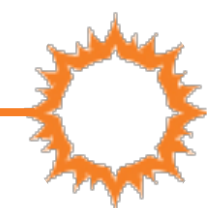
Immunization with Hypoallergens of shrimp allergen tropomyosin inhibits shrimp tropomyosin specific IgE reactivity

Christine Y Y Wai¹, Nicki Y H Leung¹, Marco H K Ho², Laurel J Gershwin³, Shang An Shu⁴,
Patrick S C Leung⁴, Ka Hou Chu¹

Affiliations + expand

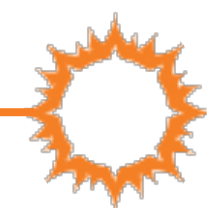
PMID: 25365343 PMCID: [PMC4218792](#) DOI: [10.1371/journal.pone.0111649](#)

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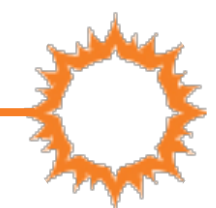
Take home messages

- Cashew/pistachio and walnut/pecan have strong clinical co-allergy.
- Desensitization to the immunodominant allergen (cashew or walnut) is adequate for desensitization to both members of the dyad in almost all cases.
- Peanut is not associated with high degree of other legume allergy, though lupin is on the rise.
- Chickpea/lentil/pea can be thought of as a legume triad with a high degree of clinical co-allergy.
- Crustaceans have a very high allergen homology and rate of co-allergy.
- Parvalbumin content is important to define degree of allergenicity of finned fish.
- Tuna in particular has a low parvalbumin content and may be tolerated even with other finned fish allergy present








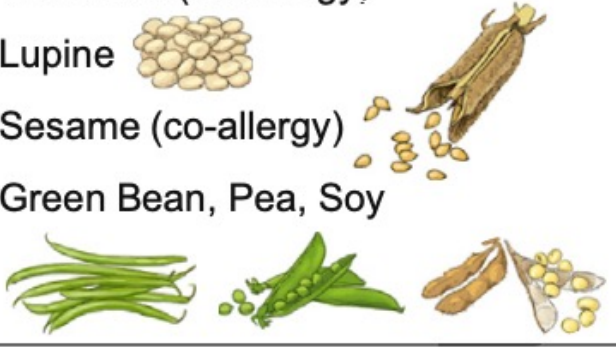






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Cross-reactivity table

Primary Food Allergy	Cross Reactive Food	Risk (varies with region)
Crustacean Shellfish 	Other Crustaceans Mollusks/Bivalves (Clam, Mussel, Oyster, Squid) 	~75% <50%
Mollusks/Bivalves 	Crustaceans (Crab, Shrimp, Lobster) 	>70%
Finned Bony Fish 	Other Finned Bony Fish Cartilaginous Fish (Dogfish, Ray, Shark) 	~50% <5%
Peanut 	Tree Nuts (co-allergy) Lupine Sesame (co-allergy) Green Bean, Pea, Soy 	~33% ~20% 10-15% 5-20%
Other Legumes 	<i>If Soy</i> Peanut <i>If Chick Pea</i> Lentil, Pea 	>75% >50%
Tree Nuts  <i>Amy Zhong</i> © 2020 Mount Sinai Health Systems	Other Tree Nuts Sesame (co-allergy) <i>If Walnut</i> Pecan <i>If Pecan</i> Walnut <i>If Cashew</i> Pistachio <i>If Pistachio</i> Cashew <i>If Peanut and Tree Nut</i> Sesame (co-allergy) 	15-33% 10-15% ~66-75% >95% ~66-83% >95% 50%

Sicherer et al, J ALLERGY CLIN IMMUNOL PRACT 2020



That's it!

