A Framework for Studying Shared-Decision Making in Treatments for Food Allergy

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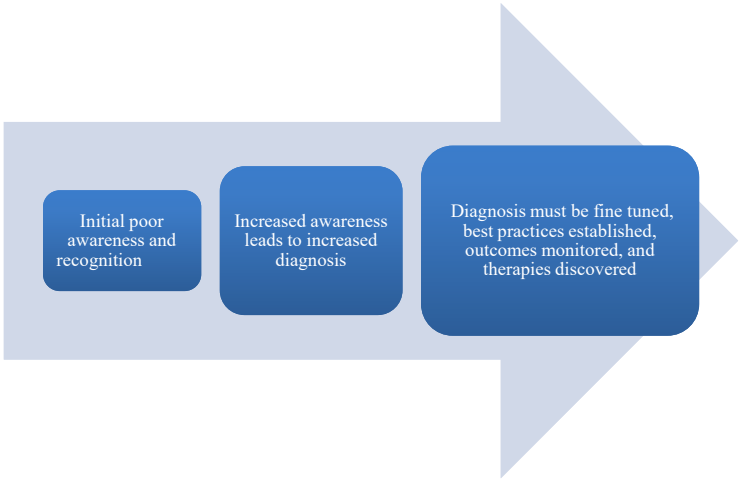
My disclosures haven't changed in the last hour!

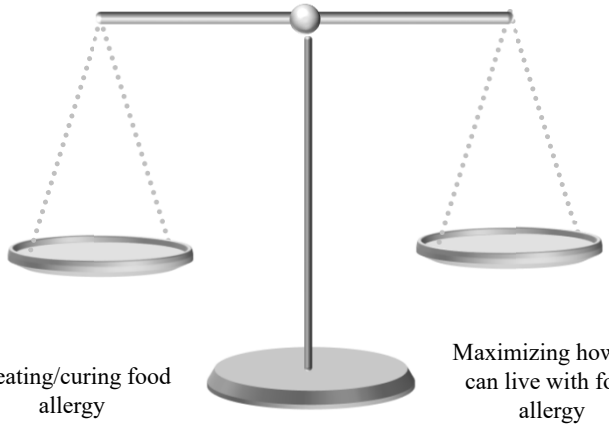
Learning Objectives

- Understand the current state of OIT
- Understand the health and economic effects related to therapy
- Understand the complexities of the choice to consider enrollment in therapy
- Understand a framework for shared decision making regarding food allergy therapy

Evolution of Food Allergy



A Delicate Balance



Treating/curing food allergy

Maximizing how we can live with food allergy

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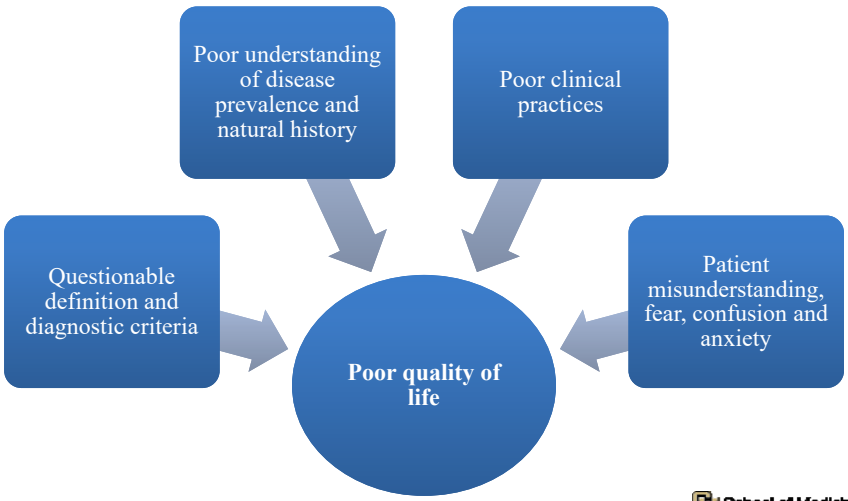
Theoretical Model



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What is Oral Immunotherapy?

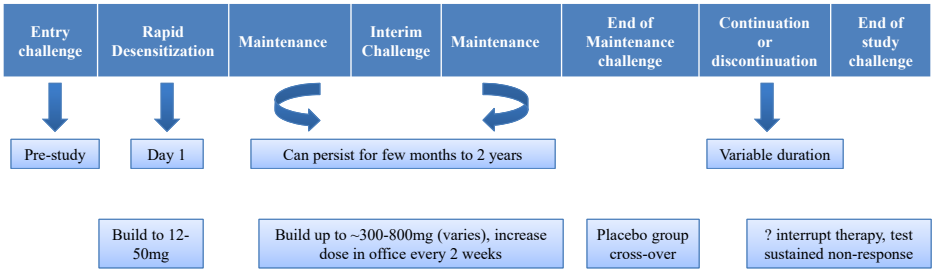
- Aim: incrementally re-feed one's food allergen
  --Increase tolerance to an allergen
  --Protect against accidental exposure vs. outright cure
- Status: experimental/investigational (NIH sponsored)
  --Unproven safety, effectiveness, mechanism of action
  --Not FDA approved, though not needed in certain instances
  --Not reimbursable through 3rd party payers
- Issues: no uniform method, poor study methods
  --Inconsistencies, poorly representative patients enrolled
  --Biotech, private practice competing with academic studies

How Immunotherapy Works

- Main effect is generation of cells that facilitate tolerance
- Tolerance = allergen exposure won't result in reaction
  --Generate master cells that dampen immune response (T_{reg})
- Suppress allergic immune system (e.g. T_h2 mediators)
  --Decrease production from IgE (allergic antibody)
  --Increase production of IgG_4 (marker of tolerance vs. blocks IgE binding)
  --Suppress mediators of reactions (mast cells, basophils, eosinophils)
- Can we distinguish tolerance vs. desensitization?

Adkis C Allergy 2006: 61 (Suppl. 81): 11–14
Adkis M J Allergy Clin Immunol 2007; 119: 780-9

OIT in Action



OIT: What Do We Know

- Many can achieve some degree of desensitization
  - --Threshold increased for most but not all, effect/success poorly predicted
  - --Few have developed sustained tolerance
  - --No indication of duration of therapy or how long effect lasts
- Fairly equal effects seen with milk, egg, peanut
- Markers of allergen sensitivity diminish significantly
  - --See shift in allergen specific IgE→IgG_4 and part of allergen recognized
- See variable effect of immune cell shut down
  - --No consistent biomarker pattern shown, but are many targets of interest
- There are high adverse event rates, and high pt dropout

Buchanan et al J Allergy Clin Immunol 2006; 119: 199-20; Blumchen et al JACI 2010: 126: 83-91
Hofman et al. J Allergy Clin Immunol 2009; 124: 1154-60 Jones SM et al J Allergy Clin Immunol 2009: 124: 292-300
Shiprak et al J Allergy Clin Immunol 2008; 122: 1154-60; Narvaez et al JACI2009; 214: 610-11
Varshney et al J Allergy Clin Immunol 2011: 127: 654-60 Kim et al J Allergy Clin Immunol 2011; 127 640-6
Burks et al. N Engl J Med 2012; 367:233-243 Fleischer et al J Allergy Clin Immunol 2013: 131: 119-27

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TABLE I. Peanut OIT studies

Reference	Year	Design	Samples size	Subject age (y)	Maintenance dose (mg)	Duration	Primary outcome
Jones et al[29]	2009	Open label	29	1-16	1800	36 mo	93% Passed 3.9-g peanut OFC
Blumchen et al[30]	2010	Randomized open label	23	3-14	500	7-d Rush escalation, 8-wk maintenance period	64% Reached maintenance of 500 mg of peanut
Varshney et al[27]	2011	Randomized, placebo controlled	19	3-11	2000	48 wk	84% Passed 5000-mg peanut OFC
Anagnostou et al[32]	2011	Open label	22	4-18	800	32 wk	64% Tolerated 6.6-g OFC
Anagnostou et al[33]	2014	Randomized, controlled	39	7-16	800	26 wk	62% Tolerated 1400-mg challenge
Vickery et al[28]	2014	Open label	24	1-16	Up to 4000	Up to 5 y	50% SU to 5000-mg OFC after 4-wk avoidance
Narisety et al[31]	2014	Randomized, placebo controlled	16	7-13	2000	12 mo	OIT > SLIT in OFC threshold, low rate of SU

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TABLE II. Egg OIT studies

Reference	Year	Design	Sample size	Subject age (y)	Maintenance dose (g)	Duration (mo)	Primary outcome
Buchanan et al[34]	2007	Open label	7	1-16	0.3	24	57% Passed 8-g OFC
Vickery et al[35]	2010	Open label	8	3-13	0.3-3.6	18-50	75% Passed OFC 1 mo after stopping OIT
Burks et al[26]	2012	Randomized, placebo controlled	40	5-11	1.6	22	75% Passed 10-g OFC but SU in only 28% at 6-8 wk later

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TABLE III. Milk OIT studies

Reference	Year	Design	Samples size	Subject age (y)	Maintenance dose	Duration	Primary outcome
Meglio et al[36]	2004	Open label	21	6-10	200 mL	6 mo	72% Desensitization to 200 mL of cow's milk daily
Longo et al[37]	2008	Randomized, open label	30	5-17	150 mL	10-d Rush escalation, 1 y of maintenance	36% Tolerant (≥150 mL) and 54% partially tolerant (5-150 mL)
Skripak et al[38]	2008	Randomized, placebo controlled	13	6-17	500 mg	23 wk	Median OFC threshold increased from 40 to 5,140 mg after OIT
Narisety et al[31]	2009	Open label (follow-up)	13	6-16	500-4,000 mg	3-17 mo	Median OFC threshold of 7,000 mg (with 33% tolerating 16,000 mg)
Pajno et al[40]	2010	Randomized, placebo controlled	15	4-10	200 mL	18 wk	67% Tolerant to 200 mL of cow's milk
Martorell et al[39]	2011	Randomized, placebo controlled	30	2-3	200 mL	1 y	90% Showing complete desensitization
Keet et al[25]	2012	Randomized, placebo controlled	20 for OIT	6-17	1,000-2,000 mg	60 wk	70% Desensitized to 8-g OFC, SU in 40% after 6 wk
Wood et al[41]	2015	Omalizumab DBPC, open-label OIT	57	7-32	3,300 mg	24 mo	80% Desensitized to 10-g OFC, SU in 42% after 8 wk

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OIT: Present Knowledge

Food	RCT	Severe pts	Young Children	Major Sx Free	Desensitization	Tolerance	Mechanism	EoE	Return of Allergy
Egg	Yes	?	No	No	Yes	4-6 week	unclear	None	NA
Milk	Yes	?	No	No	Yes	None to date	unclear	Yes	**YES**
Peanut	Yes	Non-US	Yes (DEVIL)	No	Yes	Variable but limited	Unclear, appears tolerant	Yes	NA

- Better data exist in Europe—more aggressive, studied longer, but ? if translates
- Australia: exploring use of probiotics, single study, poor design
- SLIT vs. OIT still being hashed out—SLIT appears "safer" but less effective
- Limited long-term follow up exists, few studies testing sustained non-response
- EoE ***most definitely*** occurs, and some reactions are worse than one's baseline
- Few studies have addressed any patient-oriented outcome
- Industry trials have started—how will these change the landscape?
- Omalizumab pre-tx, multiple food OIT still in infancy, studies poorly designed

Buchanan et al J Allergy Clin Immunol 2006; 119: 199-20
Hofman et al. J Allergy Clin Immunol 2009; 124: 1154-60
Skripak et al J Allergy Clin Immunol 2008; 122: 1154-60
Varshney et al J Allergy Clin Immunol 2011; 127: 654-60
Burks et al. N Engl J Med 2012; 367:233-243
Burks et al J Allergy Clin Immunol 2015; 135; 1240-8
Blumchen et al J Allergy Clin Immunol 2010: 126: 83-91
Jones SM et al J Allergy Clin Immunol 2009; 124: 292-300
Narisety et al J Allergy Clin Immunol 2009; 214: 618-11
Kim et al J Allergy Clin Immunol 2011; 127 640-6
Fleischer et al J Allergy Clin Immunol 2013; 131: 119-27
Kim et al J Allergy Clin Immunol 2011; 128:125-31

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Food Allergy QoL: Understanding the Health Benefits of Therapy

QoL in Food Allergic Disorders

- Two types of QoL being measured
  - --The patient (usually a child, directly affected by disease)
  - --The parent (indirectly affected by disease, has spillover effects)
  - --Unclear who is more affected or which is more important
- Are both generic, disease specific measures
- For food allergy, generic index is not sensitive
  - --Low mortality, rare symptoms = no large changes in health status
  - --Food allergy specific measures note the **daily burden of vigilance**
  - --Often a perception that accidental ingestion will be fatal

Flokstra-de Blok BMJ et al. Clin Exp Allergy 2012; 42: 1014-20

Food Allergy Disease Burden

- Fear/persistent vigilance for accidental reaction
- Fear of hidden ingredients
- Fear of being able to treat a reaction
- Burden of no cure for the disease
- Burden of food avoidance/label reading
- Limitation on activity/travel
- Social stigma/inclusion and interactions
- Bullying
- Empowerment (or lack thereof)

QoL as an OIT Outcome Measure

- Limited patient reported outcomes from OIT
  - --One US trial, one UK trial reported QoL improvement
- Stanford group investigating QoL in multi-food OIT
- Phase I patients in mOIT/Omalizumab-OIT trials
  - --Noted significant improvement vs. baseline score over time (0-24 months), in all domains and at each time point
  - --Noted no change in a small control group
  - --Less change noted in pts with asthma or respiratory reactions during OIT, and more change in older pts or those undergoing >4 food OIT
  - --Effect noted for both the mOIT and for the omalizumab trials
- Conclusions limited by validity and power issues but promising

Arasi et al Allergy Asthma Clin Immunol 2014; 10; 57-64
Otani et al Allergy Asthma Clin Immunol 2014; 10; 25-32

QoL Needs Assessment

- We know patients suffer, but can we fix this?
- Understand what contributes to poor QoL
- Weight/importance of child vs. caregiver QoL
- Bark worse than the bite? Perception vs. reality
- Determine/rectify clinic vs. self-report differences
- Determine effects of MD knowledge, variation
- Does QoL differ by region of the US
- Explore relationship between QoL and self-efficacy
- Integration of QoL as a clinical and research outcome

A Quick Primer on the Costs of Food Allergy in the US

Understanding the Economic Costs that Factor into Decision Making and Potential Benefits of Therapy

Individual and Societal Costs

Gupta, RS et al. JAMA pediatrics 167.11 (2013): 1026-1031.
Slide courtesy of Ruchi Gupta and adapted.

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Willingness to Pay

	Annual Costs, US$			
			95% CI	
Characteristic	Total (in Billions)	Per Child	Total (in Billions)	Per Child
WTP	20.8	3504	(15.7-25.7)	(2652-4344)
Costs borne by families				
Out-of-pocket treatment	5.5	931	(4.7-6.4)	(793-1080)
Lost labor productivity	0.77	130	(0.53-1.0)	(89-175)
Opportunity	14.2	2399	(10.5-18.4)	(1771-3104)
Total				
Reported costs borne by families	20.5	3457	(16.7-24.9)	(2816-4208)
Direct medical costs	4.3	724	(2.8-6.3)	(472-1063)
Reported costs	24.8	4184	(20.6-29.4)	(3475-4960)

Gupta, RS et al. JAMA pediatrics 167.11 (2013): 1026-1031.
Slide courtesy of Ruchi Gupta and adapted.

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Direct Medical Costs

Characteristic	Children With Visit, % (SE)	Visits per Child, Mean (SE)	Cost, US $		
			Visit	Child	Overall Annual (in Millions)
Visits					
Pediatrician	42 (2)	.82 (.05)**	112	92	543
Allergist	41 (2)	.79 (.05)**	175	138	819
Pulmonologist	14 (1)	.07 (.01)**	175	12	71
Nutritionist	17 (1)	.16 (.04)**	100	16	96
Alternative Provider	17 (1)	.23 (.05)**	100	23	136
Emergency Department	13 (1)	.18 (.02)***	711	129	764
Inpatient Hospitalization Stays	4 (1)	.05 (.01)***	6269	314	1863
Total Direct Medical Costs				724	4292

*Direct medical costs are medical costs borne by the health care system associated with prevention, diagnosis, and treatment of food allergies.

Gupta, RS et al. JAMA pediatrics 167.11 (2013): 1026-1031.
Slide courtesy of Ruchi Gupta and adapted.

Out-of-Pocket Costs

Variable	% Reporting Cost (SE)	Mean Direct Out-of-Pocket Costs, US$ (SE)	Cost Per Child, US$	Overall Annual Cost (in Millions), US$
Visits to the physician's office of health clinic (including copays)	52.5 (2.2)	160 (14)	84	499
Visits to the emergency room (including copays)	16.1 (1.6)	247 (42)	40	235
Overnight Stays at the hospital	10 (1.4)	411 (182)	41	244
Travel to and from health care visits (including ambulance use; parking expenses)	27.7 (1.8)	91 (14)	25	149
Epinephrine injectors	35.9 (1.9)	87 (4)	31	184
Antihistamines	50.8 (2.2)	62 (4)	32	188
Other prescription/nonprescription medications	29.3 (1.9)	122 (13)	36	211

Gupta, RS et al. JAMA pediatrics 167.11 (2013): 1026-1031.
Slide courtesy of Ruchi Gupta and adapted.

Opportunity Costs

Characteristic	Cost			
		US$		
	Reporting, % (SE)	Opportunity, Mean (SE)	Per Child	Overall Annual (in Billions)
Career has been restricted	5.7 (0.9)	15 655 (2471)	892	5.3
A job had to be given up	4.9 (0.7)	29 657 (4151)	1453	8.6
A job was lost through dismissal	1.9 (0.6)	14 849 (7479)	282	1.7
A job change was required	2.5 (0.6)	10 605 (3161)	265	1.6
Any job-related opportunity cost (total amount)**	9.1 (1.0)	32 719 (4166)	2977	17.6
Any job-related opportunity cost (maximum amount)***	9.1 (1.0)	26 363 (2545)	2399	14.2

*Opportunity cost is the additional cost associated with activities forgone as a result of a child's food allergy
**All possible responses were used to calculate job-related opportunity cost
***Only the maximum of 4 possible responses was used to calculate job-related opportunity cost

Gupta, RS et al. JAMA pediatrics 167.11 (2013): 1026-1031.
Slide courtesy of Ruchi Gupta and adapted.

Income Disparity of Costs

Type of Cost	Mean Annual Costs (SE), US$		
	<$50K	$50K-99K	≥$100K
Total Direct Costs borne by health care system	**1374 (274)**	**1024 (125)**	**940 (128)**
ER and Hospitalization costs*	**1021 (209)**	**434 (106)**	**416 (94)**
Specialist costs**	**228 (21)**	**330 (27)**	**311 (18)**
Total Out-of-Pocket Costs borne by families	**3174 (858)**	**3434 (658)**	**5062 (1168)**
Medication costs***	**171 (26)**	**275 (30)**	**366 (44)**
Special food costs	**744 (216)**	**941 (230)**	**1545 (347)**

*p<0.05, **p<0.01, ***p<0.001 for F-test of equality of means across groups.

Gupta, RS et al. JAMA pediatrics 167.11 (2013): 1026-1031.
Slide courtesy of Ruchi Gupta and adapted.

Racial/Ethnic Cost Disparity

	Mean Annual Costs (SE), US$			
Type of Cost	White	Black	Hispanic	Asian
Total Direct Costs borne by health care system***	999 (104)	493 (109)	643 (224)	885 (514)
ER and Hospitalization costs***	504 (79)	108 (60)	395 (220)	1271 (630)
Specialist costs***	310 (13)	157 (40)	127 (37)	101 (36)
Total Out-of-Pocket Costs borne by families***	4203 (750)	395 (452)	1093 (856)	1327 (1,948)
Medication costs***	312 (28)	52 (18)	148 (78)	87 (37)
Special food costs***	1213 (200)	177 (501)	219 (281)	148 (290)

*p<0.05, **p<0.01, ***p<0.001 for F-test of equality of means across groups.

Gupta, RS et al. JAMA pediatrics 167.11 (2013): 1026-1031.
Slide courtesy of Ruchi Gupta and adapted.

Why Choose Therapy

- Food allergy affects 8% of children
  - --Direct/Indirect cost of $24.8B/yr
  - --Personal cost of $4,184/patient/yr
- No known cure or treatment
- Nut, seed, seafood allergies lifelong and severe
- Reaction severity poorly predictable
- Accidental reactions from trace amounts occur
- Reduced HRQL associated with food allergy

Gupta et al JAMA Pediatr 2013; 167: 1026-31
Greenhawt M. Ann Allergy Asthma Immunol 2014; 113: 506-12
Sampson HA J Allergy Clin Immunol 2014; 134: 1016-25

Why Not Choose Therapy

- It's effect is unproven at best
  - --Still in phase II→III, cannot predict who will be successful
  - --No proven long term clinical or immunologic effects
  - --Unclear outcomes, duration of therapy, long term costs
- Highly subjective designation of safe
  - --High % of participants react, reaction severity worsens
  - --Some develop EoE (possibly a worse disease)
- Not FDA approved, but private practices may offer it
- Are risks worth the benefits, considering natural hx?
- Health utility for avoidance as management is 0.9

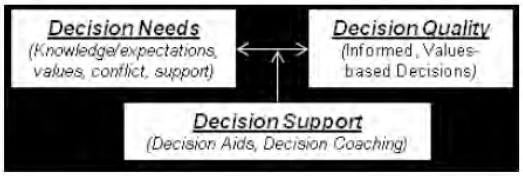
Buchanan et al J Allergy Clin Immunol 2006; 119: 199-20; Hofman et al. J Allergy Clin Immunol 2009; 124: 1154-60; Shirpak et al J Allergy Clin Immunol 2008; 122, 1154-60; Varshney et al J Allergy Clin Immunol 2011; 127: 654-60; Burks et al. N Engl J Med 2012; 367:233-243; Burks et al J Allergy Clin Immunol 2015; 135: 1240-8; Blumchen et al J Allergy Clin Immunol 2010; 126: 83-91; Jones SM et al J Allergy Clin Immunol 2009; 124: 292-300; Narisety et al J Allergy Clin Immunol 2009; 214: 610-11; Kim et al J Allergy Clin Immunol 2011; 127 640-6; Fleischer et al J Allergy Clin Immunol 2013; 131: 119-27; Kim et al J Allergy Clin Immunol 2011; 128:125-31

Decisions to Make

- Is the process of OIT worse than living with disease?
- What are the caregiver goals of therapy
- What are the caregivers trade-offs and relative value of the therapy compared to avoidance
- What are the caregiver health beliefs"
- How likely does the caregiver think the chances of success are?
- With other potential therapies, is OIT the best choice?

Ottawa Decision Support Framework

Figure 1. Ottawa Decision Support Framework



- Framework guiding development/evaluation of decision support interventions.
- Participants 'decisional needs' (e.g. knowledge, values, support) will affect the decision quality (informed, values concordant decisions) which impacts outcomes such as emotions (regret, blame), behavior, and use of health services.
- Stakeholders include caregivers, family members, and clinicians.
- The framework asserts that decision support can improve decision quality by addressing unresolved 'decisional needs.'

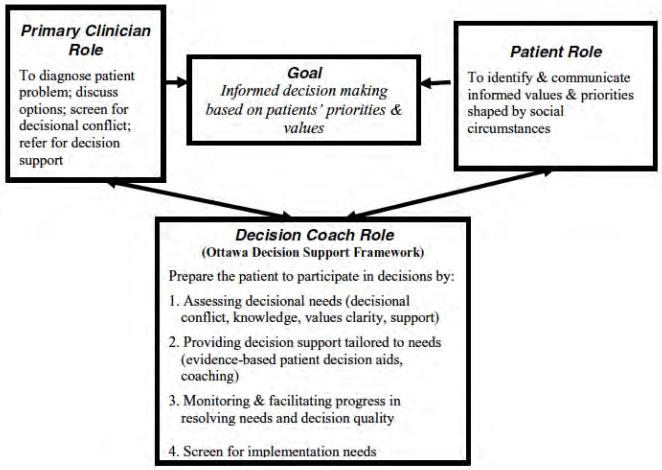
O'Connor AM. Ottawa Decision Support Framework to Address Decisional Conflict. www.ohri.ca/decisionaid

Principles of Shared Decision Making

- Develop a partnership with the patient.
- Establish or review the patient's preference for information, e.g. amount and format.
- Establish or review the patient's preferences for role in decision-making.
- Ascertain and respond to patients' ideas, concerns, and expectations.
- Identify choices and evaluate the research evidence in relation to the individual patient.
- Present (or direct to) evidence, taking into account the above steps, and help the patient reflect upon and assess the impact of alternative decisions with regard to their values and lifestyles.
- Make or negotiate a decision in partnership, manage conflict.
- Agree upon an action plan and complete arrangements for follow-up.

Elwyn et al British Journal of General Practice, 2000, 50, 892-897.

Coaching a Shared Decision



Stacey et al. Worldviews on Evidence-Based Nursing 2008; 5(1):25–35.

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Choosing Wisely-Reprise

Pros of Therapy

- Affects 8% of children
  --$24.8B/yr, $4,184/patient/yr
- No cure or treatment, some allergies lifelong
- Reaction severity poorly predictable
- Reduced HRQL associated with food allergy
- WTP of ~$3500/child
- Multiple options, hot area of focus/funding

Cons of Therapy

- Effect is unproven
  --Still in phase II→III
  --Cannot predict success
  --Unclear outcomes, duration, costs
- Safety is subjective
  --High OIT% react
  --Reaction severity worsens, EoE develops
- Not FDA approved, but offered in some practices
- Are risks worth the benefits?
- Avoidance health utility=0.9

Buchanan et al J Allergy Clin Immunol 2006; 119: 199-20; Hofman et al. J Allergy Clin Immunol 2009; 124: 1154-60 Shiraak et al J Allergy Clin Immunol 2008; 122; 1154-60; Varshney et al J Allergy Clin Immunol 2011; 127: 654-60 Burks et al. N Engl J Med 2012; 367:233-245 Burks et al J Allergy Clin Immunol 2015; 135; 1240-8

Blumchen et al J Allergy Clin Immunol 2010; 126: 83-91 Jones SM et al J Allergy Clin Immunol 2009; 124: 292-300 Narisety et al J Allergy Clin Immunol 2009; 214: 610-11 Kim et al J Allergy Clin Immunol 2011; 127:640-6 Fleischer et al J Allergy Clin Immunol 2013; 132: 119-27 Kim et al J Allergy Clin Immunol 2011; 128:125-31

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More Decisions to Make

- Is the process of OIT worse than living with disease?
- What is the bill of goods sold to parents?
- Why would a parent enroll their child?
  --High risk therapy, but disease is not fatal
  --Health utility for avoidance as option is very high
- Who is an optimal candidate
- Is therapy even cost-effective—biggest unknown!
- With multiple therapies, which is the best choice?
- What are caregiver goals and preferences?

Conclusions

- Entering therapy a very complex decision
- Highly personal, based on preferences and trade-offs acceptable to caregiver
- Data support high utility for avoidance, low WTP, risk-averse preferences, but that therapy betters QoL
- Cost-effectiveness of therapy will be crucial to determine
- Providers must learn how to coach a shared decision