FDA/UMD PUBLIC WORKSHOP
Accelerating Drug Development in Pediatric Patients

What Criteria Justify Use of a 'Bridging Biomarker' for Extrapolation to Pediatric Patients?

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Pediatrician: Lamenting a "reliance on 'animal studies' "

Cautionary Illustration:

Sildenafil in Pulmonary Arterial Hypertension (PAH)

~ Setting: Adults with PAH receiving Sildenafil

✓ Substantial evidence of safety & efficacy of Sildenafil in adult patients with PAH ⇒ Regulatory Approval

- Established beneficial effects on 6MWD
- Supportive evidence: Effects on hemodynamics biomarkers revealed increasing benefit with increasing doses

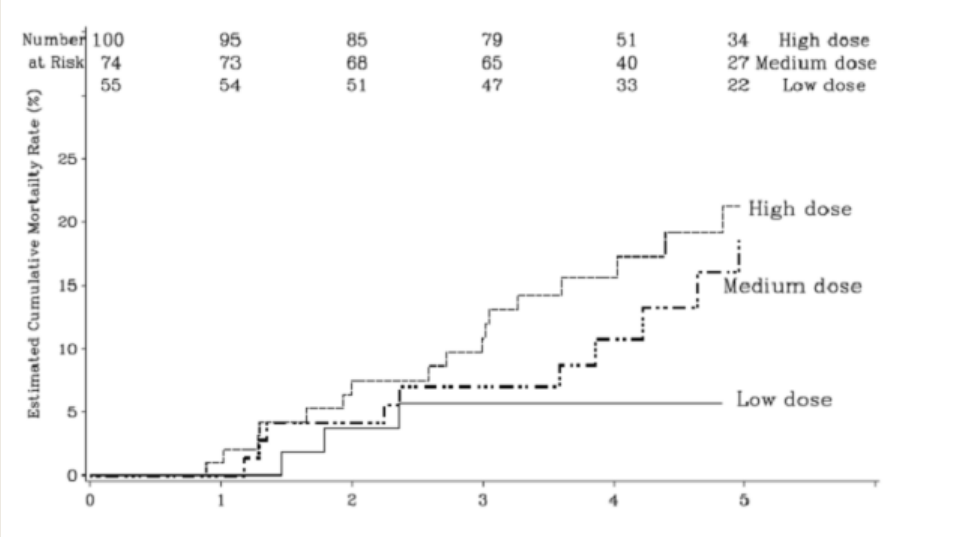
~ Setting: Pediatric Patients with PAH receiving Revatio (i.e., Sildenafil)

✓ Pediatric Written Request, linked to Viagra (i.e., Sildenafil) in ED

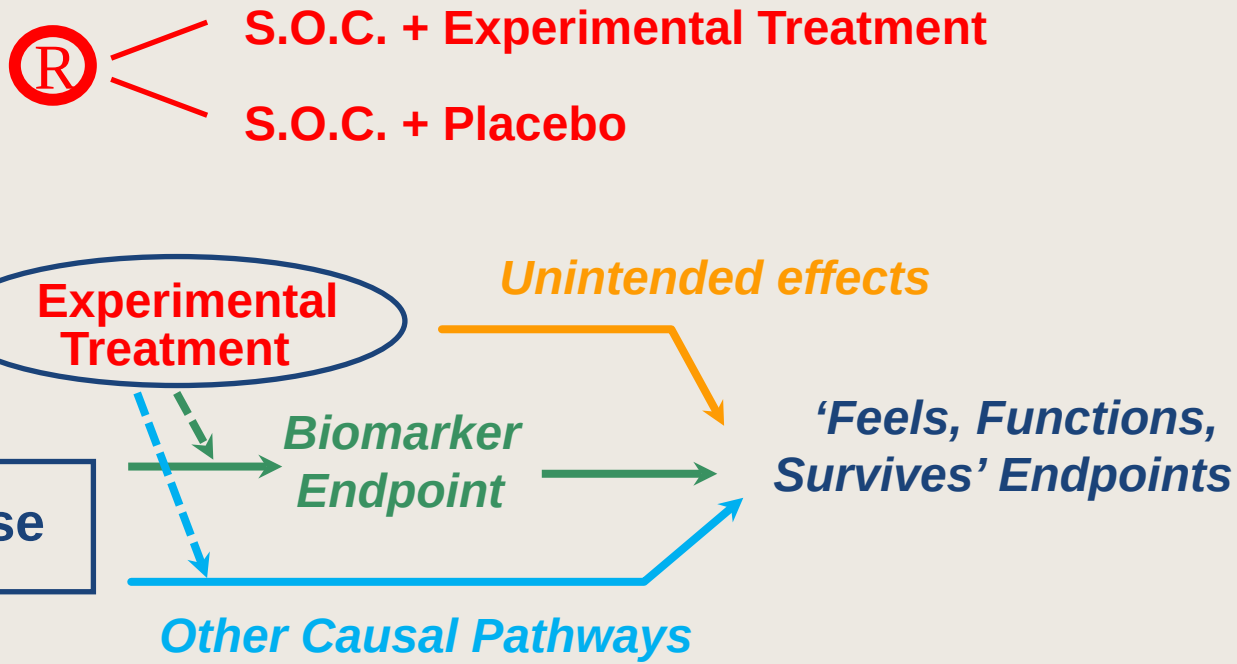
- As in adults, beneficial effects on hemodynamics biomarkers with increasing benefit with increasing doses
- Substantial evidence of increased mortality with increasing doses

“FDA Drug Safety Communication: FDA recommends against use of Revatio in children with pulmonary hypertension”

“Plot of mortality in the pediatric clinical trial as a function of Revatio dose.”

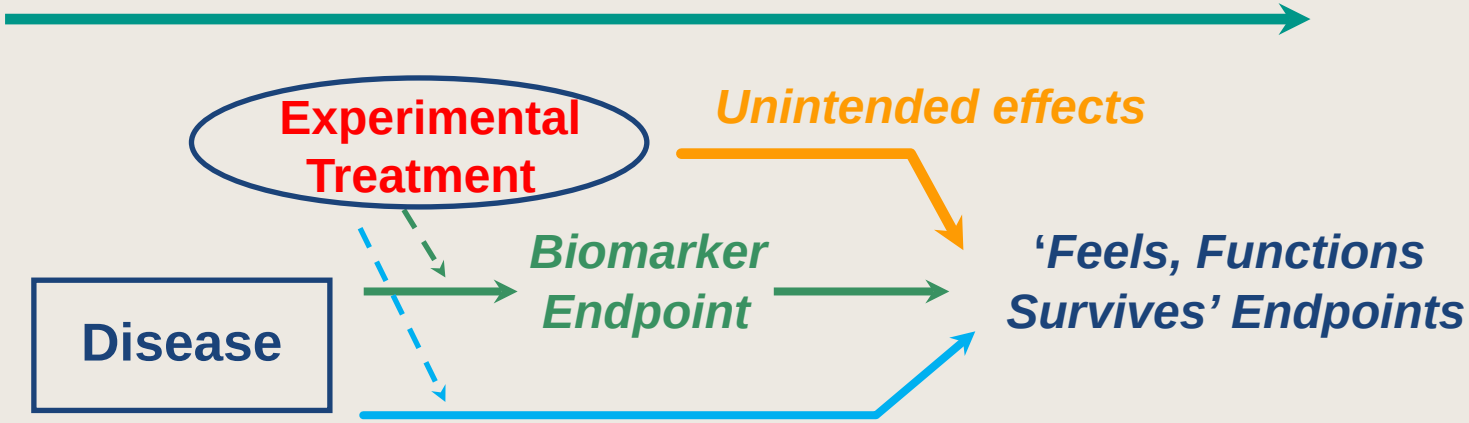


“The hazard ratio for high dose compared to low dose was 3.5 (p=0.015)”

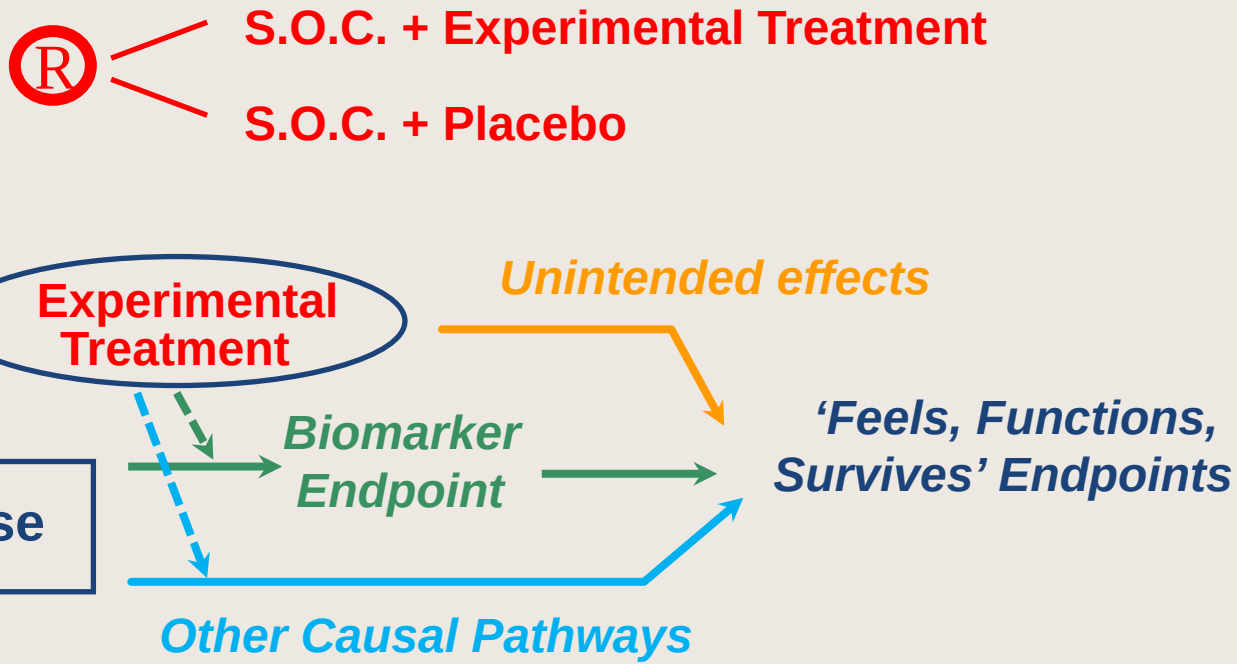


*The treatment's effect on the **Biomarker Endpoint** could **overestimate** or underestimate the treatment's true clinical efficacy*

Interventions having Mechanisms of Action Independent of the Disease Process



ESAs: ↑ **Thrombosis** ⇒ ↑ Mortality
Cox-2s: Vioxx, Bextra: ↑ **CV Risk Factors** ⇒ ↑ CV Death/ MI /Stroke
Troglitazone: ↑ **Serious Hepatic Risks** ⇒ ↑ Morbidity
Natalizumab: ↑ **Prog. Multifocal Leukoencephalopathy** ⇒ ↑ Morbidity / Mortality
Ezetimibe/Simvastatin: **Block pathways linked to CA protection** ⇒ ↑ Cancer Mortality?
Long Acting *β*-Agonists: ↑ Asthma-related deaths
Torcetrapib: **Activates renin angiotensin system** ⇒ ↑ **BP** ⇒ ↑ Mortality



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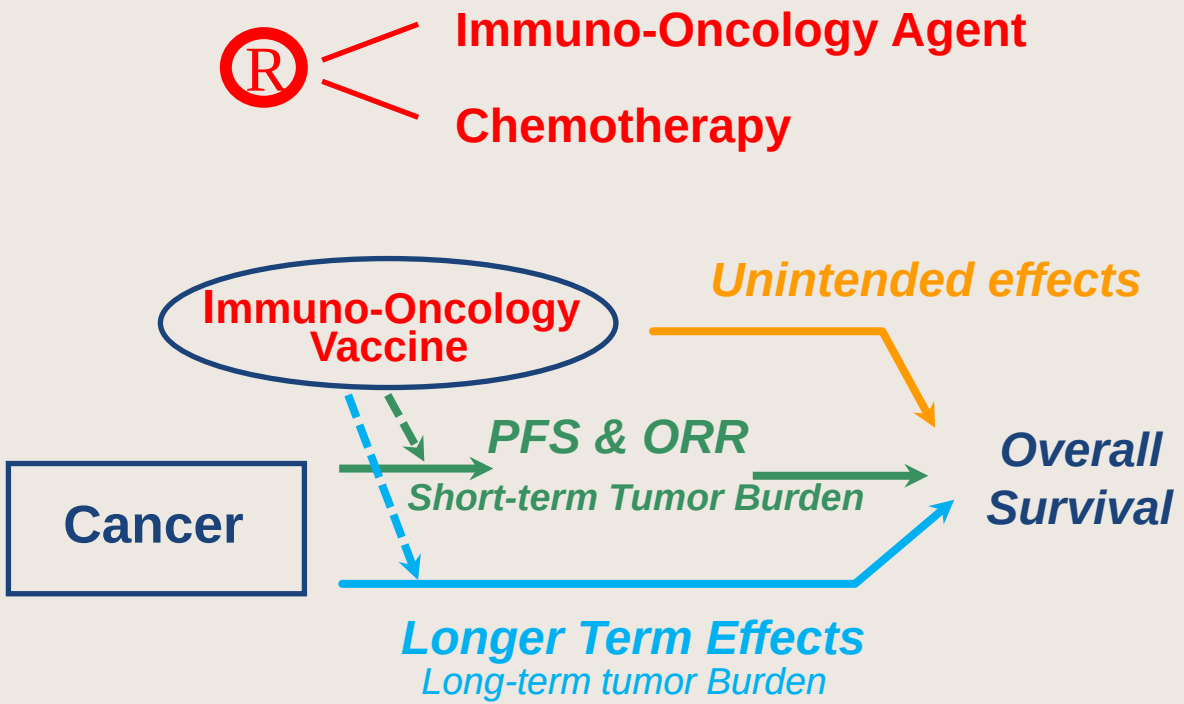
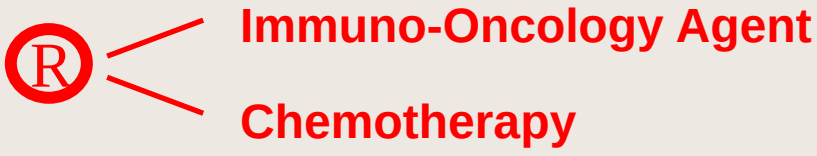
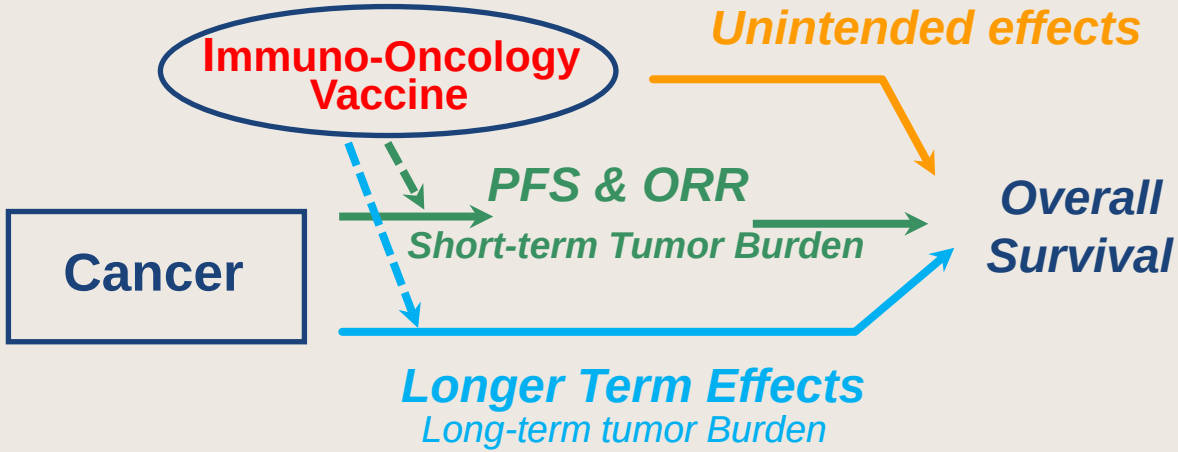


DeMets DL, Psaty BM, Fleming TR. When can intermediate outcomes be used as surrogate outcomes? *JAMA* February 27, 2020

Different Classes of Agents





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Establishing Validity of a Replacement Endpoint

How does one establish a biomarker endpoint to be valid as a replacement endpoint for direct measures about how an individual 'feels, functions or survives'

Key Evidence:

The **net** effect of the treatment
on the '*Replacement*' Endpoint
reliably predicts
the **net** effect of the treatment
on the *'Feels, functions, survives'* Endpoint

Illustration: Validating a Biomarker Surrogate

FDA Cardio-Renal Advisory Committee: 6/15/2005

- **Anti-Hypertensives**

Effects on ***Blood Pressure*** predicting effects on each of the following, considered individually:

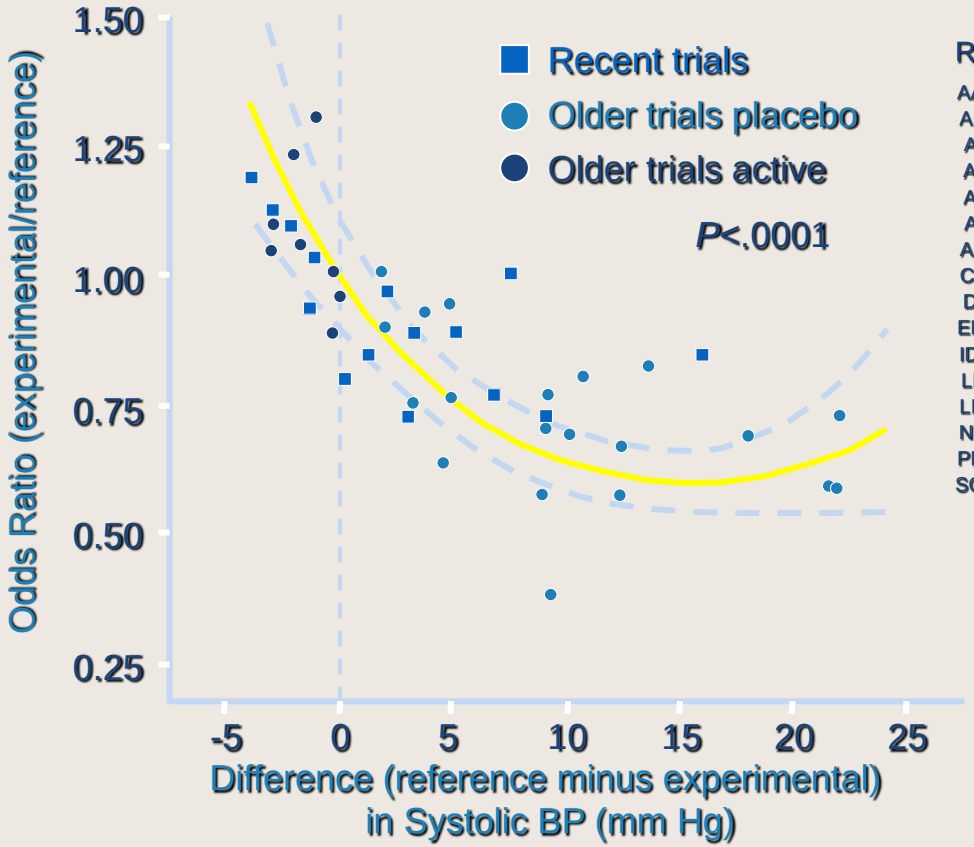
✓ *Stroke, MI, CVD, Mortality, Heart Failure*

… **> 500,000 patients from 43 randomized trials…**

Key: validation was done for each class of agents

…**β-blockers, low dose diuretics, ACE-I, CCBs, ARBs**…

Odds Ratio for CV Events and Systolic BP Difference: Recent and Older Trials



Recent	Older
AASK L vs. H	ALLHAT/Dox
ABCD/NT L vs. H	ATMH
ALLHAT/Aml	EWPHE
ALLHAT/Lis	HEP
ALLHAT/Lis ≥65	HOPE
ALLHAT/Lis Blacks	HO
ANBP2	HOT M vs. H
CONVINCE	INSIGHT
DIABHYCAR	MIDAS/NICS/VHAS
ELSA	L vs. H
IDNT2	MRC
LIFE/ALL	MRC2
LIFE/DM	PART2/SCAT
NICOLE	PATS
PREVENT	PROGRESS/Per
SCOPE	PROGRESSION/Com
	RCT70-80
	RENAAL
	SHEP
	STONE
	STOP 1
	STOP2/CCBs
	STOP2/ACEIs
	Syst-China
	Syst-Eur
	UKPDS C vs. A
	UKPDS L vs. H

43 clinical trials

Staessen et al. *J Hypertens*. 2003;21:1055-1076.

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Institute of Medicine, 2010
"Evaluation of Biomarkers as Surrogate Endpoints"

- ***Addressing Assay Performance***
  …analysis of analytical performance of an assay…
  e.g., limit of quantitation, across lab reproducibility, etc

- ***Evidentiary Assessment***
  …relationship between biomarker & disease state
  …data regarding **effects of interventions on both biomarker and clinically meaningful outcomes…**

- ***Justifying the Proposed Use***
  …determining whether available evidence provides sufficient justification for the **context of use** proposed…

Replacement Endpoints

- A replacement endpoint **cannot** be assumed to be a generic surrogate endpoint for a particular disease

Reasons why use needs setting-specific justification:

- Multiple causal mechanisms of action
- *Breadth*, *Magnitude* and *duration* of effect matters
- Intended and *unintended* effects of intervention

- How does evaluating replacement endpoints impact the public?

Response: Need "*reliable*" as well as "*timely*" evaluation
…not simply *"a choice"*; rather, "*an informed choice*"

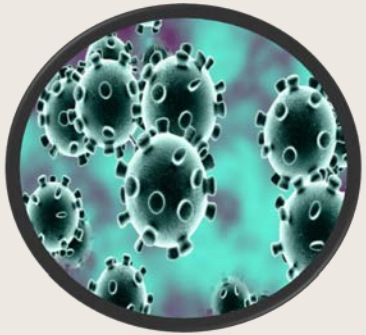
Some Uses of Biomarkers/Replacement Endpoints

- As Measures of **Biologic Activity** of Experimental Treatments
  - ✓ In Proof-of-Mechanism or Proof-of-Concept Trials
  - ✓ In Registrational Trials
- As **Replacement Endpoints** for Registrational Evaluations, in studies specifically intended to evaluate:
  - ✓ Booster dosing strategies to address waning longer-term efficacy
  - ✓ **Extrapolation across populations, e.g., adult to pediatric setting**
  - ✓ New treatments in the class of established effective treatments
  - ✓ New treatments that are in new classes

Straightforward justification

Very Challenging

…The Way Forward…



R

- **SARS-CoV-2 Vaccine**
- **Placebo**

Immune Protective Mechanisms

- **Neutralizing Antibody titre**
- **Binding Antibody titre**
- **IgG & IgA Mucosal Antibody**
- **CD4+ T-cells & CD8+ T-cells**
- **Memory B-cells**

SARS-CoV-2 Vaccine

Unintended effects

Immunologic Biomarker

Risk of Exposure

Virologically Confirmed Symptomatic Covid-19 Disease

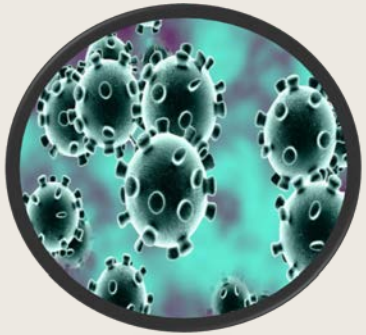
Other Immunologic Biomarkers

…Extrapolating Adults ⇒ Pediatrics:

…The Way Forward…

R → **SARS-CoV-2 Vaccine**

R → **Placebo**



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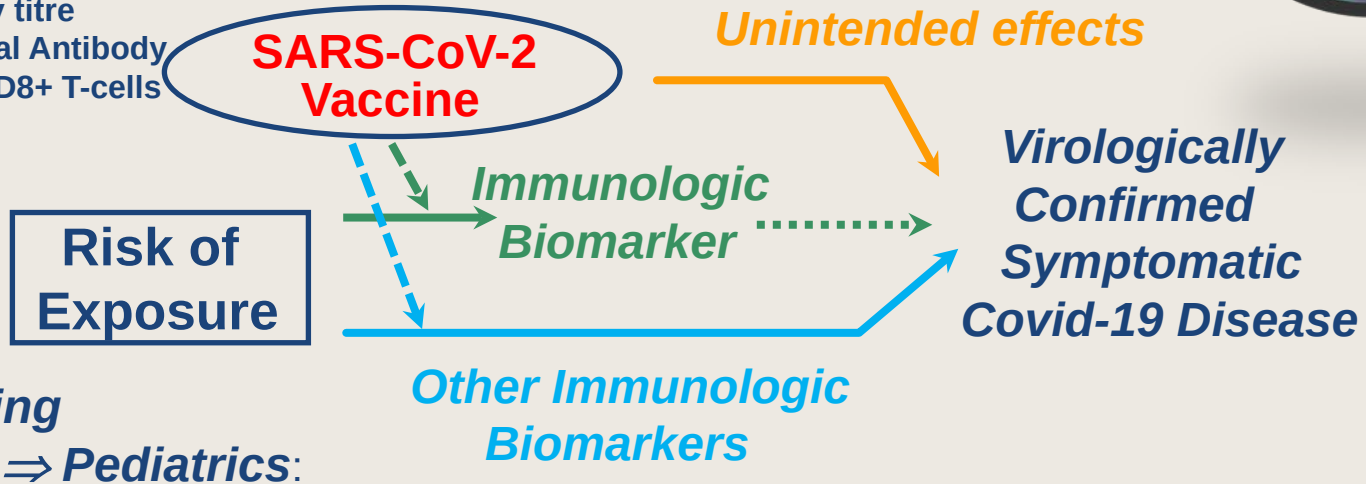

…Extrapolating Adults ⇒ Pediatrics:

- Persuasive evidence of effects on **'feels, functions, survives'** measure(s) in adults
- Evidence that proposed 'bridging biomarker' predicts protective effect of immune responses, including evidence regarding required timing, magnitude, duration of effect on that biomarker
- Justification that '**unintended effects**' would not be substantively more influential in pediatric setting relative to adult setting, to be supplemented by post-marketing data

Conclusions

Biomarkers often have an influential role in
the extrapolation from adults to pediatrics
…keeping in mind that

"A Correlate does not
A Surrogate Make."

* Fleming TR, DeMets DL: Surrogate endpoints in clinical trials: Are we being misled? *Annals of Internal Med* 1996; 125:605-613.

* IOM, 2010. "*Evaluation of Biomarkers & Surrogate Endpoints in Chronic Disease:*. Washington DC. National Academies Press

* Fleming TR, Powers JH: Biomarkers and Surrogate Endpoints in Clinical Trials *Statistics in Medicine* 2012; 31: 2973-2984