



Analysis of trials of orphan diseases: slouching towards Bayesalem

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Or...How I am coming kicking and screaming toward Bayes



Confessions

- I have not used Bayes in phase 3 studies since phenformin
- I do use Bayes in:
 - Dose-finding
 - Sample size calculation
 - Predictive power
- If I were to use Bayes, I wouldn't use flat priors

Orphan diseases

- Problem---not world enough, and time
 - Too few people for a study with adequate power
- Solution
 - Don't study treatments in these diseases
 - Design studies with low power and hope
 - Use Bayes



Rare, orphan, ultra-orphan, neglected....

- Not defined precisely
- We shall use “orphan” from Orphan Drug Act

What is an orphan disease?

- A disease not "adopted" by industry
 - little financial incentive
- An orphan disease may be:
 - Rare
 - US: <200,000 people in the US (5000-7000 of these)
 - A common disease ignored by industry
 - E.g., TB, malaria, typhoid, dengue,

The law in the US

- The US Orphan Drug Act of 1983
 - tax incentives for clinical trials
 - 7 yrs marketing exclusivity for orphan drugs
- Similar laws in Japan, Australia
- EU: "orphan medicinal products" legislation
 - Rare + disorders prevalent only in developing world
 - No tax incentive
 - 10 years of marketing exclusivity

Current US law: “rare disease or condition”

- (1) for drugs: any disease or condition which
 - (A) affects < 200,000 persons in the United States, or
 - (B) affects > 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drugs
- (2 & 3) medical device or a medical food
 - any disease or condition that occurs so infrequently in the United States that there is no reasonable expectation that a medical device or food for such disease or condition will be developed without assistance under subsection (a)



Ultra-orphan disease (cases/50,000 pop)

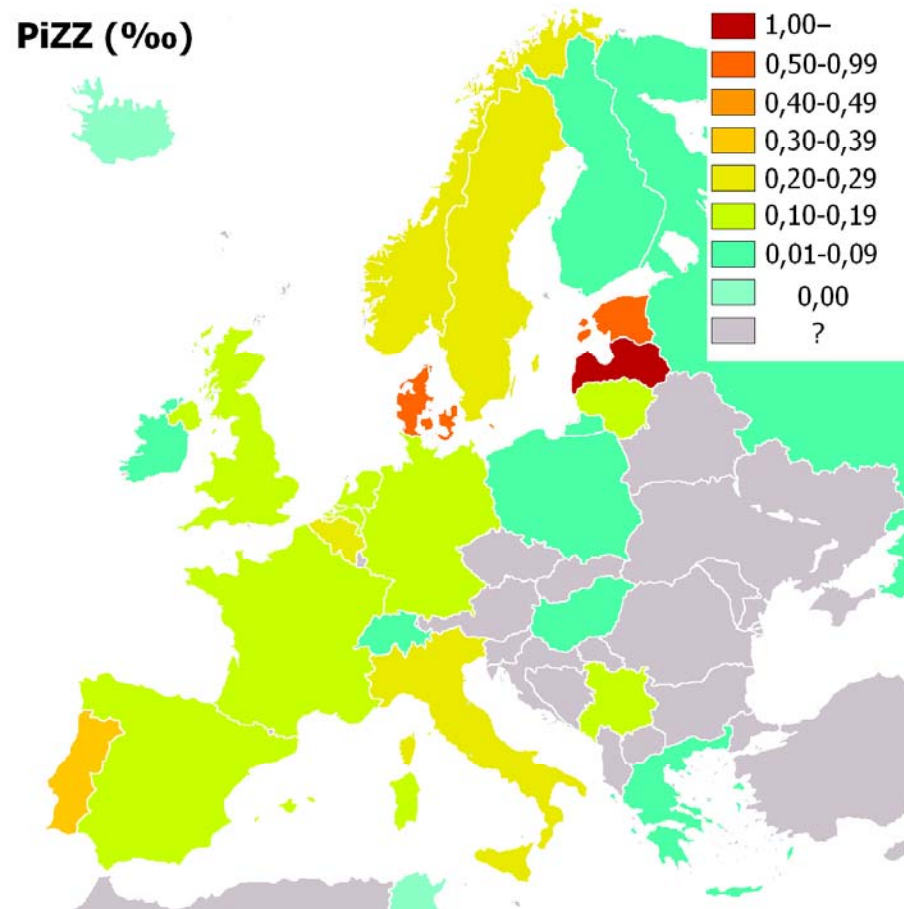
- US: <35
- EU: <25
- Japan: <12.5
- UK: <1



Other issues with ultra-orphans

- Many are infectious
- Many are rare cancers
- Many are genetic
 - So...they are geographically heterogeneous

α -1 antitrypsin (PiZZ) emphysema





Having a rare disease is not uncommon

- European Organization for Rare Diseases:
 - 6% and 8% of EU has at least one rare disease
- National Organization for Rare Diseases (NORD)
 - 20 to 30 million Americans have a rare disease



Wouldn't it be nice to define a family of ultra orphans?

- And then borrow information from one to the other
 - Can we do that with solid tumors?
 - Can we do that with infections?
 - Consider a family of inborn errors of metabolism



The MPS family (mucopolysaccharidoses)

- Mucopolysaccharides (AKA glycosaminoglycans)
 - Long-chain sugar molecules
 - Found in mucus and fluids around joints
 - Connective tissue, cartilage, tendons, bone
 - Cornea
- MPS characterized by an enzyme deficiency

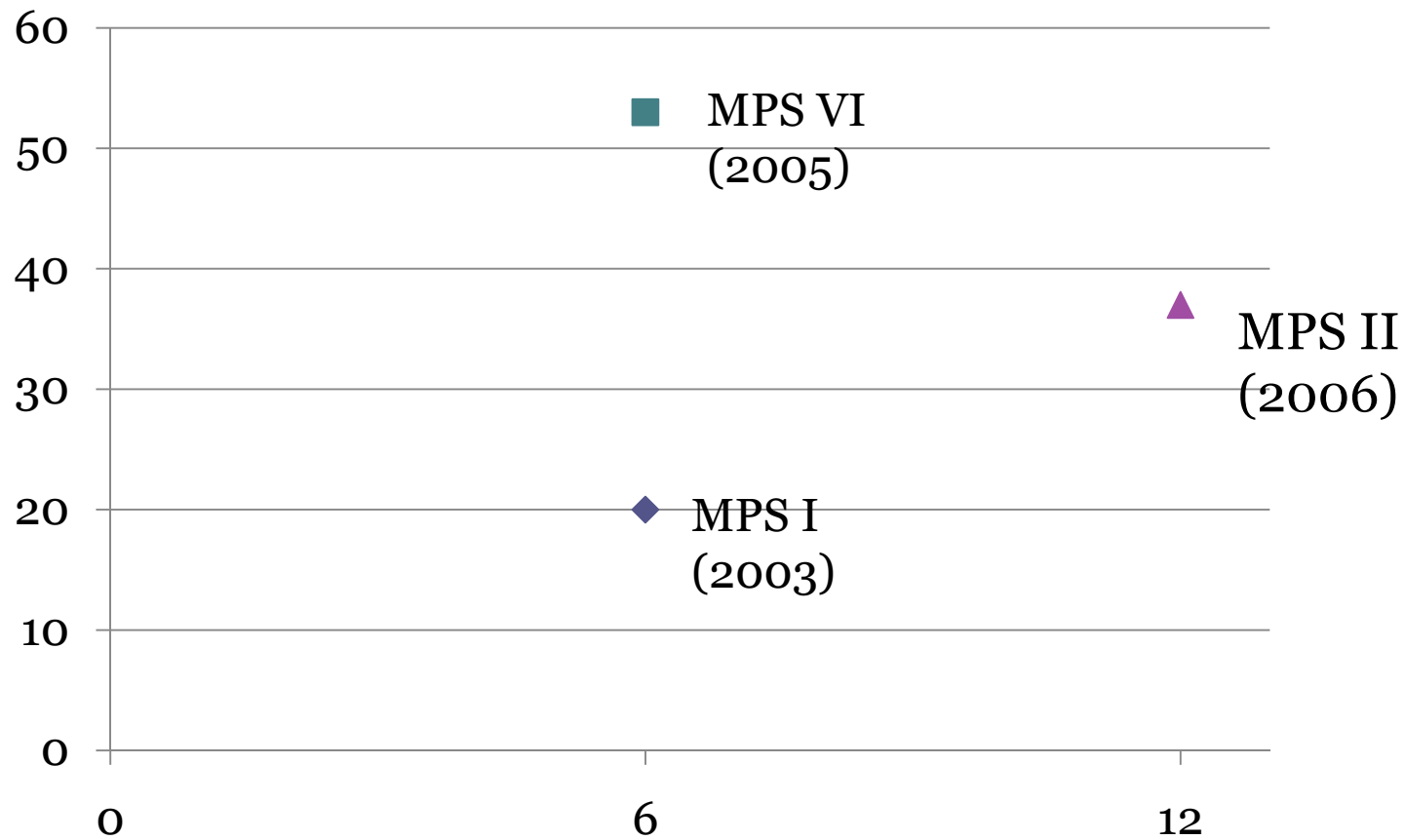
The MPS diseases

#	AKA	Effects
I	Hurler, Sheie	Breathing, heart, corneal clouding, joint stiffness
II	Hunter	Breathing, heart, joint stiffness, cognition
III	Sanfillipo	Hearing, bowel problems, epilepsy, sleep problems
IV	Morquio	Spine, knees, heart, teeth, hearing
VI	Marteau-Lamy	Skeleton, joint stiffness, heart, corneal clouding, teeth
VII	Sly	Retardation, corneal clouding, joint stiffness, skeleton
IX	Only one case	

6 Min Walk Test Results (Δ meters)



6 Min Walk Test Results (Δ meters)



What could we have done after MPS I?

- Could we have made a prior to use for II and VI?
- What about the other MPS diseases?
 - Are we willing to construct a prior from I, II, & VI?
 - Then for a new enzyme we use that prior?
 -

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- If yes, how far can we go?
 - Other families?
 - Infectious disease?
 - Solid tumors?