Changes and Opportunities: The Role of Medical Genetics in the Era of Genomic Testing

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Austin Larson, MD
University of Colorado School of Medicine
Children's Hospital Colorado

Children's Hospital Colorado

School of Medicine
UNIVERSITY OF COLORADO

Financial Disclosure

- I was previously a scientific advisor for HumanCode (a consumer genetics company)
- I will not be discussing consumer genetics in this talk

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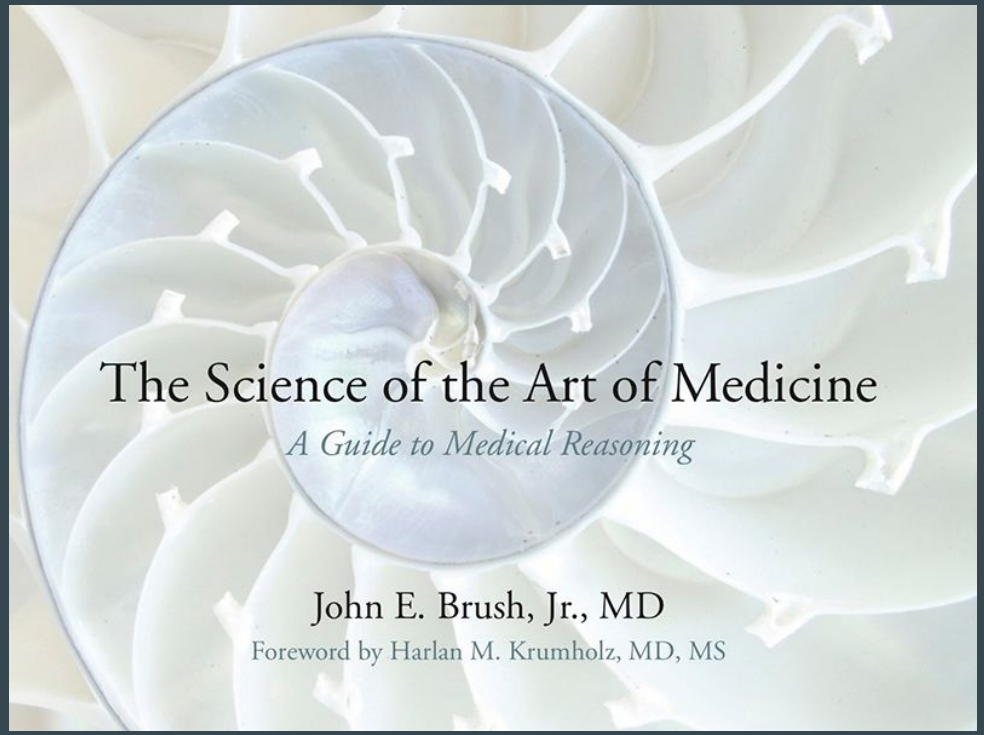
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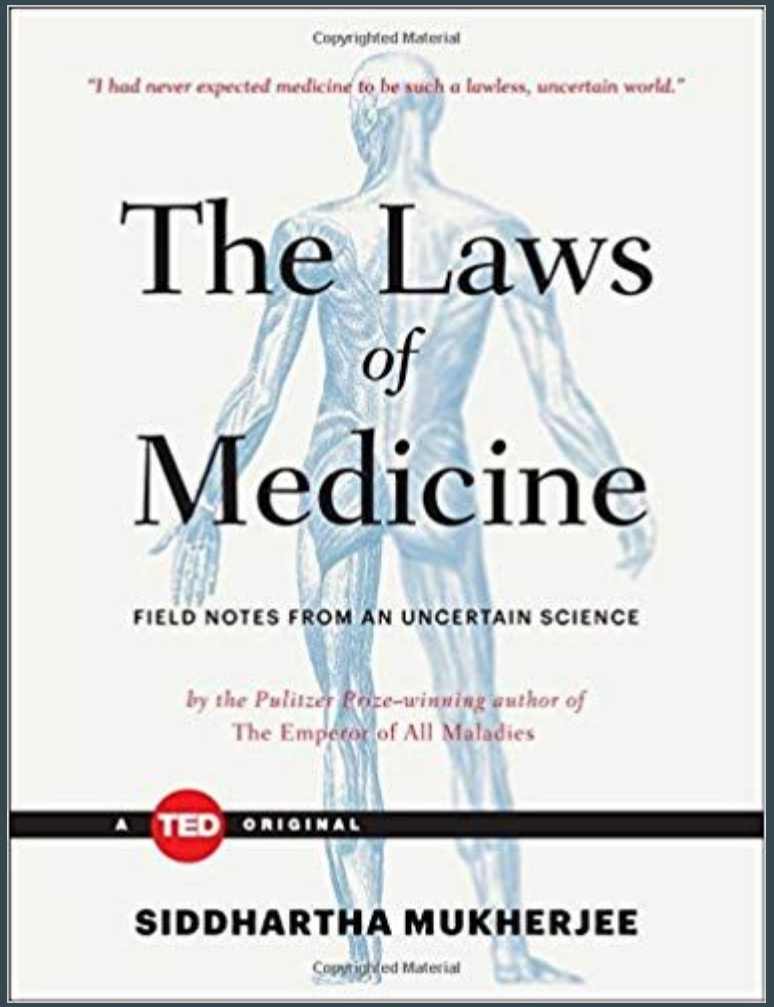
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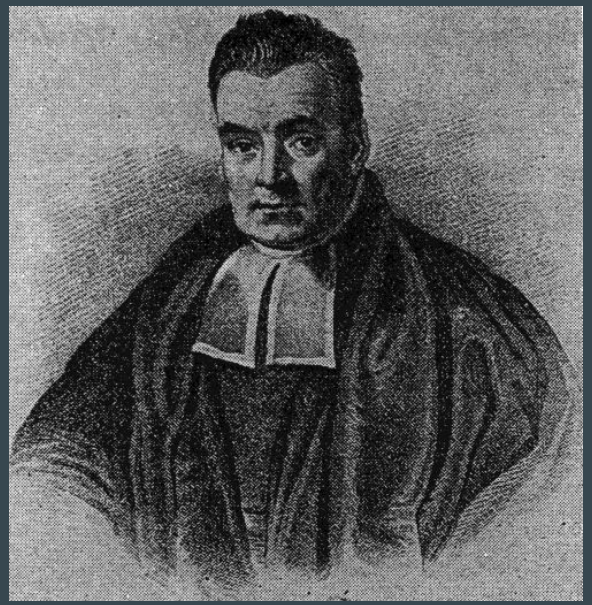
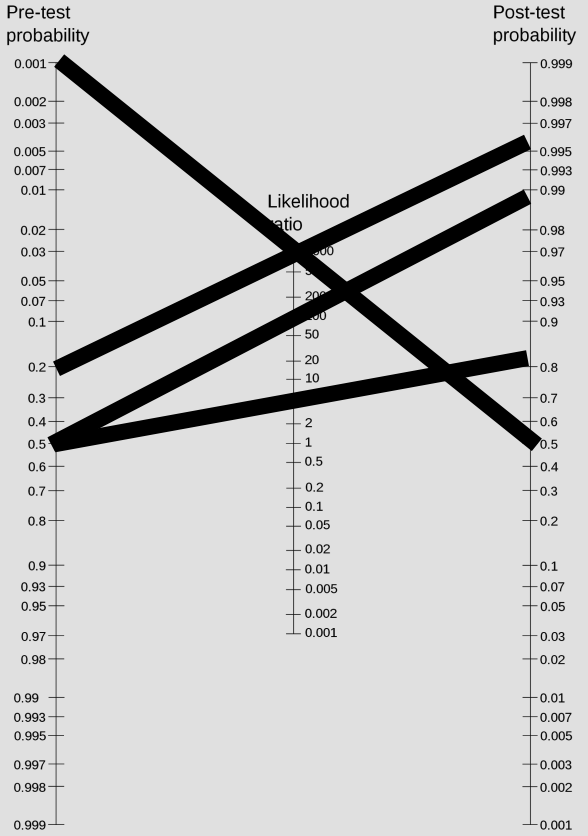
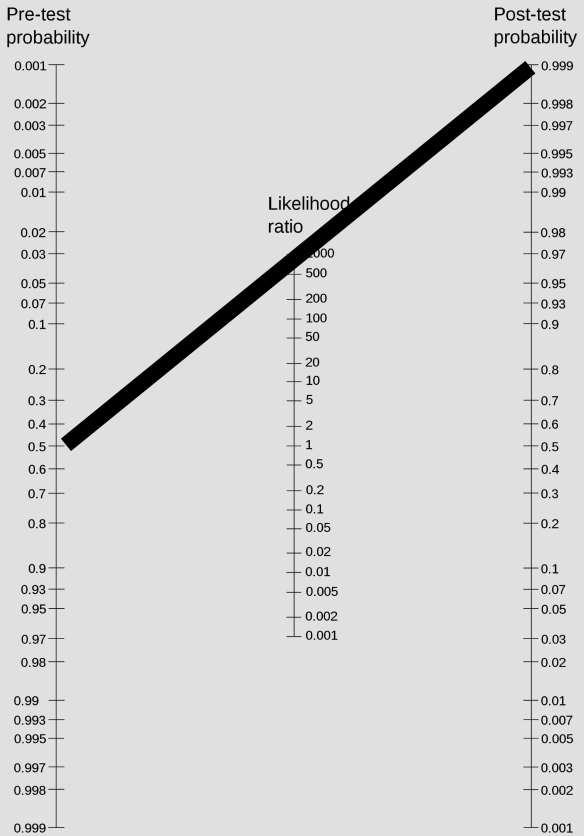


LII. *An Essay towards solving a Problem in the Doctrine of Chances. By the late Rev. Mr.* Bayes, *communicated by Mr.* Price, *in a letter to* John Canton, *M. A. and F. R. S.*

Fagan's Nomogram





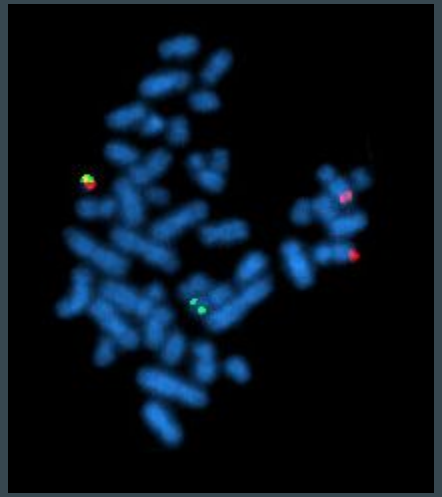
Fagan, T. J. "Nomogram for Bayes's theorem." *New England Journal of Medicine* 293 (1975): 257.

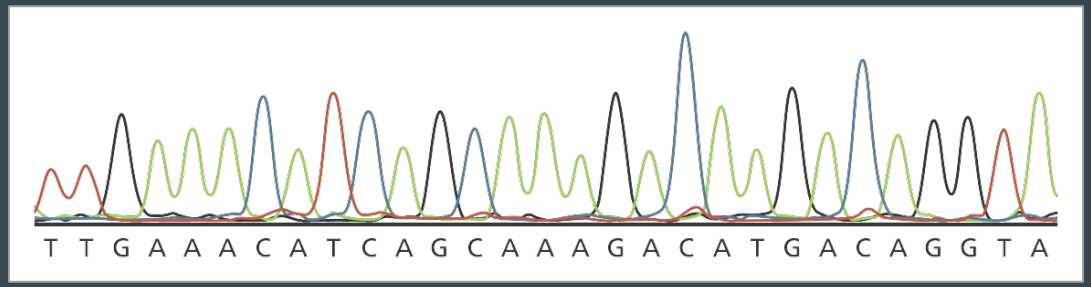
Targeted vs untargeted testing

By Christian Gidlöf - Photo taken by Christian Gidlöf, Public Domain, https://commons.wikimedia.org/w/index.php?curid=2065930

Clinical diagnosis

Targeted testing: FISH or Sanger sequencing





Cognitive biases

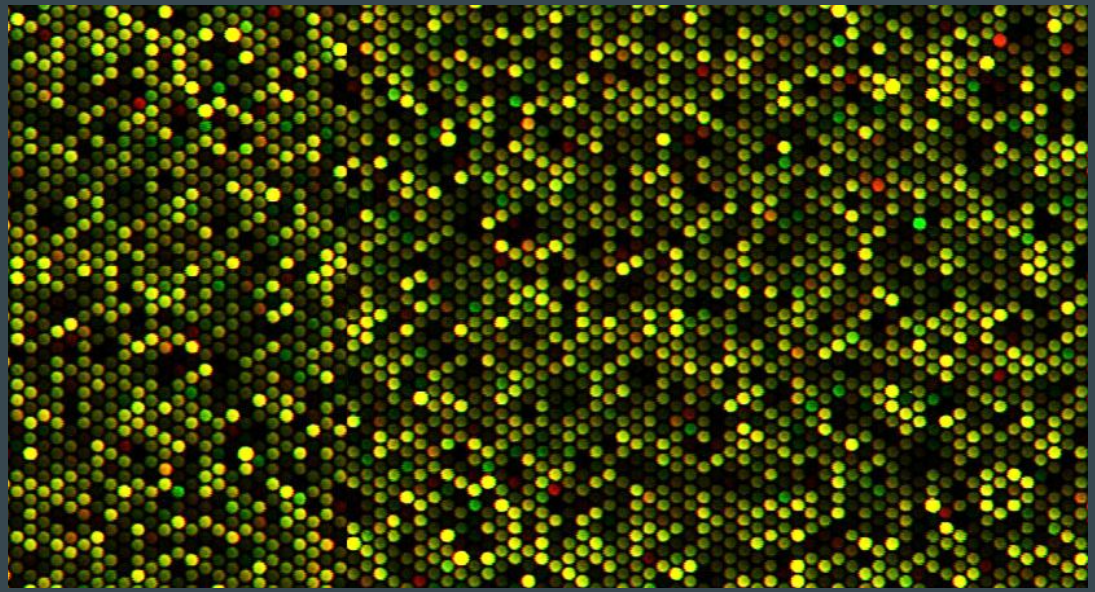
- Base rate neglect
- Diagnostic momentum (anchoring)
- The availability heuristic
- The possibility effect

The use of untargeted testing allows us to bypass many of these biases

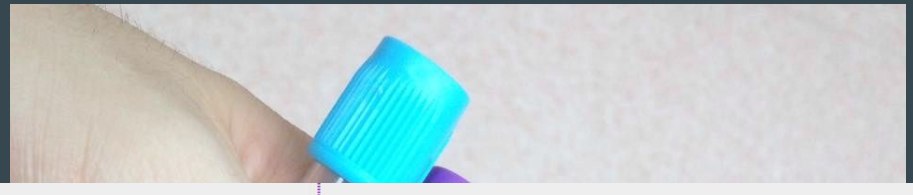
Untargeted testing: Chromosome analysis

Courtesy: National Human Genome Research Institute

Untargeted testing: chromosomal microarray



Metabolic testing



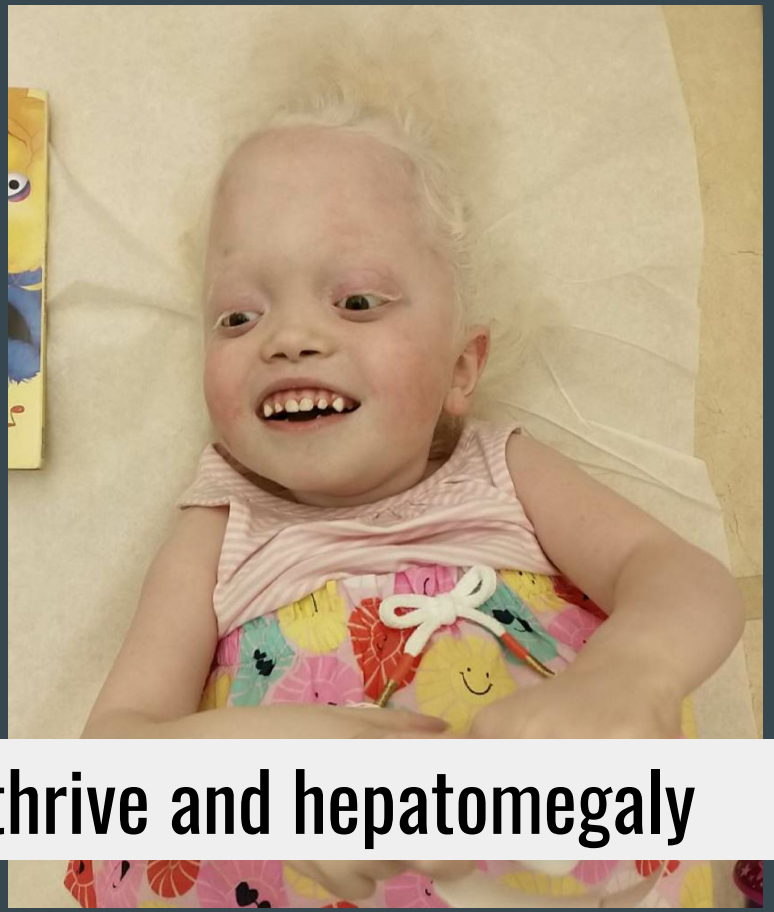
Screening Tests

- Plasma Amino Acids
- Plasma Total Homocysteine
- Urine Creatine Metabolites
- Urine Organic Acids
- Urine Purine & Pyrimidines

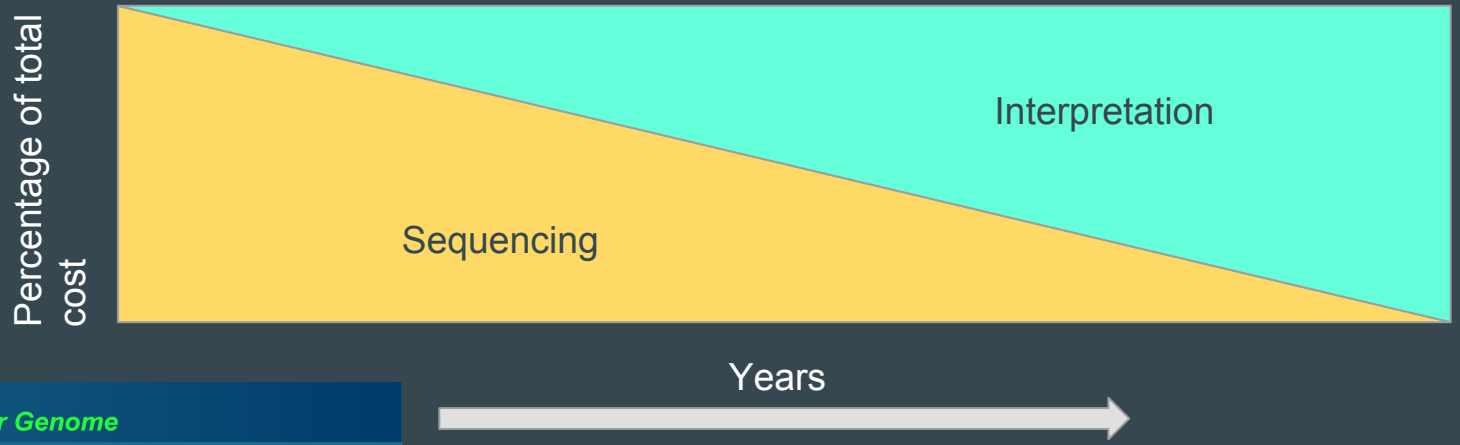
Specific Tests

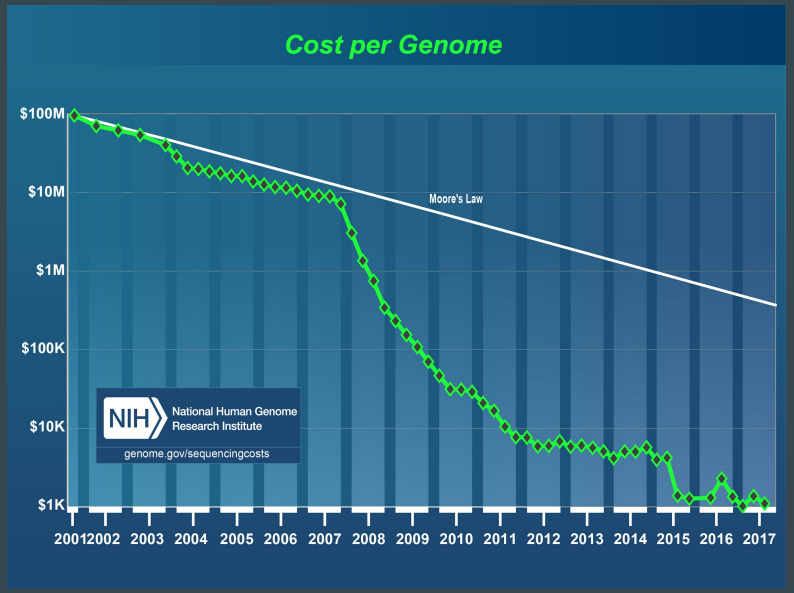
- CSF Amino Acids
- CSF Neurotransmitters
- CSF Other
- Enzyme Activity
- Metals
- Molecular testing
- Miscellaneous
- Urine Glycosaminoglycans
- Urine Oligosaccharides

Lydia's case



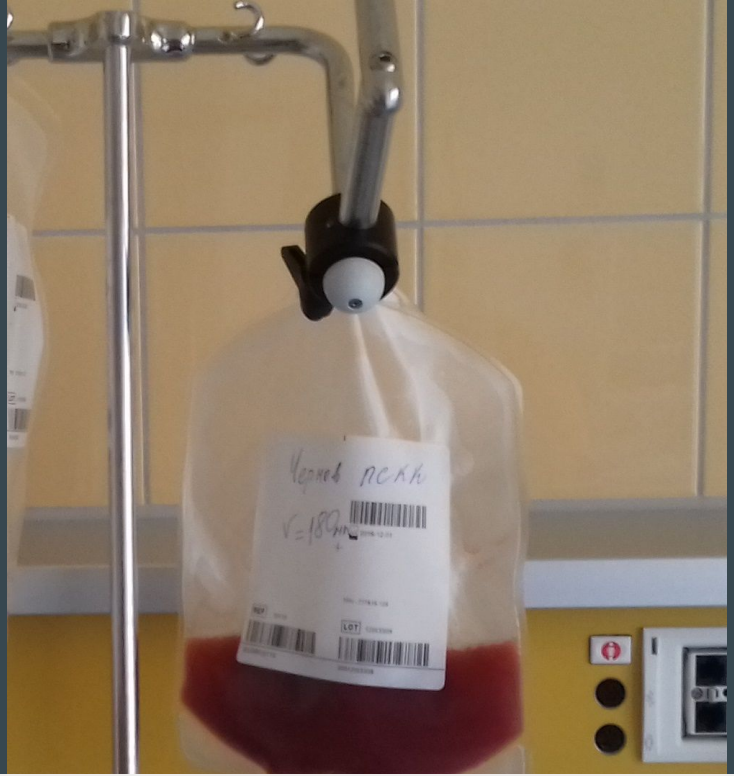
Inpatient consultation for failure to thrive and hepatomegaly





Whole genome sequencing

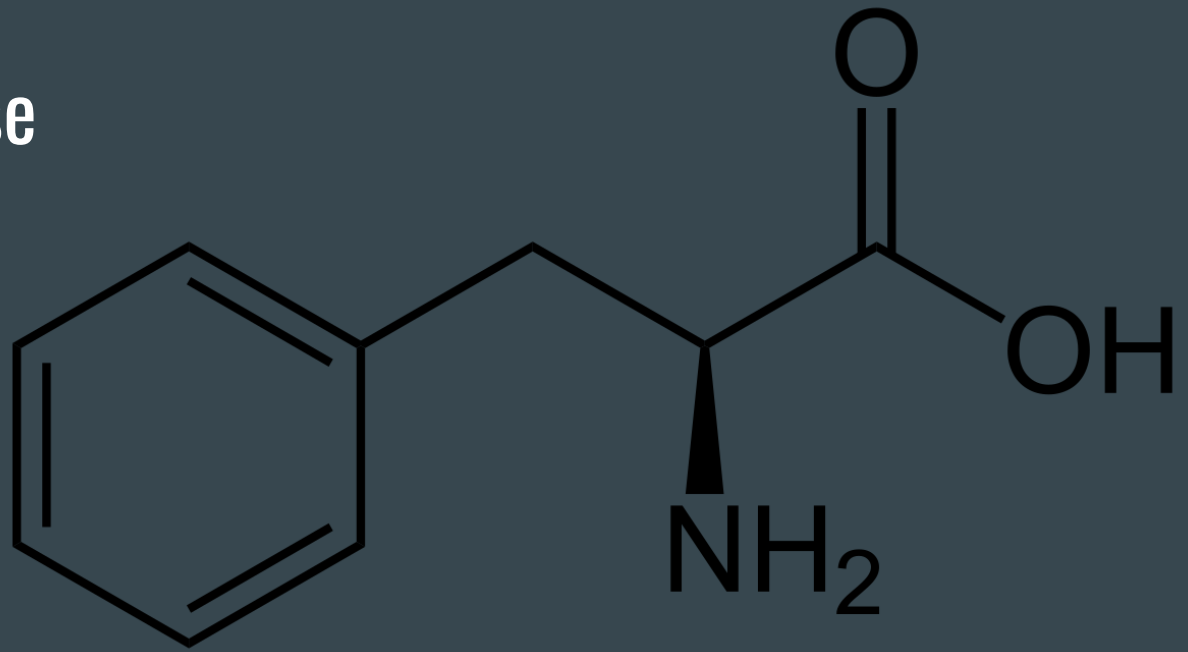
A case



Urgent visit for NBS indicative of SCID in a baby with rhizomelia; immunology team considering bone marrow transplant

Bounded rationality - Herbert Simon

A second case

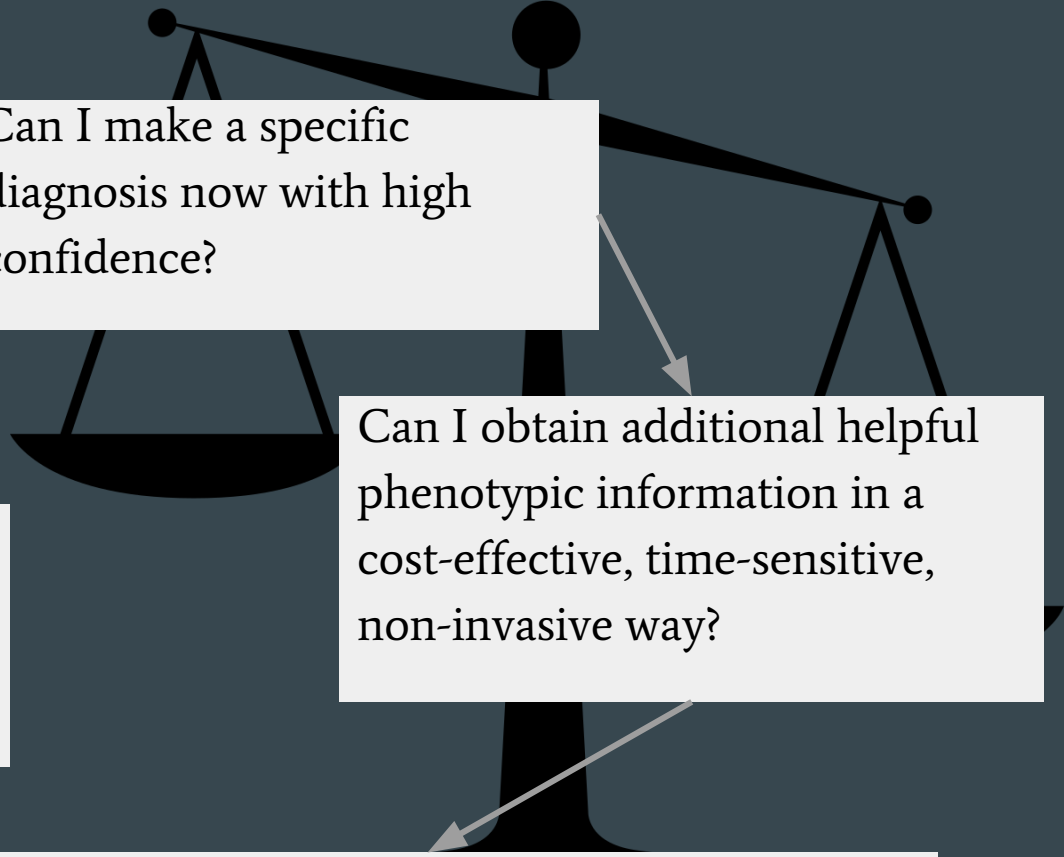


Referral to genetics clinic for moderate developmental delay and hyperphenylalaninemia

Higher sensitivity, faster turnaround, cheaper testing increases the clinical utility of genomic testing in a wider range of clinical contexts and decreases the complexity of choosing a test

If a definite clinical diagnosis or choice of a targeted test is rarely the outcome of a genetics consultation then what is the role of the medical geneticist in the era of genome sequencing?

The judgement calls



How high is the likelihood of any genetic diagnosis?

Can I make a specific diagnosis now with high confidence?

Can I obtain additional helpful phenotypic information in a cost-effective, time-sensitive, non-invasive way?

How high is suspicion for mosaic, epigenetic or repeat-mediated diseases?

How time sensitive is the diagnosis?

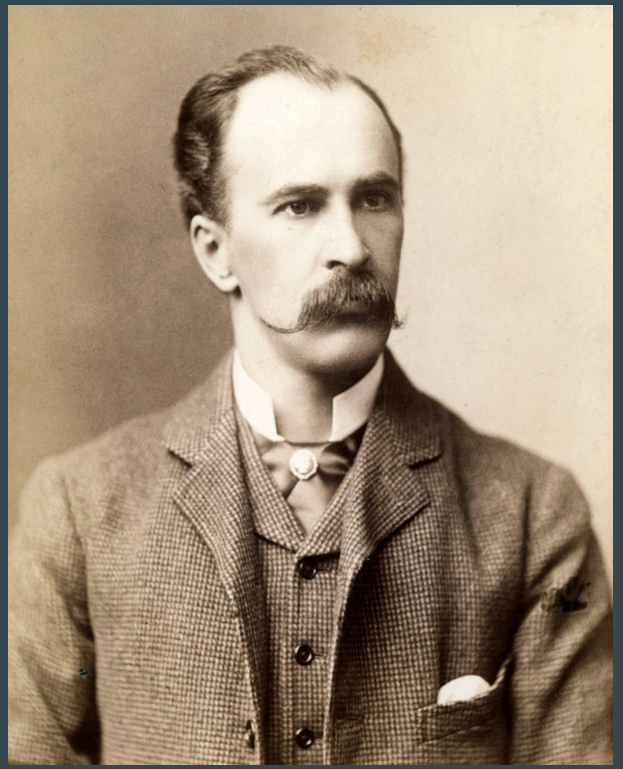
How certain do I need to be? What intervention is hinging on the diagnosis?

Implications for the clinic/ consult service

- Shorter initial visits for diagnostic evaluation
- Potential for diagnostic testing process to start with PCP, prior to genetics visit
- The need for more scheduled positive results time and longer positive results visits
- More engagement with research community
- More participation in diagnostic evaluation and medical decision making for acutely ill hospitalized patients

“Medicine is a science of uncertainty and an art of probability”

- William Osler



Questions?