Functional Validation:
The Right Data to make the Right Interpretation

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Conversations with Scientists

MCW ADVANCING A HEALTHIER WISCONSIN ENDOWMENT

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- Molecular Genetics

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The Cancer Genome Atlas

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- Yonghong Xiao, MD, PhD
- Ray Monnat, PhD, and others…

Conversations with Scientists

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The Right Data to make the Right Interpretation

1. Why it matters
   - Association ≠ Causation
   - Precision Medicine and the "N of One"
2. How we got it Right for SanFilippo
3. Tools and Context
   - Functional Genomics Toolbox
4. Where we're going
   - Tools to illumine parts of the genome, darkly understood

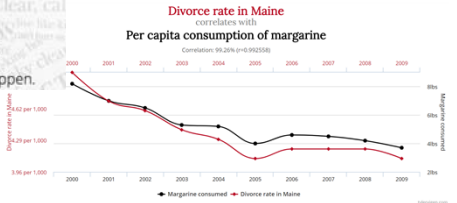
Conversations with Scientists

MCW ADVANCING A HEALTHIER WISCONSIN ENDOWMENT

The Right Data to make the Right Interpretation

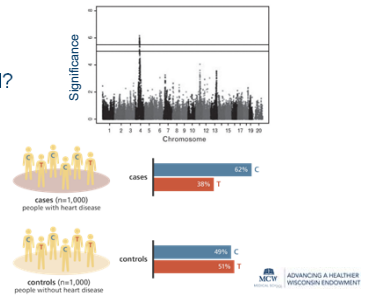
- Data → Knowledge
  - "Data is frozen knowledge. We need science to melt the ice of data, so that knowledge can flow out" ~Atul Bute
- How?
  - Testing Hypotheses
  - Finding Mechanisms
  - Running experiments (in theory, *in silico*, *in vitro*, *in vivo*)
  - Checking with experts & patients
    - clinical trials, case studies, …

Why we Need Mechanisms



Why we Need Mechanisms

- Genetic Associations & Discovery
- How do we know it's real?



Why we Need Mechanisms

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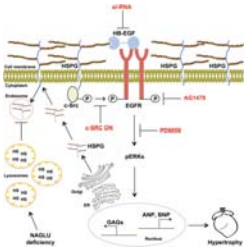
- We test the mechanism.
  - Genes/proteins
  - Model organisms
  - Patient cells
- If mechanism holds, we believe.
- Molecular diagnosis.



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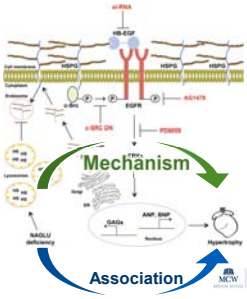
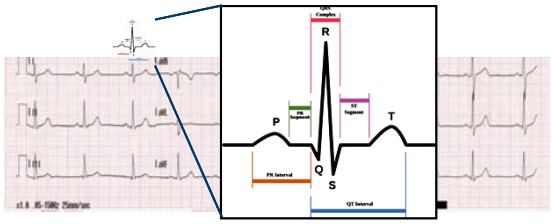
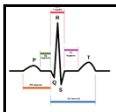


Why we Need Mechanisms
A Clinical Example



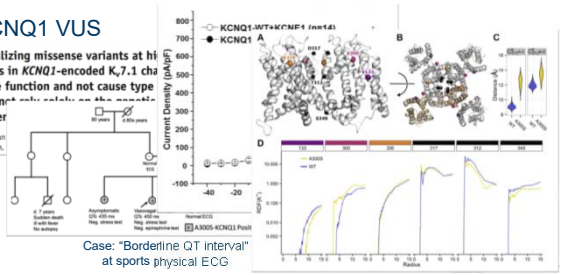


Why we Need Mechanisms

- KCNQ1 VUS

Even pore-localizing missense variants at hi
conserved sites in *KCNQ1*-encoded $K_v7.1$ cha
have wild-type function and not cause type
syndrome: Do no
company's inter

Ashley Paquin, BA,* Dan
Michael T. Zimmermann,

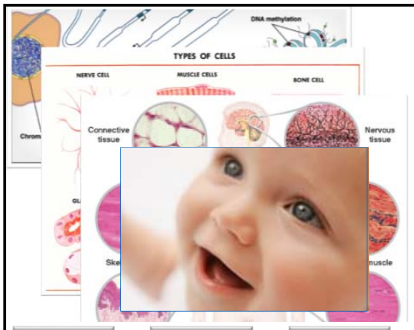


Case: "Borderline QT interval" at sports physical ECG

The Right Data to make the Right Interpretation

Star Ledger, 2002.
Human Genome Project Completed in 2003.

Genomic Variant → Molecular Mechanism → Molecular Phenotype → Cellular Phenotype → Patient Phenotype



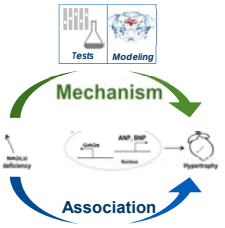
What's happening for your:

- Molecules
- Cells
- Tissues
- Organ Systems
- Whole Self

Genomic Variant → Molecular Mechanism → Molecular Phenotype → Cellular Phenotype → Patient Phenotype

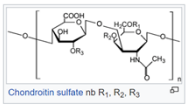
How we got it Right for SanFillipo

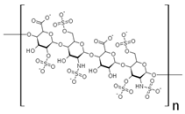
- SanFillipo syndrome
  - NAGLU enzyme doesn't work
  - Enzyme replacement therapy
- How did we come to know this?
  - Functional Genomics
  - Need to know the protein, chemistry, pathway, & location



How we got it Right for SanFillipo

- NAGLU = N-acetyl-alpha-glucosaminidase
- Step-wise breakdown of large molecules called glycosaminoglycans (GAGs)
- Specifically, Heparin Sulfate





NAGLU Protein

>sp|P54802|ANAG_HUMAN
MEAVAVAAAVGVLLLAGAGGAAGDEAREAAAVRALVARLLGPGPAADFSVSVERALAAKP
GLDTYSLGGGAARVRVRGSTGVAAAAGLHRYLRDFCGCHVAWSGSQLRLPRPLPAVPGE
LTEATPNRYRYYQNVCTQSYSFVWWDWARWEREIDWMALNGINLALAWSGQEAIWQRVYL
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EAVNGGPEAARLFPNSTMVGTGMAPEGISQNE
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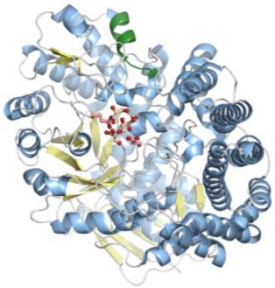
RLLLTSAPSLATSPAFRYDLLDLTRQAVQELV
ELLPALDEVLASDSRFLLGSWLEQARAAAVSE
KQLAGLVANYYTPRWRLFLEALVDSVAQGIPF
GDTVDLAKKIFLKYYPRWVAGSW

NAGLU Protein

Genomic Sequence: NC_000017.11 Chromosome 17 Reference GRCh38.p12 Primary Assembly

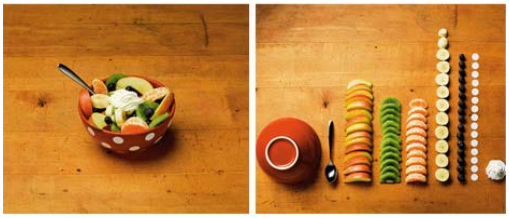


Precision Medicine & Accelerating Translation

- 1980: Vance use twins to show genetics affect NAGLU activity
- 1995: Neufeld & Muenzer, “The Mucopolysaccharides”
- 1996: Zhao showed the genetic basis of MPS-IIIB
- 1998: Schmidtchen expanded the genetics
- 1999: Li showed mice with variants have related symptoms
- 2000: Yu, ERT in mice restored liver, but not brain
- 2007: Ryazantsev, characterize brain secondary accumulites
- 2008: Ficko-Blean, structure & enzyme inhibitor studies
- 2015: US/UK trial for “SBC-103”
- 2017: Enzyme replacement therapy, “BMN 250”

Laboratory & Genetic Tools

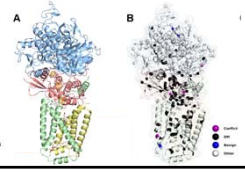
Systems Biology & Data Integration



Artist: Ursus Wehrli

The Right Data to make the Right Interpretation

- Variants cause rare diseases (e.g. San Filippo)
- Additional variants seen in healthy people
  - Untested, unknown effects
  - Molecular Modeling & Functional Genomics



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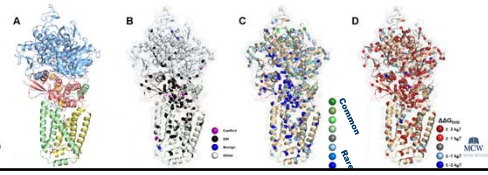

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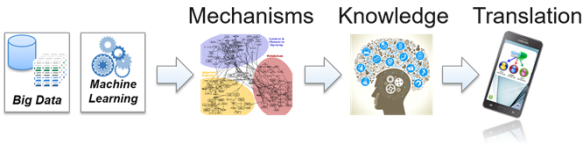
Thank you!