Large Data and the Opportunity to Regain Previously Lost Opportunities

– Drug Repurposing as an example

Stefan Jovinge MD PhD

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Disclosure

- Advisor to OneCell™
- Stanford University
- University of Texas South Western
- Michigan State University
- Lund University

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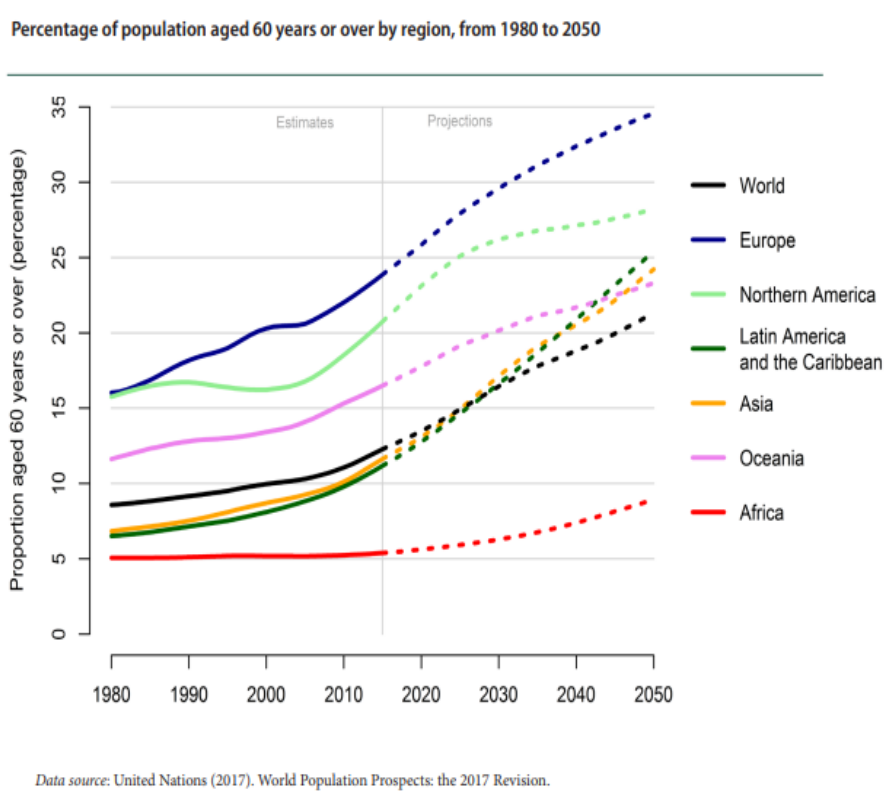
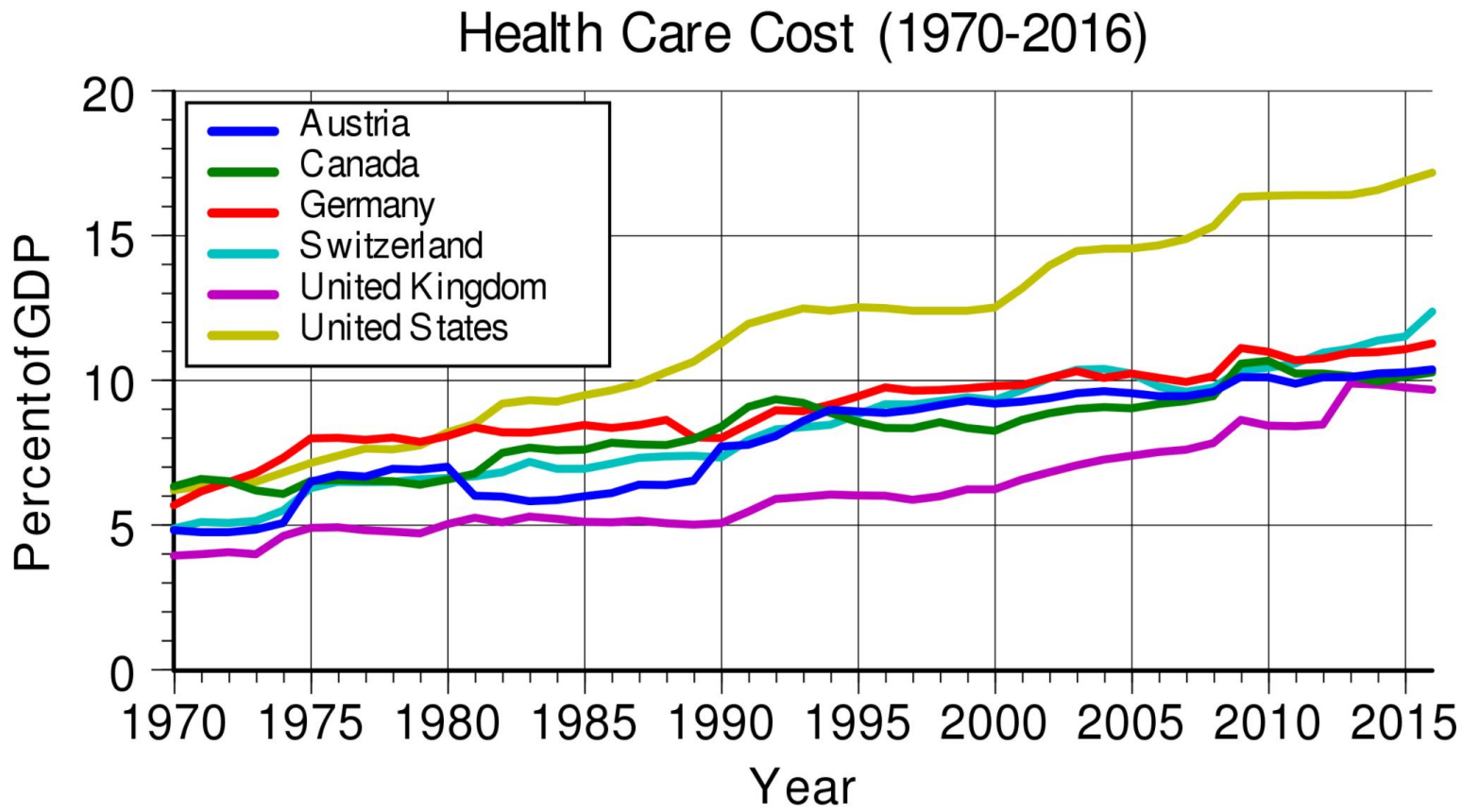
Growing Health Burden





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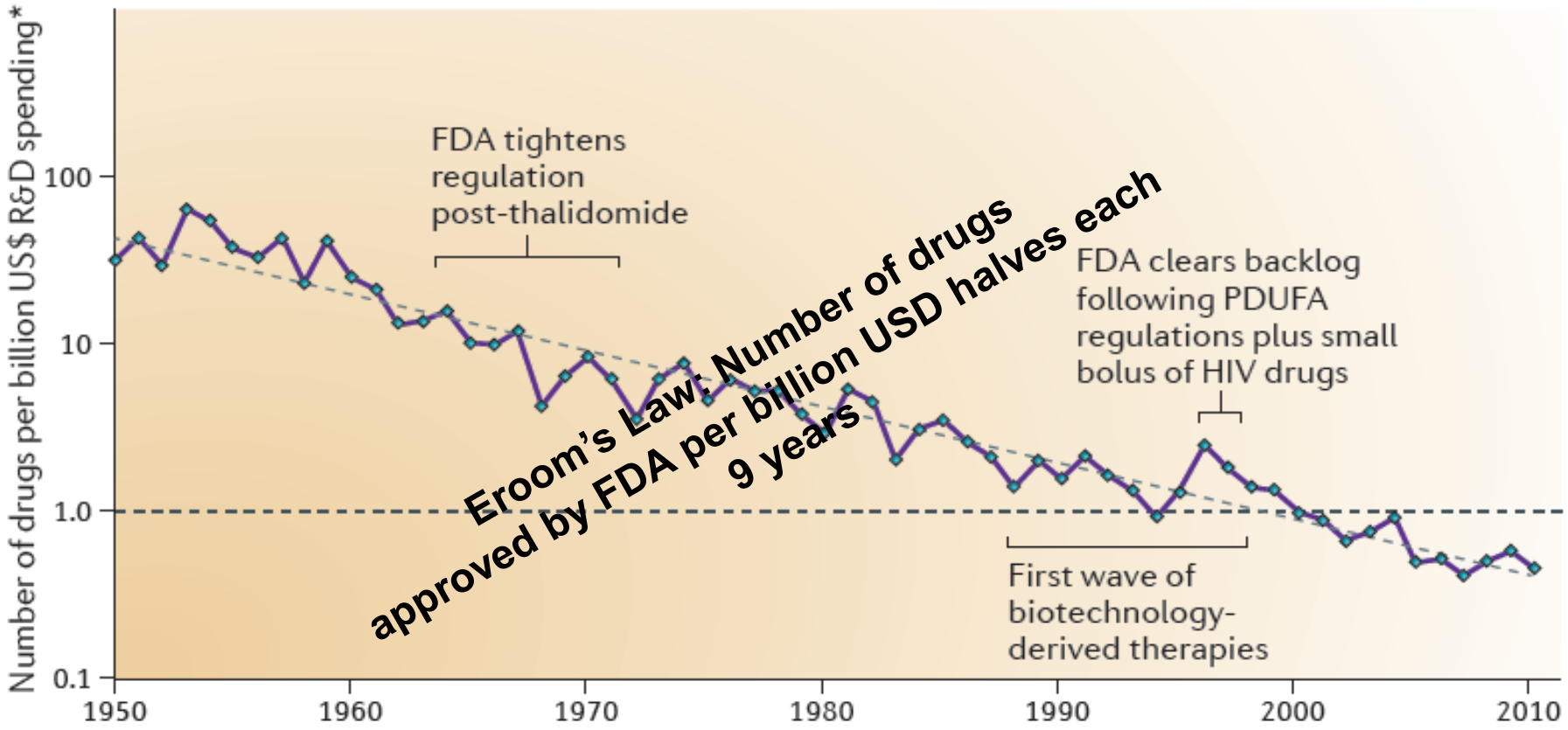
Drug Development – Losing Grounds



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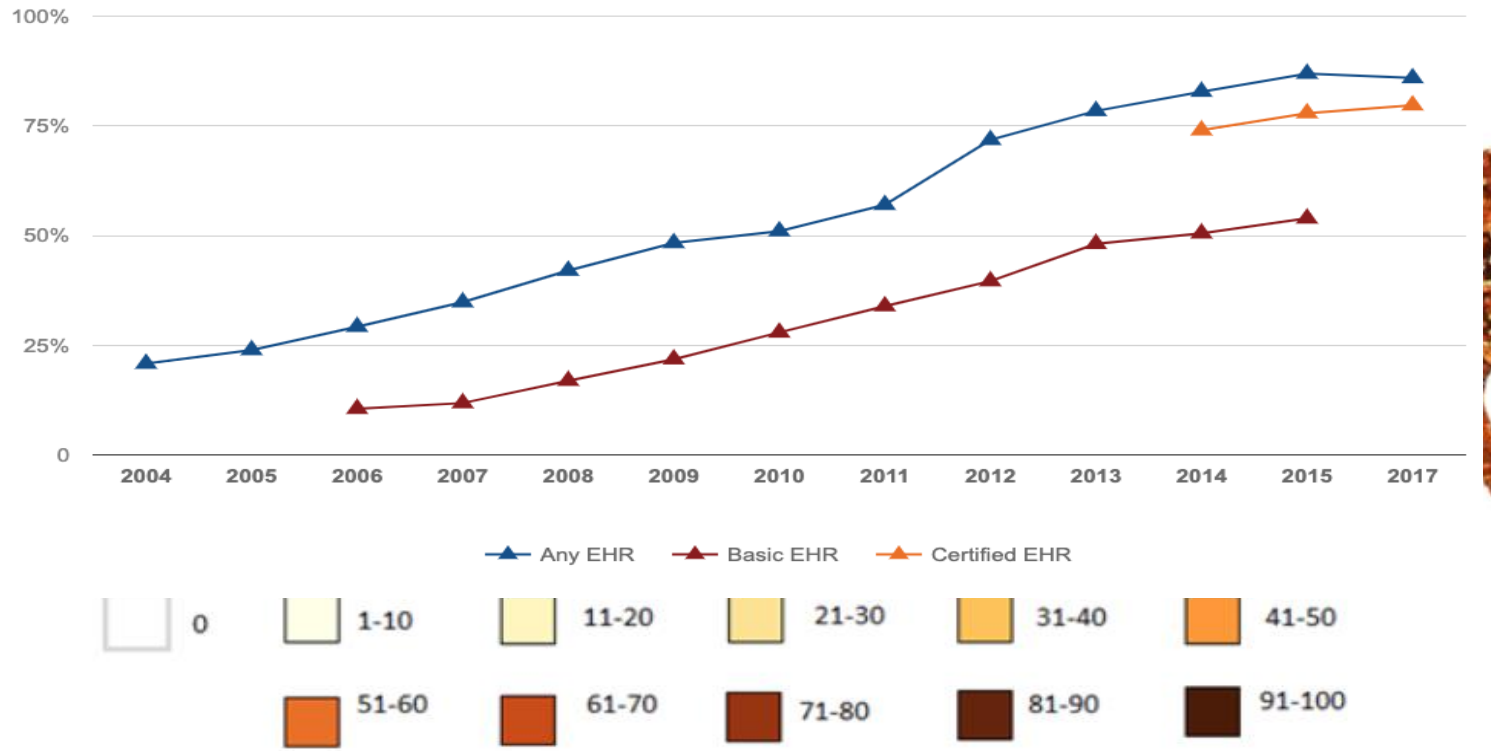
Use of Electronic Medical Records in US

Sources



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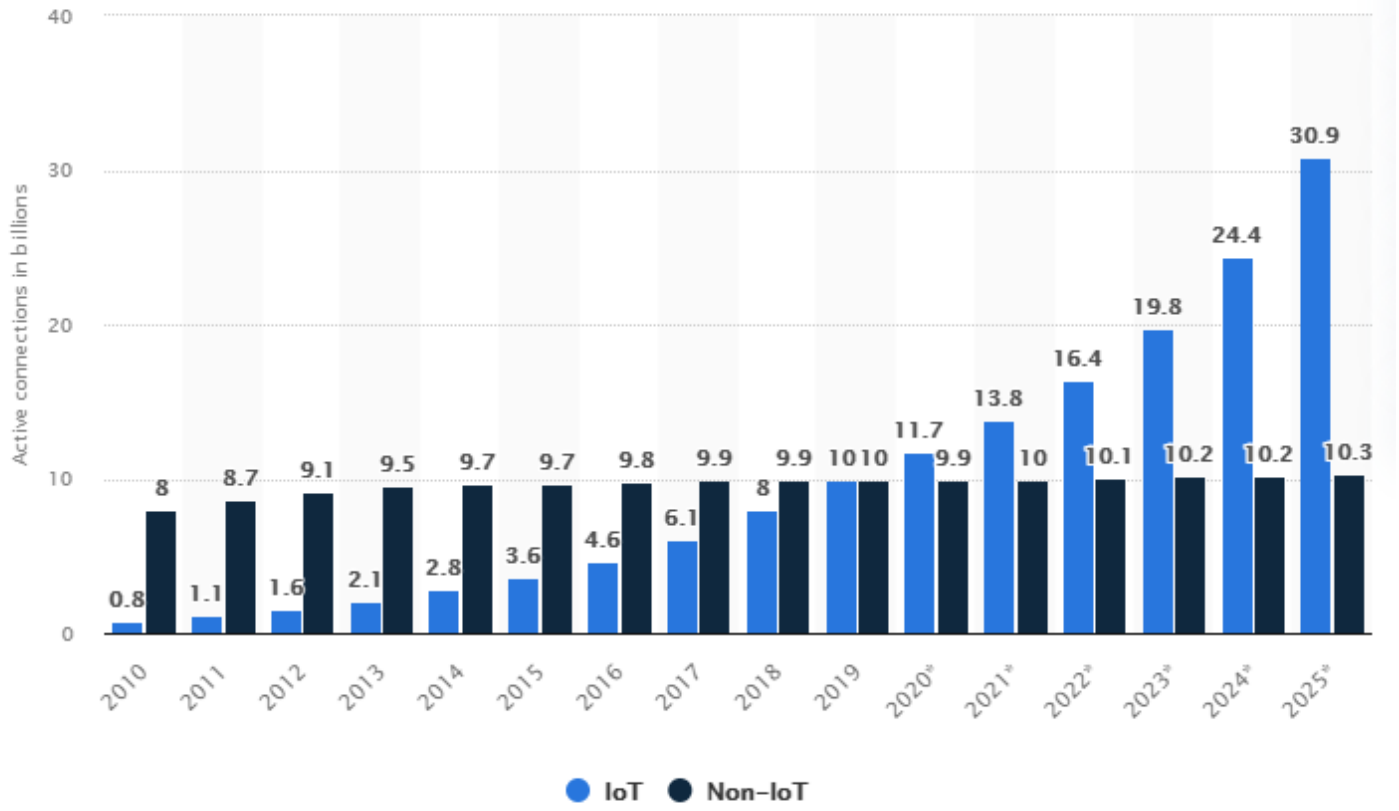
Internet of Things

Sources



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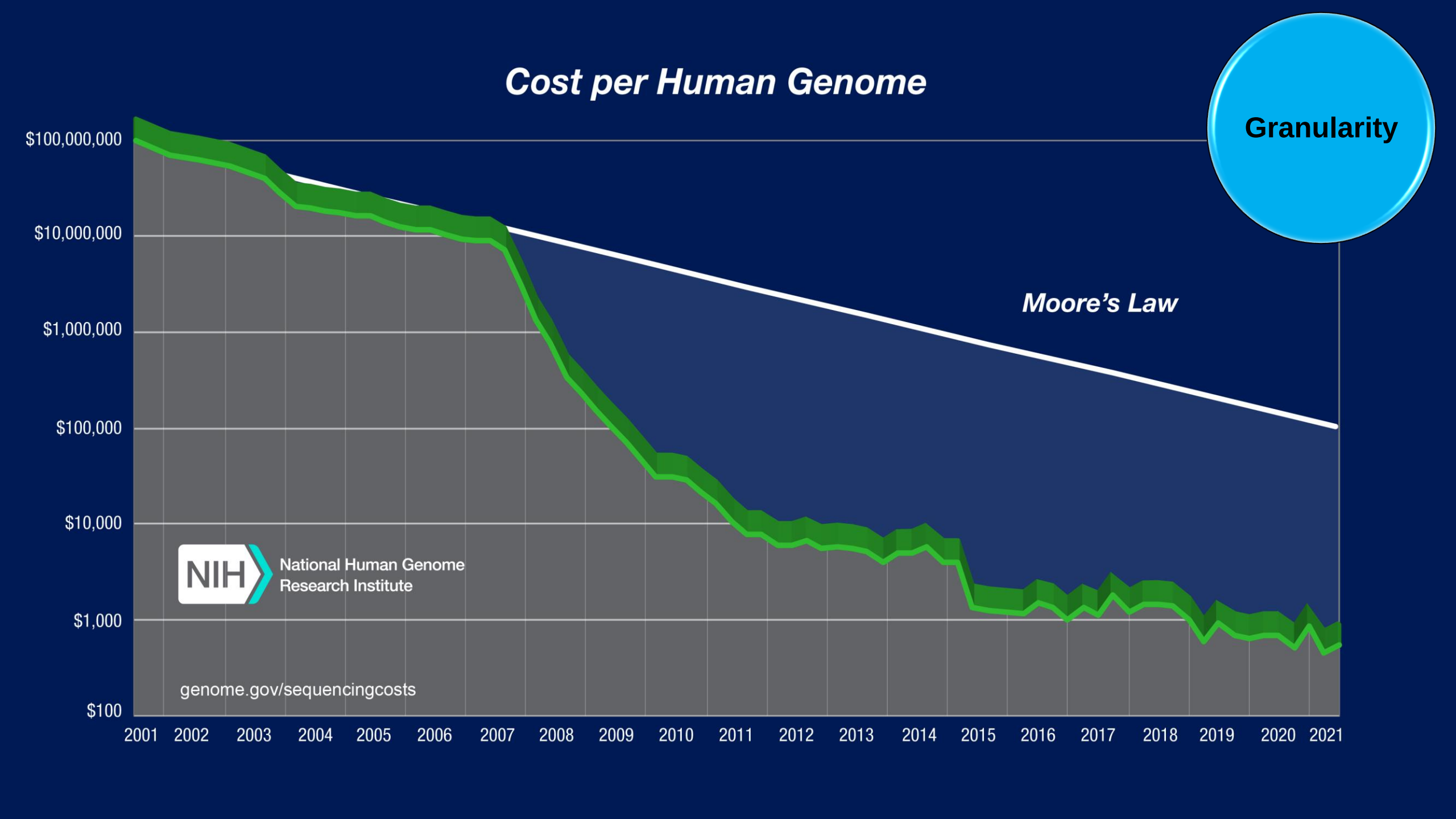
Cost per Human Genome
Granularity
Moore's Law
$100,000,000
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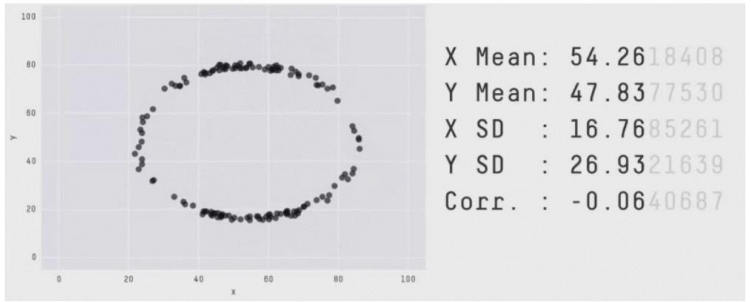
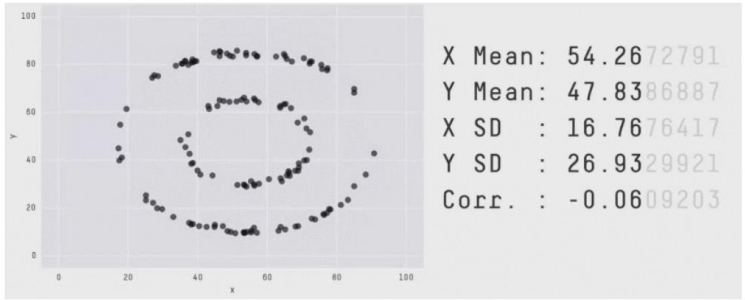
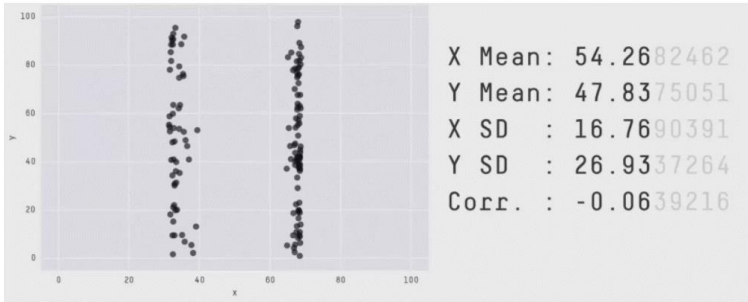
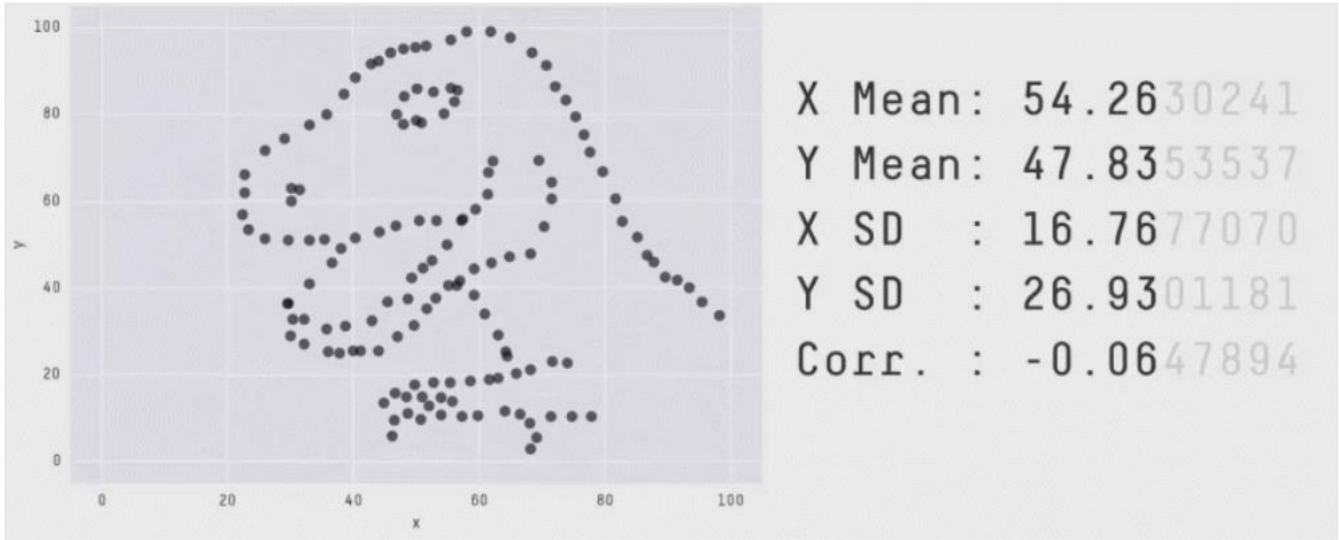
NIH
National Human Genome
Research Institute
genome.gov/sequencingcosts

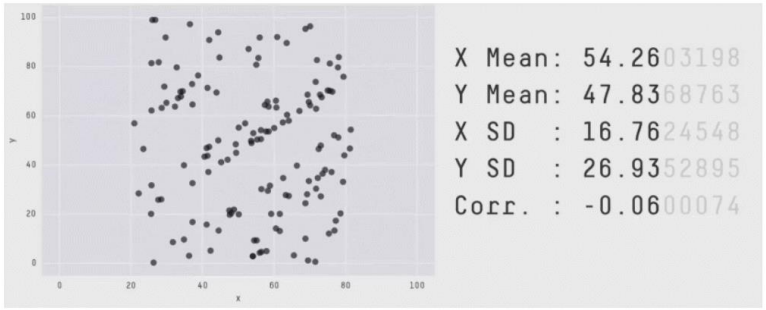
Large Data – The Danger of Averaging

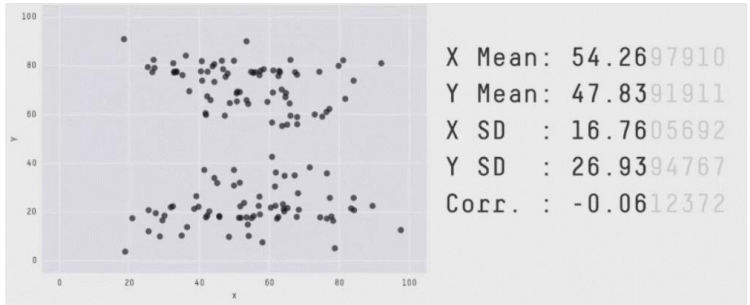


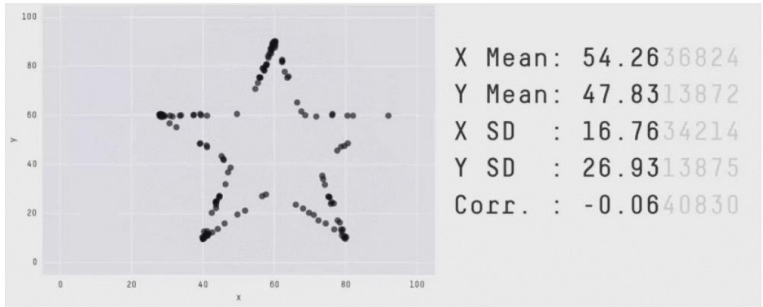












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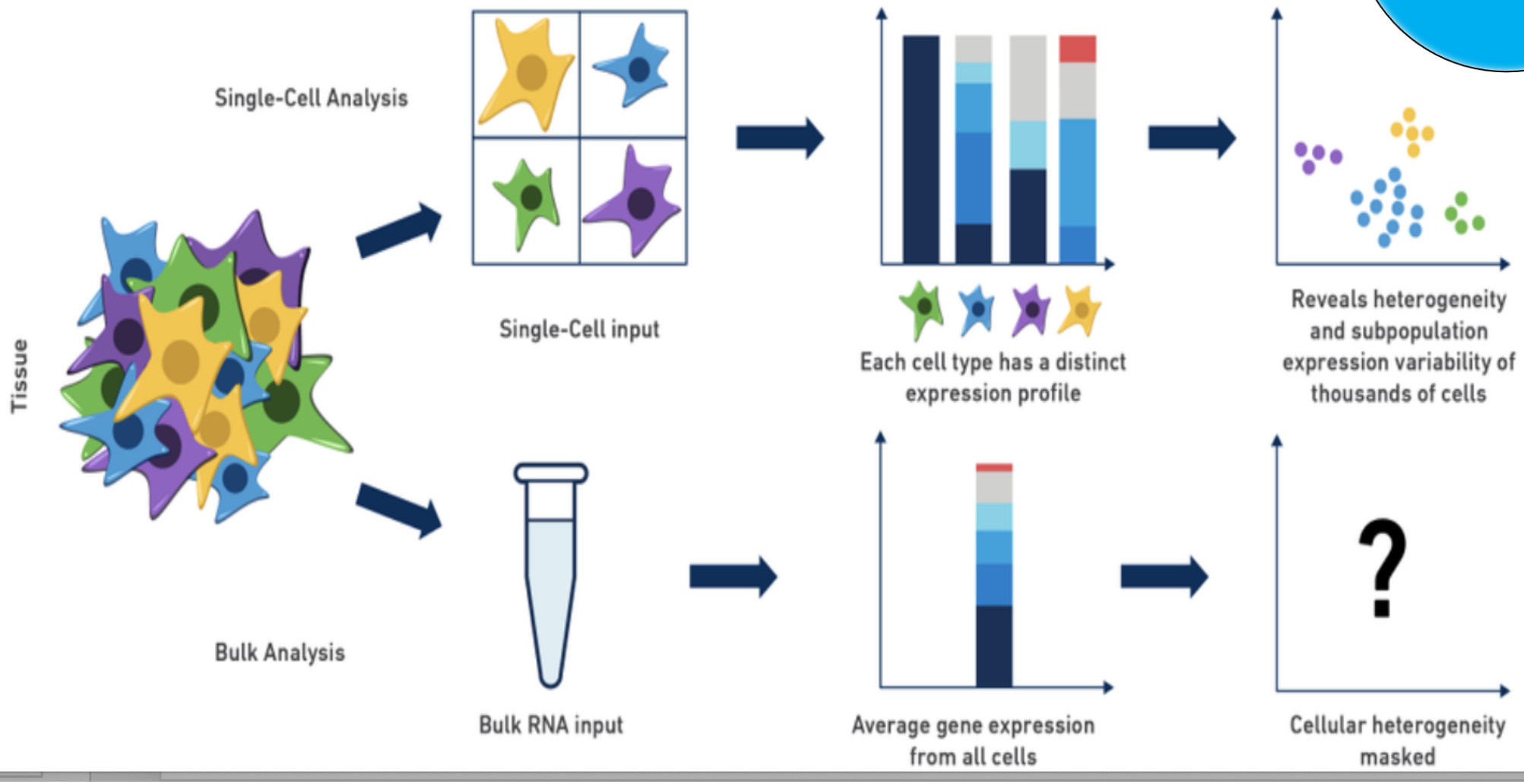
Large Data – The Danger of Averaging

Granularity



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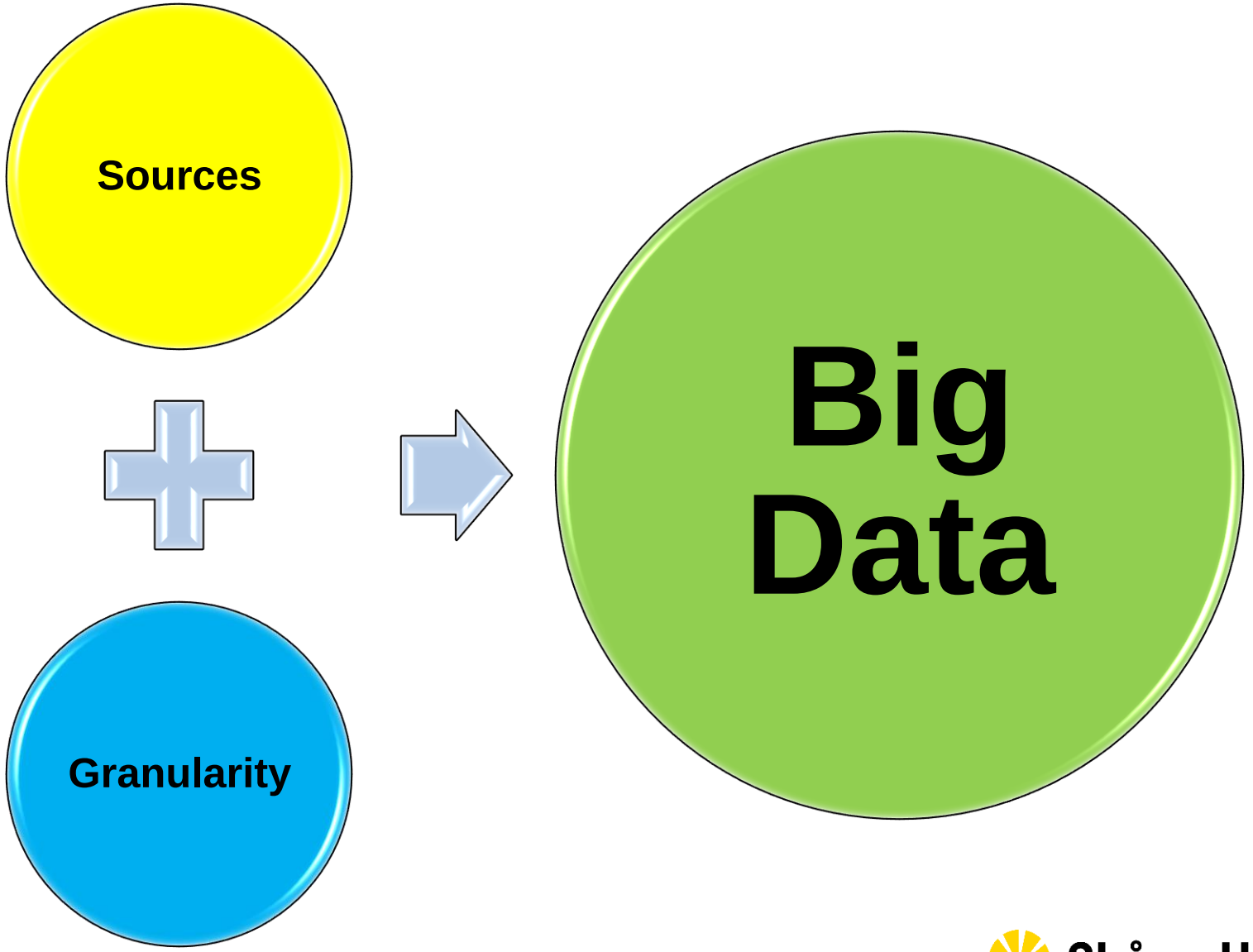

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Rare Diseases Are Common

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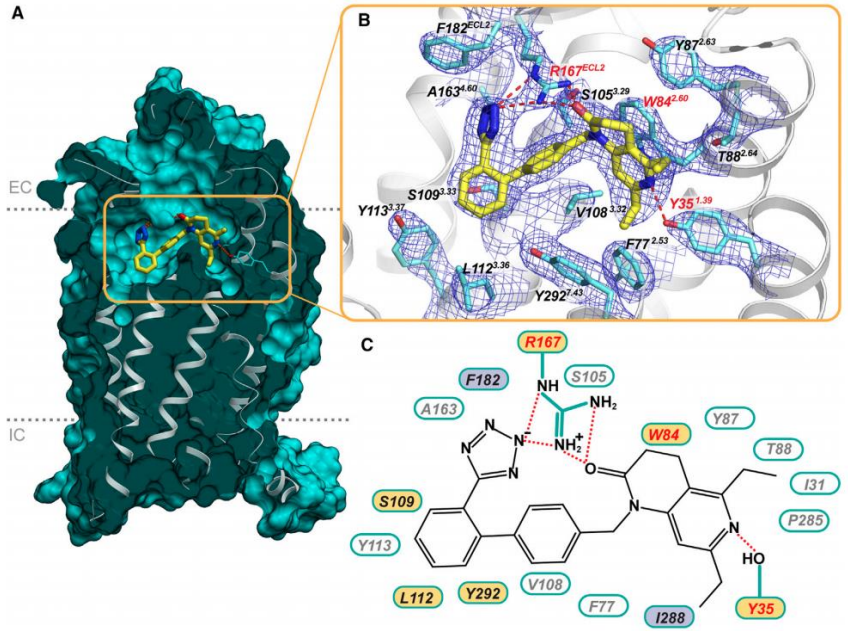
Why would this work?

- Because drugs are not “one trick ponies”
  - Even though we think of them that way.
- Additional direct effects
- Additional down stream effects
- Drugs are complex three dimensional entities



Zhang et al., 2015, Cell 161, 833–844

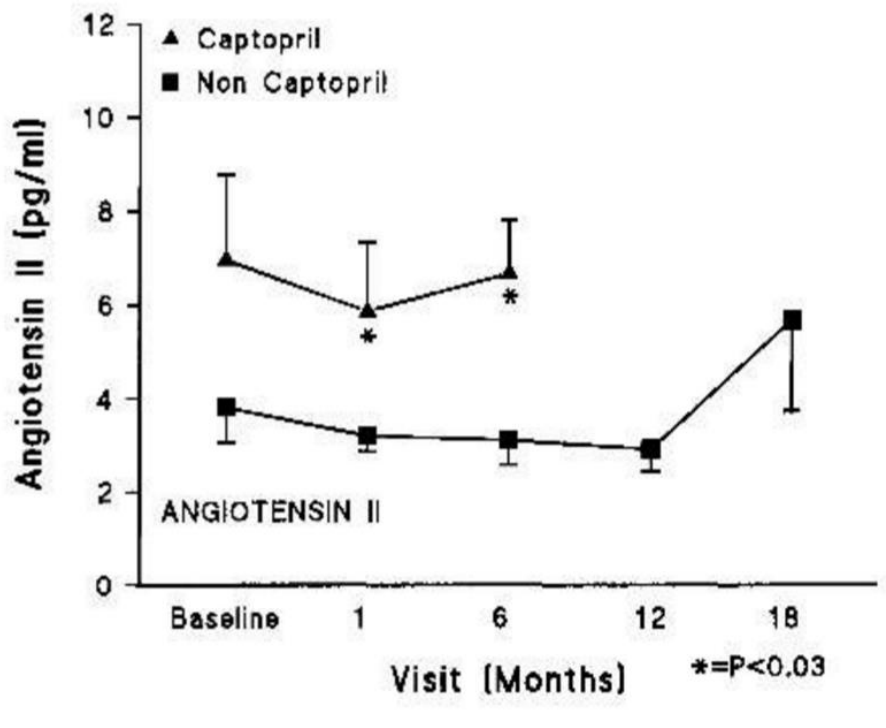
Heart Failure

European Journal of Heart Failure 1 (1999) 401–406 www.elsevier.com/

Extended short report

Neurohormonal reactivation in heart failure patients on chronic ACE inhibitor therapy: a longitudinal study

Alison F.C. Lee[a,*], Robert J. MacFadyen[b], Allan D. Struthers[c]



The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 APRIL 10, 2008 VOL. 358 NO. 15

Telmisartan, Ramipril, or Both in Patients at High Risk for Vascular Events

The ONTARGET Investigators*

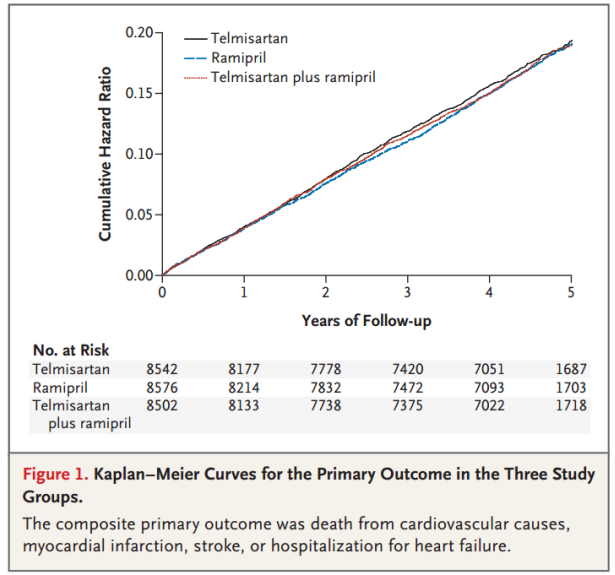


Figure 1. Kaplan–Meier Curves for the Primary Outcome in the Three Study Groups.

The composite primary outcome was death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure.

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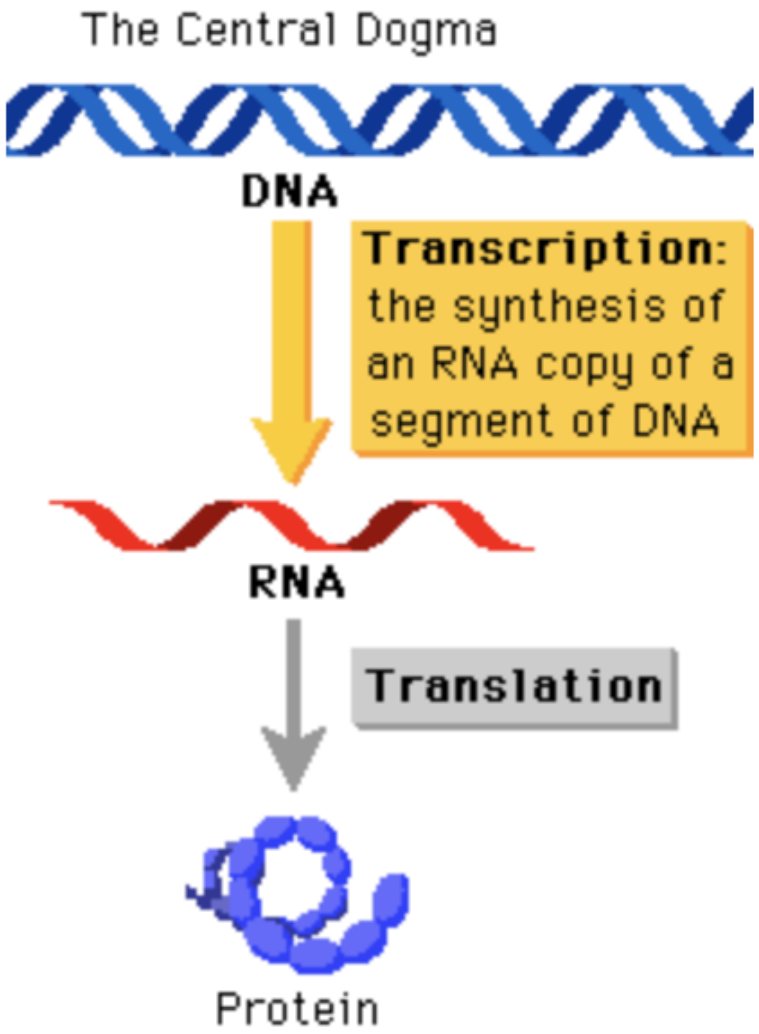
Transcriptomics – Beyond Proteomics



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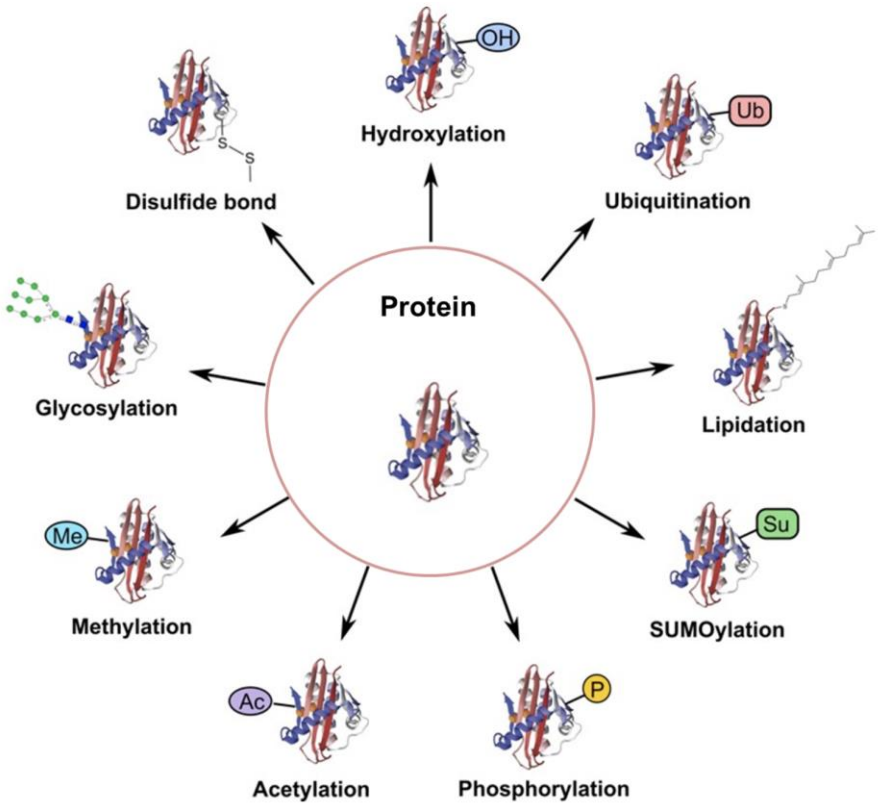
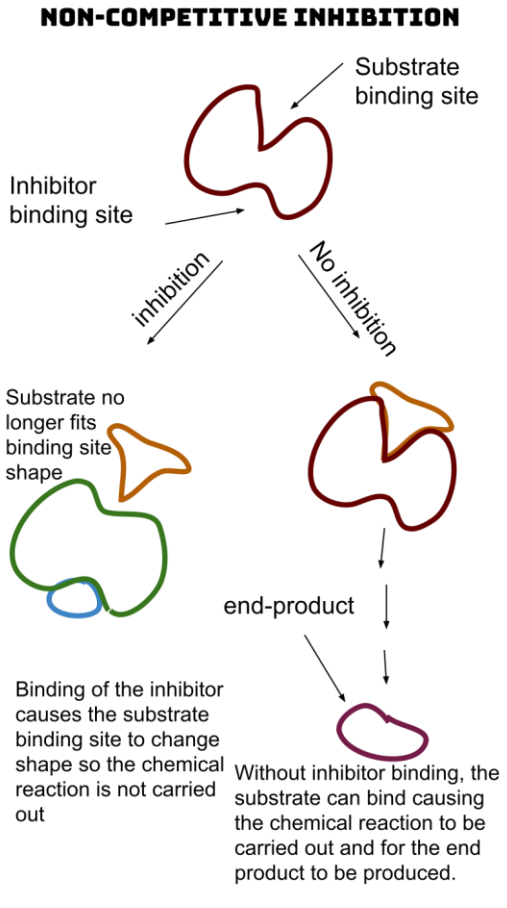
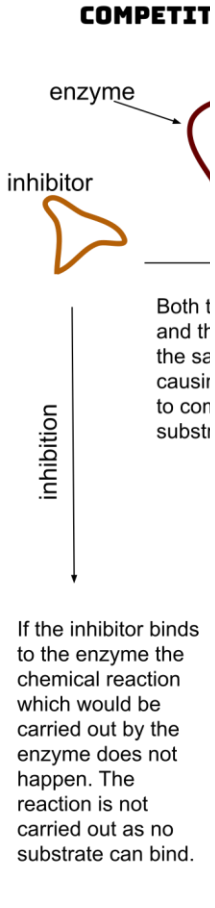
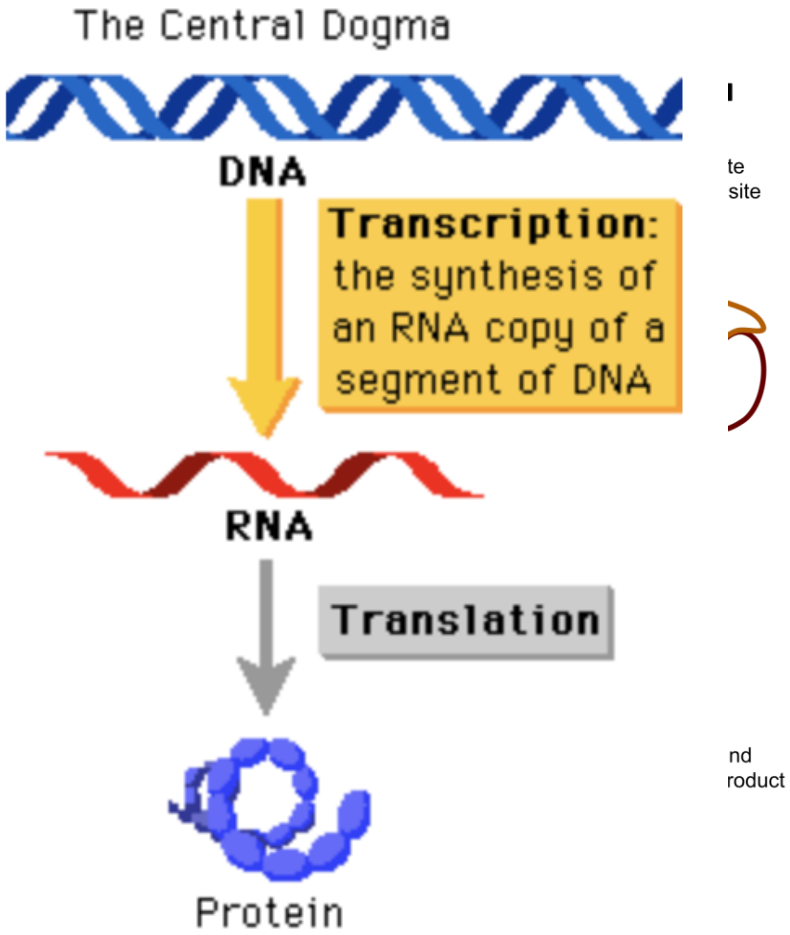
Transcriptomics – Beyond Prot

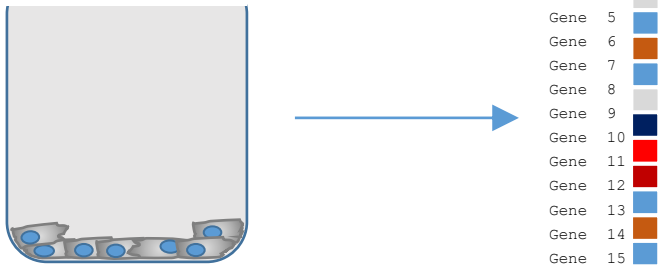


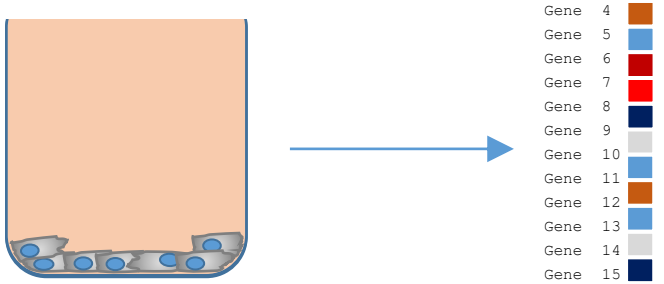


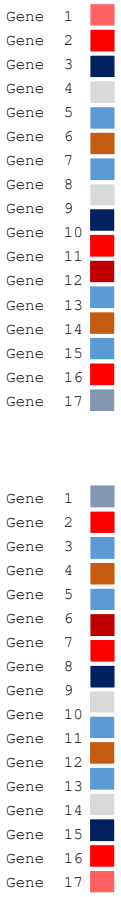




FINGER-PRINTING DRUGS







70 cell lines

,000 Compounds

Gene Fold Change (Treat /

1.3 billion datapoints

One empirical gene signature

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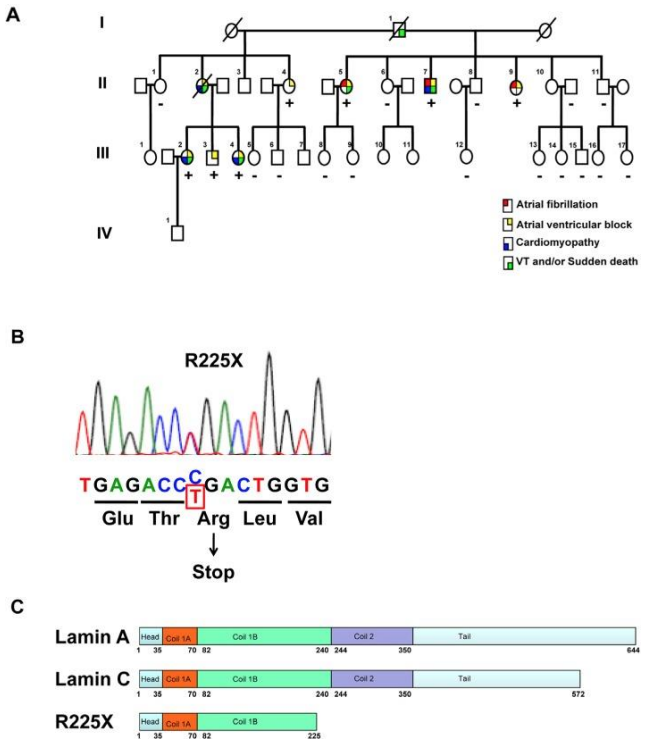
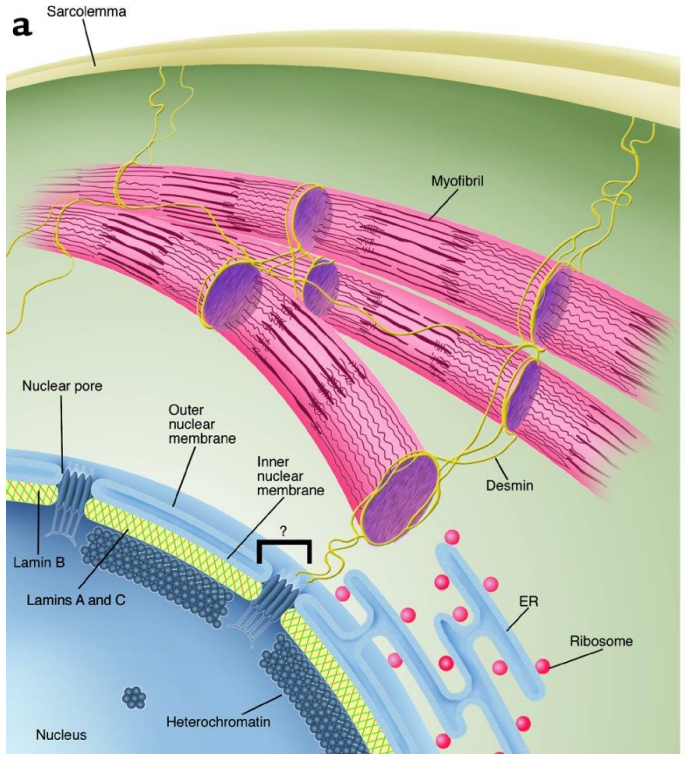
Lamin A/C Haploinsufficient Cardiomyopathy



Healthy Allele

Disease Allele



Chung-Wah Siu et al *Aging 2012*

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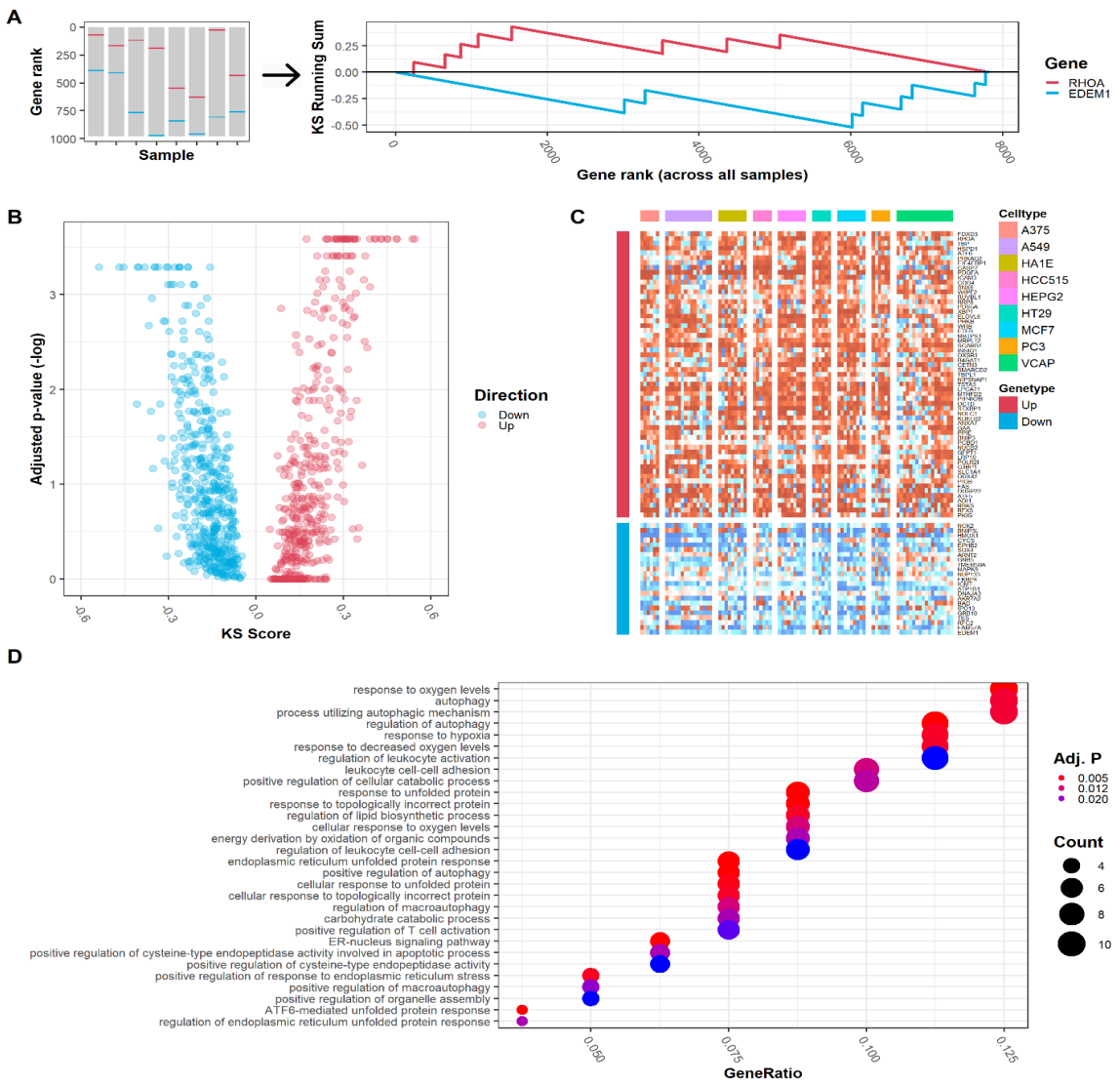
LMNA Haploinsufficiency Signature Definition



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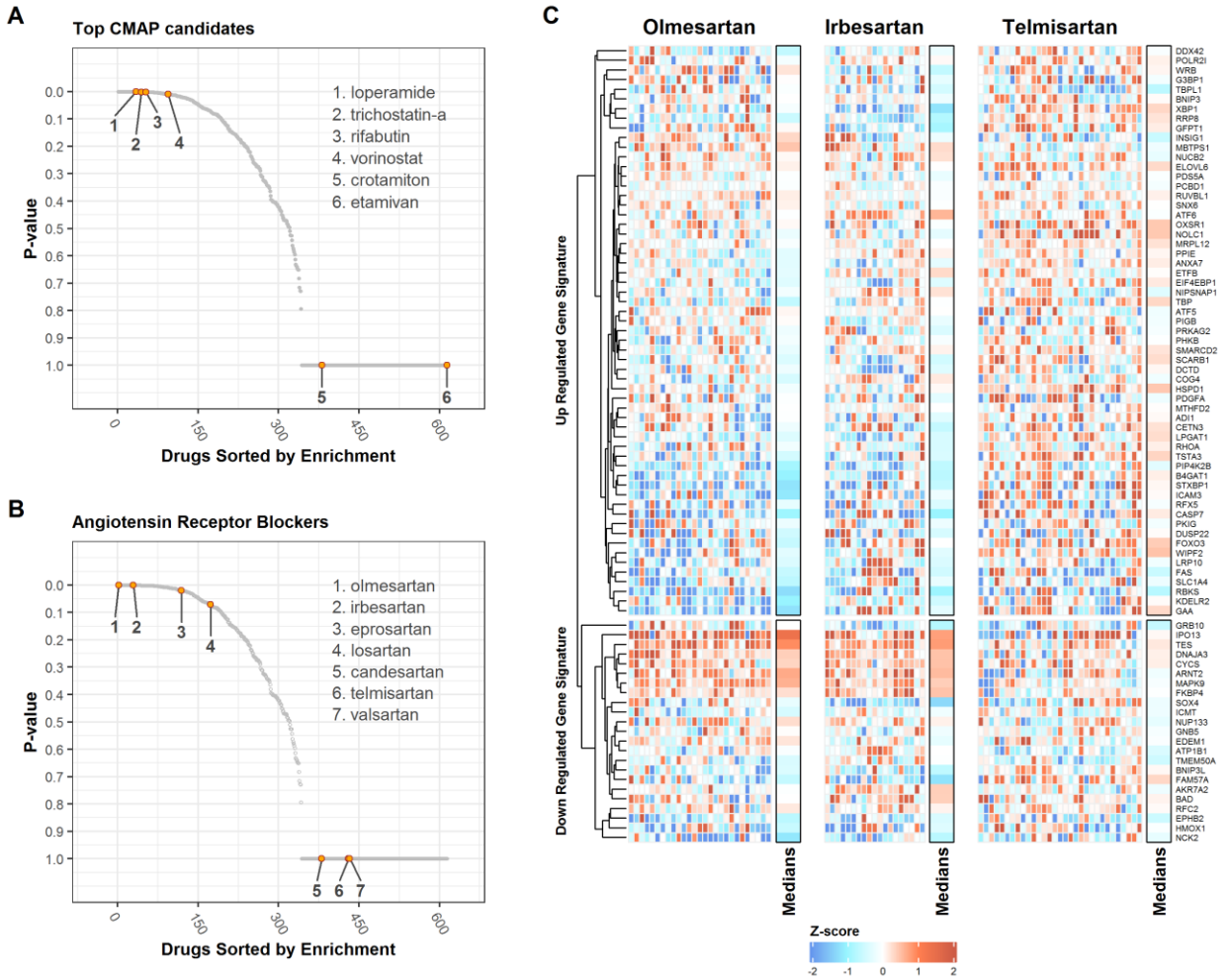
LMNA Knockdown Signature Reversion



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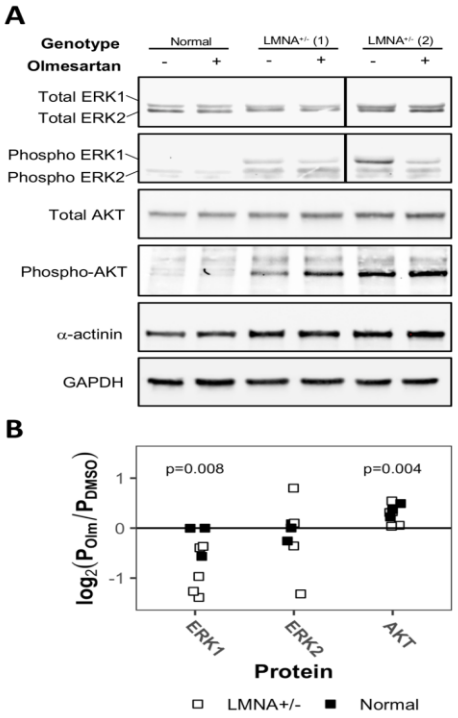
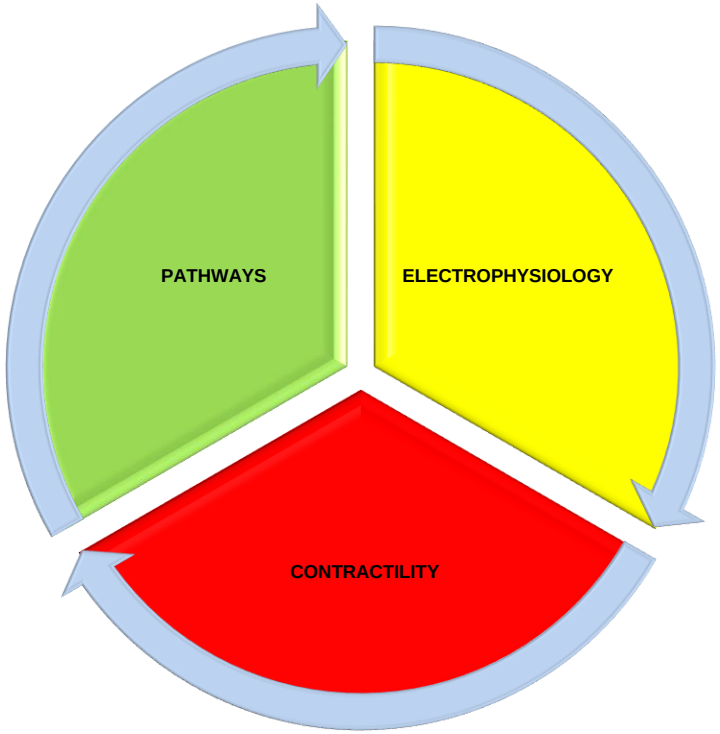
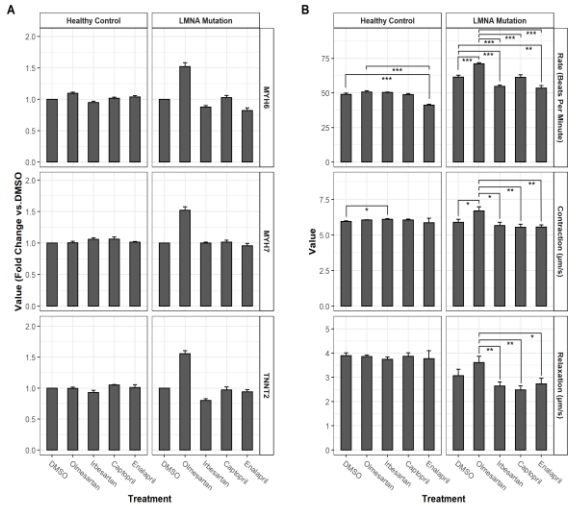
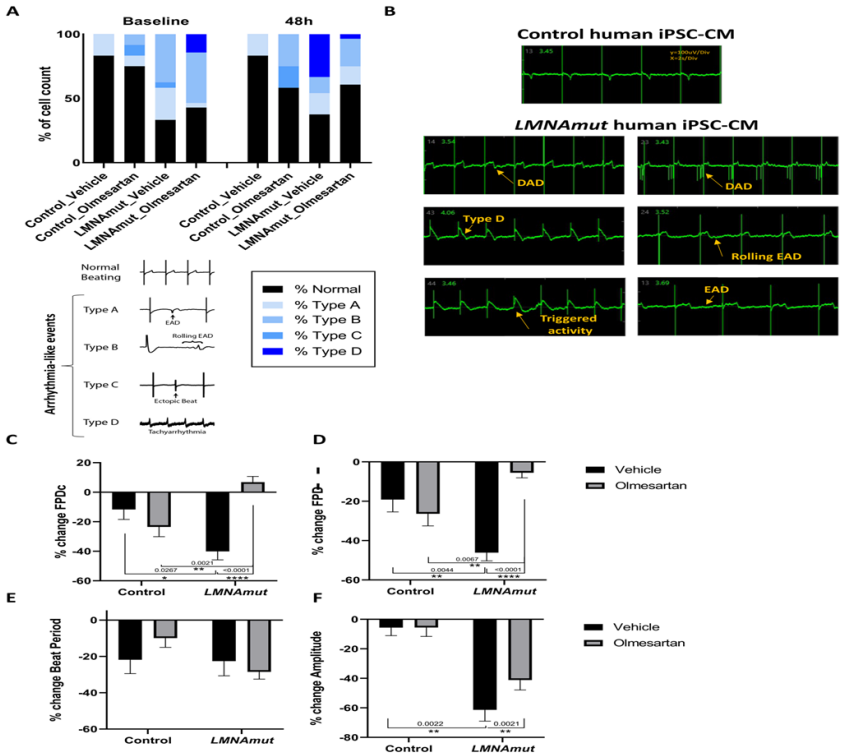
In Vitro Validation – Transcriptomics and Function









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Drug Repurposing Principle

Candidate Selection: 1 week
< $500

Validation: 3
< $50,

NIH LINCS
L1000 Dataset
Phase I Data Release:
~5000 genetic perturbagens
~20000 chemical perturbagens
~700 FDA approved compounds

↓

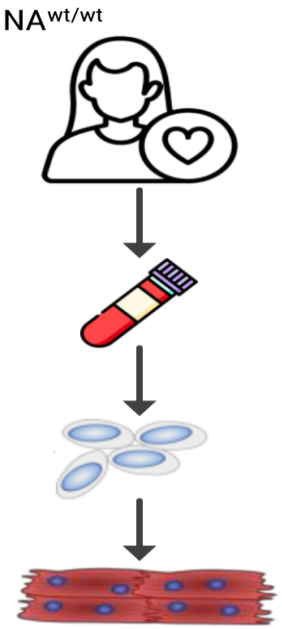
Vehicle Control Z-scores

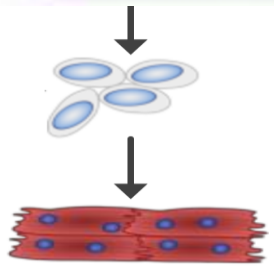
↓

Define LMNA Signature

↓

Score FDA Approved Drugs





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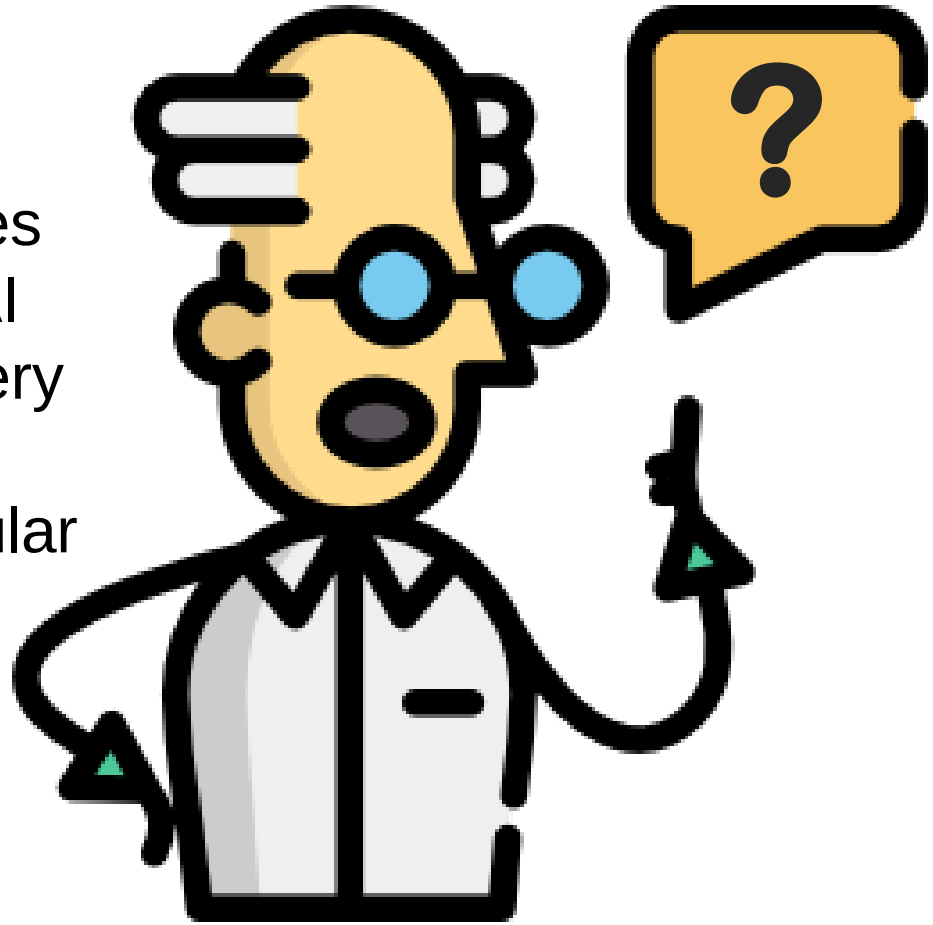
Summary

- Older population increases the need of healthcare
- The cost drug development has risen to the level where it doesn’t cope with the challenges
- Big data offers opportunities not only within AI but also with detailed analyzes and the delivery of care
- One major challenge we face is to stay granular with our data as it grows

Questions / Comments



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Acknowledgements

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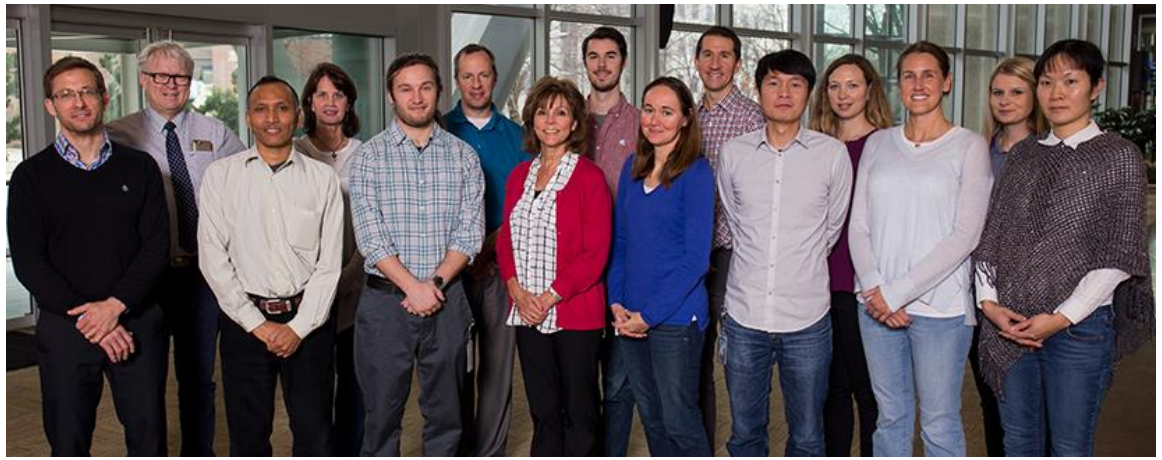
- Nabin Shrestha, PhD
- Matthew Weiland, MS



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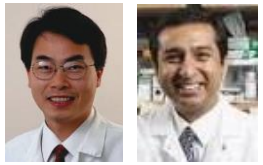
Joseph C Wu MD PhD

- Nazish Sayed MD PhD



Eric Kort MD

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