The Realization of Genomic Medicine

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Context

- Experience in 15 years natural history and molecular genetics of malformations
- Followed sequencing technology
- Expanded into common disease - ClinSeq™ cohort to pilot new sequencing in common disease

Assumptions

- Substantial component of common disease is an amalgamation of rare processes
- Genetic testing facilitates genotype-phenotype correlation
- Prediction
- Limited to germline
- Evolution preferable to revolution

Current Basic Research Paradigm

- Gather background information
- Formulate hypothesis
- Apply a biologic assay to a system to test
- Interpret data, refine, and extend hypothesis

Current Clinical Research Paradigm

- Gather background information
- Formulate hypothesis
- Phenotype subjects
- Apply a biologic assay to subject to test
- Interpret data, refine, and extend hypothesis

Current Clinical Practice Paradigm

- Gather history
- Examine patient
- Formulate differential diagnosis
- Apply clinical test(s) to patient
- Interpret result(s), refine differential, diagnose
- Treat

Low Throughput Paradigms

- Must frontload hypotheses, differentials and phenotyping because the assays or clinical tests are
  - Rate/time limiting
  - Expensive
  - Noisy

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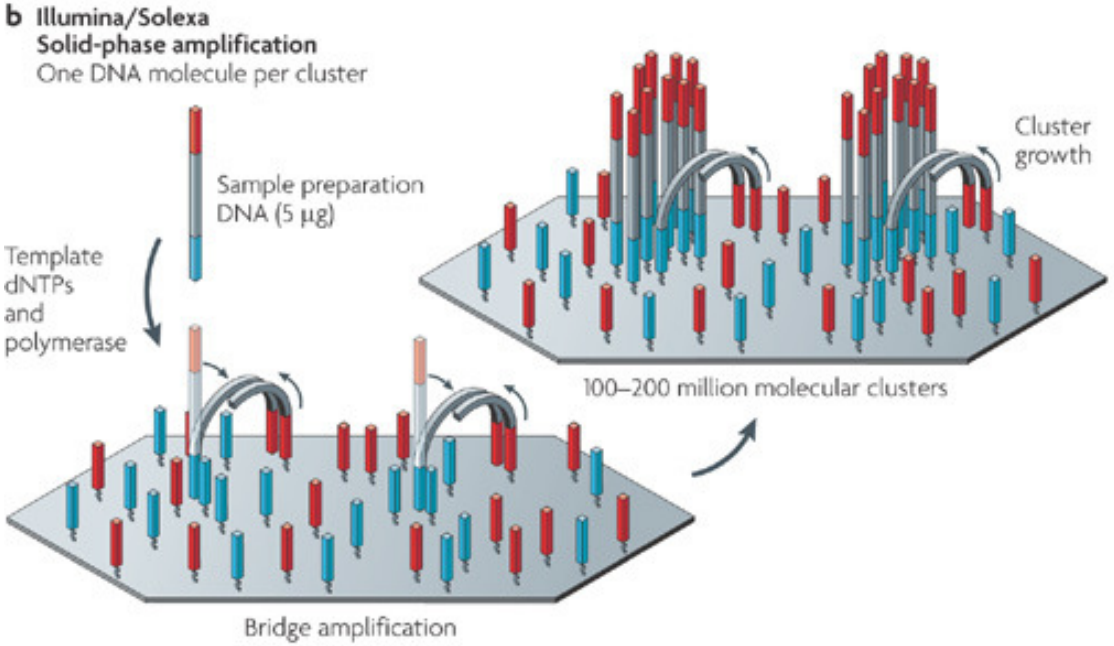
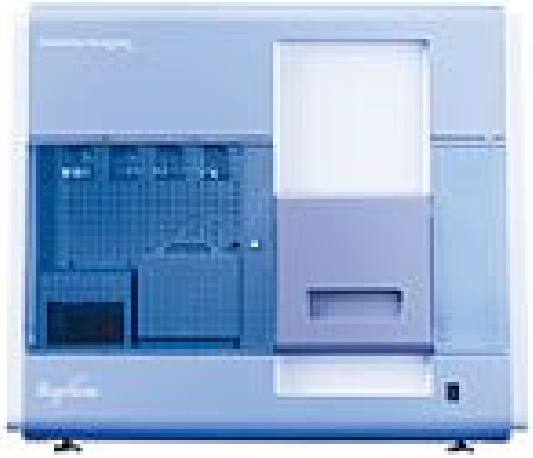
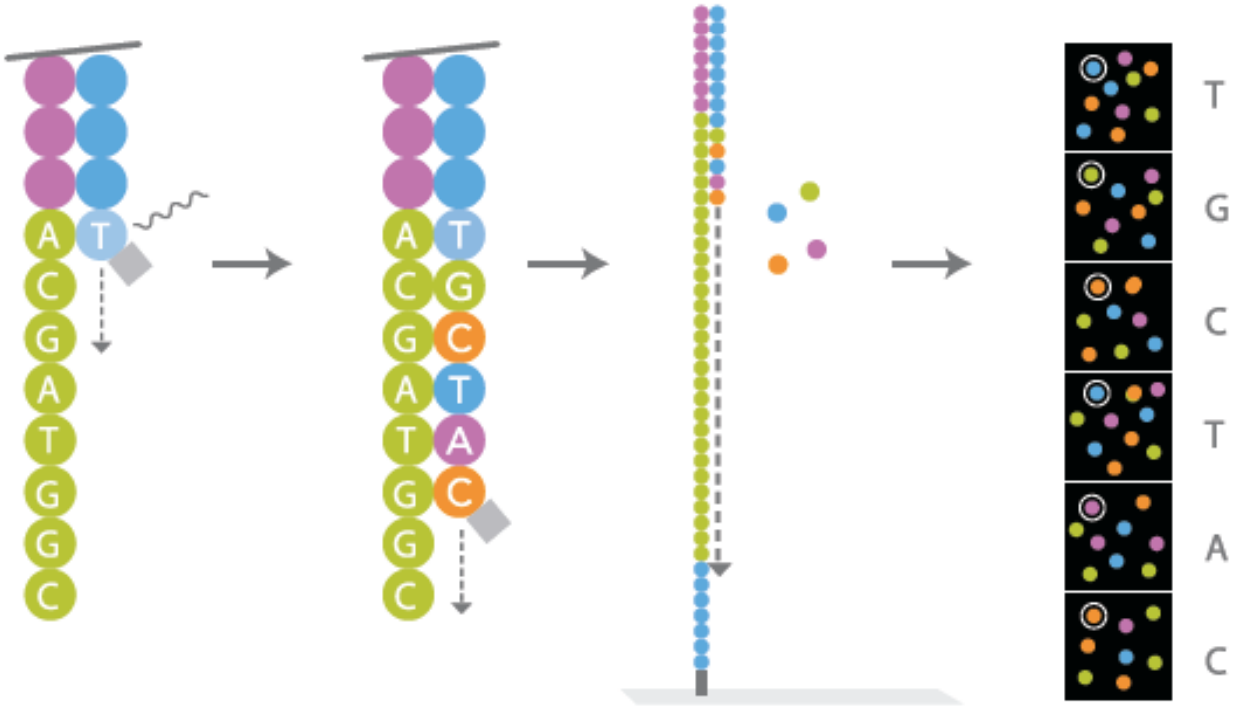
“Next-gen” Sequencing







‘Omics and Biology

- Key attributes of genomics
  - Scaling of data acquisition
  - Hypothesis-generating research
  - Generate data set
  - Parse dataset for patterns, perturbations, etc.
  - Make hypothesis for how the ‘omic attribute affects the system
  - Test the hypothesis

‘Omics and Clinical Research

- Assemble a cohort of subjects
- Generate large-scale dataset
- Parse dataset for patterns, perturbations, etc.
- Generate a hypothesis for how the ‘omic attribute affects the subject
- Test the hypothesis with clinical research

‘Omics and Clinical Care I

- Newborn exam – normal
- Genome sequenced from cord blood
- Using parent and clinician key, interrogate genome for NBS gene panel
- Order recommended follow-up tests
- Restrict diet
- Consult to metabolic expert

‘Omics and Clinical Care II

- Patient presents to clinic for asthma
- History and pertinent examination
- Using patient and clinician key, interrogate genome for susceptibility and pharmacogenetic data
- Prescribe treatment

‘Omics and Clinical Care III

- Couple presents to clinic for preconceptual counseling
- Using patient, partner, and clinician key, interrogate genomes for carrier states
- If one hit each in a gene, refer for counseling and consideration of PND, PGD, etc.

‘Omics and Clinical Care IV

- Patient presents to clinic for routine healthcare evaluation
- Patient reviews interactive educational tool on breast/ovarian cancer susceptibility
- Using patient and clinician key, interrogate genome for susceptibility alleles
- If abnormal allele identified, refer to cancer genetics clinic

Why Not?

- Infrastructure to generate, store, distribute data
- Clinical research to define utility of approach
- Clinician-friendly analytic software & robust databases
- Changing clinician training, attitudes, & practice

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- *All of these are hard to do and will take time*

Data Infrastructure

- Interrogate genome once
  - Prediction is that doing this once will be cheaper than lifetime cost of multiple interrogations
    - Secondary benefit is instant availability
  - Consequence is that one gets *much* more data than anyone needs or wants

This is not a New Problem

- MS/MS in Newborn Screening
- Acquire large data set
- Filter output based on analytes known to be useful
- Discard the rest

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- Secure storage with ready accessibility
- Robust database of correlation of variants with phenotypes

Define Utility of the Approach

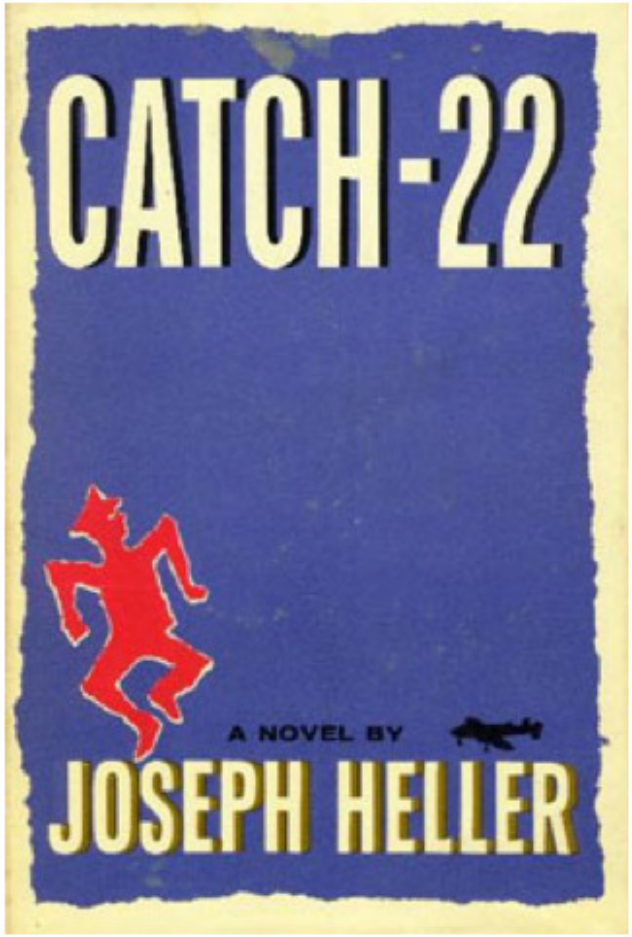
- Need to develop trials to test utility of sequence-driven algorithm v current practice
- These results should not be compared to the ideal – instead compare to real practice
- Threshold for implementation should be when average lifetime use of whole genome = cost of multiple individual tests or panels

Clinician-Friendly Algorithms

- Most genetics and genomics should disappear into general and non-genetic subspecialty practice
- Flag mutations for which it is essential to practice highest standard of non-directive counseling
- Rare, atypical, outlier cases *efficiently* shunted to an expert

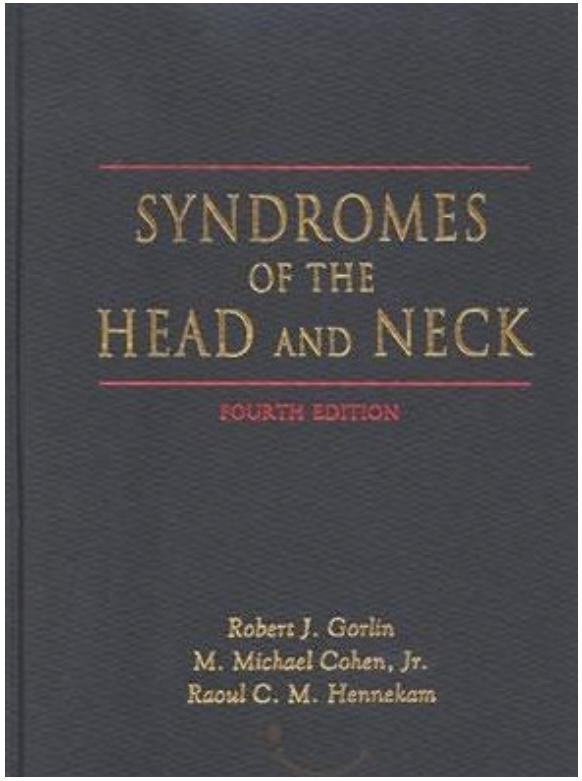
But We Are Stuck

- Many components to develop and test
- Need to find a way forward



Rare Disease Challenge

- How many syndromes?
  - Syndromes Head & Neck
    - >2,500 entities
  - London Medical Database
    - >4,500 entities
  - Many rare, few with genes, few with natural history



Build Out From Rare Diseases

- Build sequencing & data infrastructure
- Start with specialists using informatics tools
- Specialists teach generalists
- Learn about many ‘incidental’ findings from these families

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- The clinician's role will evolve
  - From a test *selector*
  - To a test *integrator*

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- A key change will be adapting to large-scale, *pre-differential* testing

Hypothesis-Generating Research

- Isolated causative mutations for metabolic disorder
- ClinSeq™ database included subject with homozygous change
- Retrieved serum and urine
- 20x-50x elevation of metabolites
- Abnormal MRI

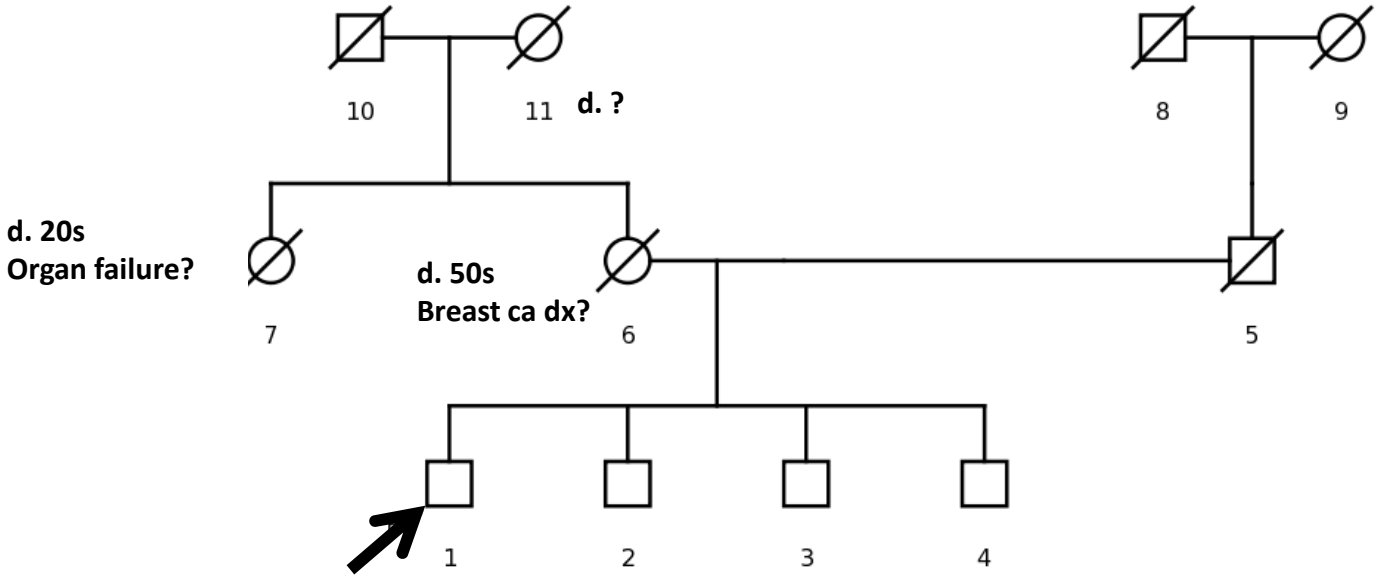
ClinSeq™ Cohort

- Enrolled >900 subjects
- Primary phenotype atherosclerosis
- Consented for
  - Full sequencing
  - Downstream phenotyping - *any*
- 575 exomes

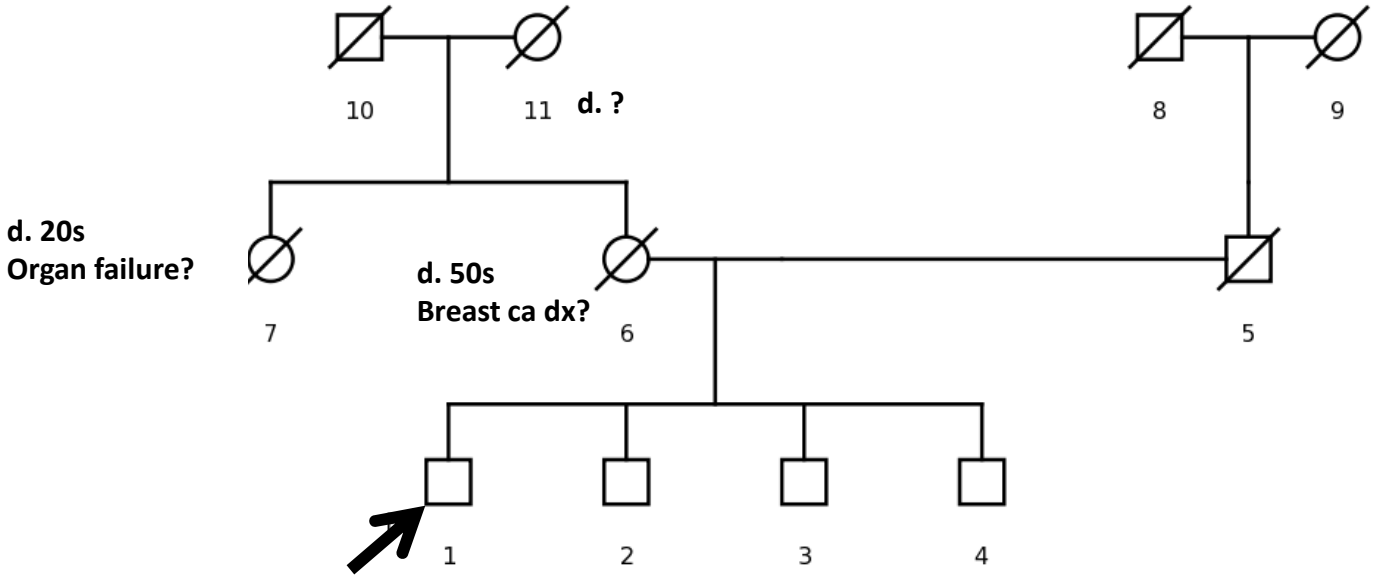
Example 1

- Exome of patient with rare metabolic disorder
- Identified causative mutations, novel gene
- Scanned ClinSeq™ cohort > patient with homozygous mutation
- Pulled banked serum & urine
- Diagnosed disorder

Example 2



Example 2



- Known pathogenic *BRCA2* allele

Prognostic Tool