Bio-Medical Computing (6.872/HST.950)

Peter Szolovits, PhD
Gil Alterovitz, PhD
+ *guest lecturers*

Medical Informatics

- Intersection of medicine and computing
- Plus theory and experience specific to this combination
- =Medical Computing, ~Health Informatics

- Science
- Applied science
- Engineering

Types of Bio-Medical Informatics

- Cellular level: *Bioinformatics, Systems Biology*
- Patient level: *Clinical Informatics, Health I., Medical I., …*
- Population level: *Public Health I.*
- Imaging Informatics

Bio-Medical Informatics

- Phenotype = Genotype + Environment
- In humans, we rely on “natural experiments”
- Measurements
  - Genotype: sequencing, gene chips, proteomics, etc.
  - Environment: longitudinal surveys, etc.
  - Phenotype: clinical records, assembled to longitudinal data

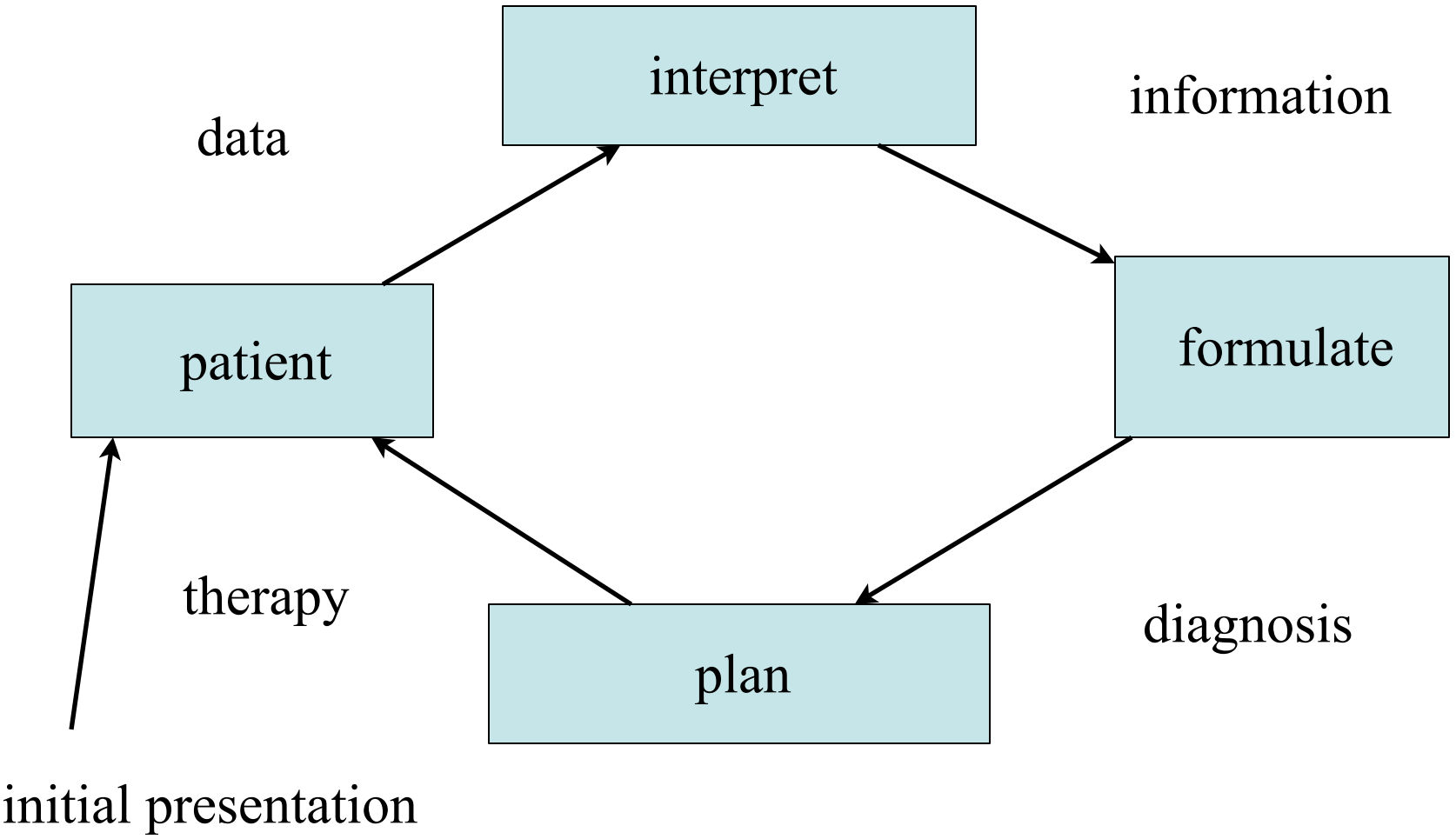
Outline
(today)

- What is biomedical informatics?
- BMI is defined by goals and methods of health care
- The genomic revolution
- The science of health care
  - Genotype, phenotype, environment
  - From associations to mechanisms
- What is health?
- Practice of health care
- Challenges

Outline
(semester)

- Clinical and Genomic Data
- Methods of modeling
- Combining clinical and genetic data
- “Translational medicine”
- Engineering the health care system
- Decision support to improve health care
- Personalized medicine
- Public health
- The developing world
- *Your* projects

The Medical Cycle



Care Processes

- Data: instrumentation, monitoring, telemetry
- Information: interpretation, filtering, sampling, smoothing, clustering
- Diagnosis: inference, model-based reasoning, classification
- Prognosis: prediction, natural course, experience
- Therapy: planning, predicting effects, anticipating

Meta-level processes

- Acquisition and application of knowledge
- Education
- Quality control and process improvement
- Cost containment
- Reference (library)

Enterprise-level Clinical Process Automation...

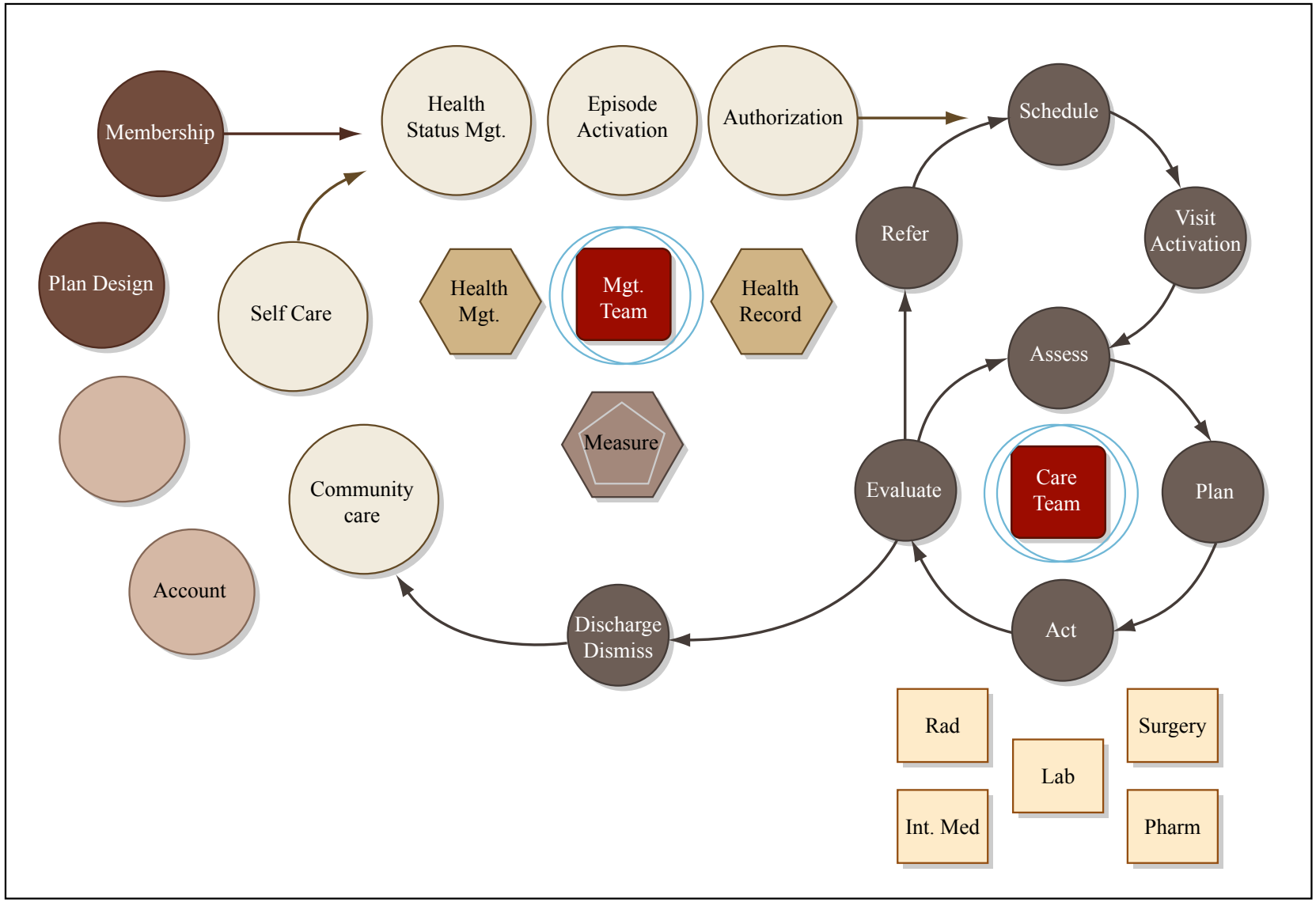
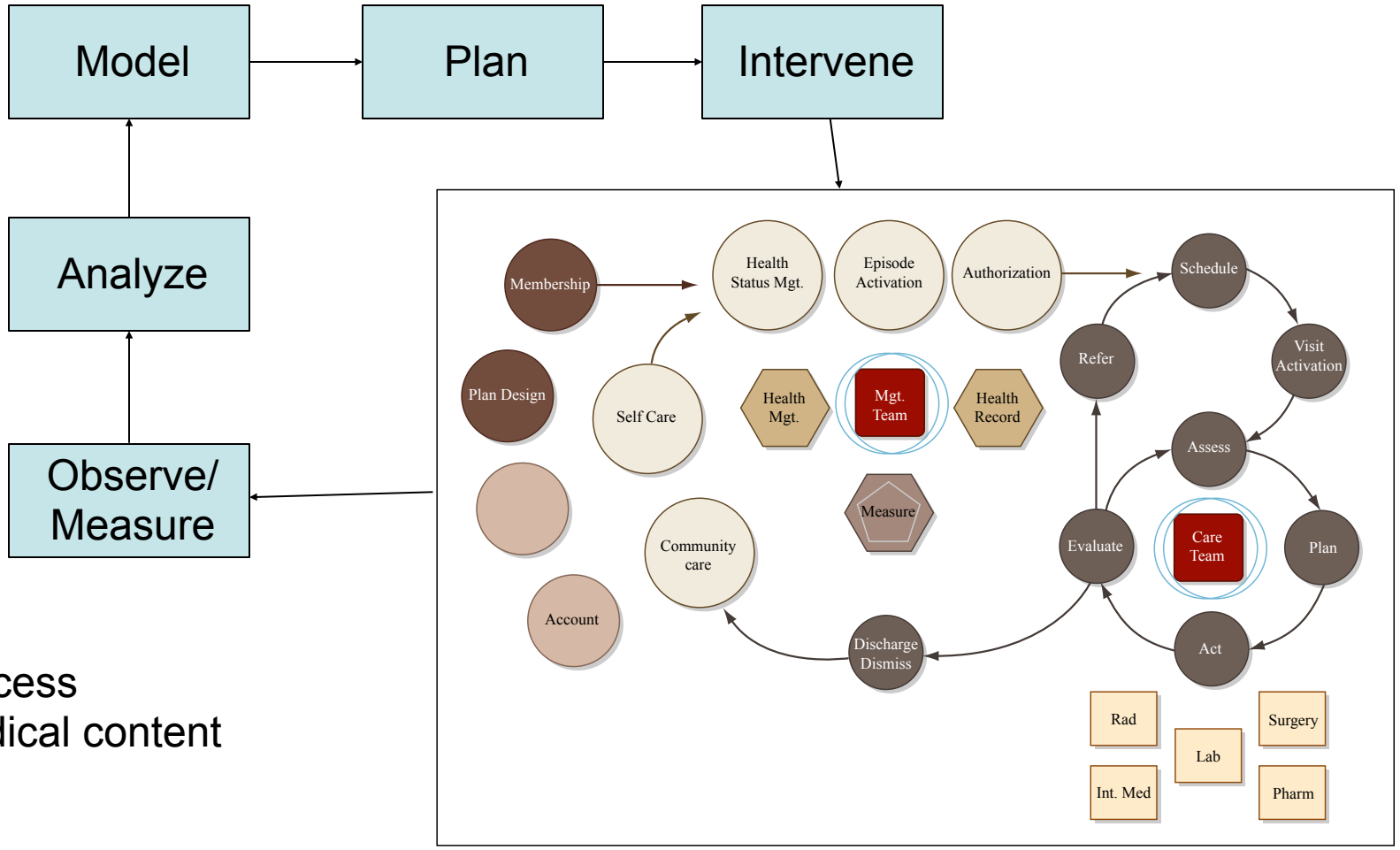


Image by MIT OpenCourseWare. Adapted from figure by David Margulies.

figure from David Margulies

The “Learning Health Care System”



- Process
- Medical content

Image by MIT OpenCourseWare. Adapted from figure by David Margulies.

Dogma

Phenotype	=	Genotype	+	Environment
Traits		Gene sequence		Diet, smoking, drugs, …
Diseases		SNP's		Insults and injuries
Behaviors		Expression data		Exposures
…		…		…

- What is the functional form?
- How do we investigate these relationships?
- Can we take advantage of the exponential growth of genomic data?

Growth in Gene Expression Omnibus Measurements

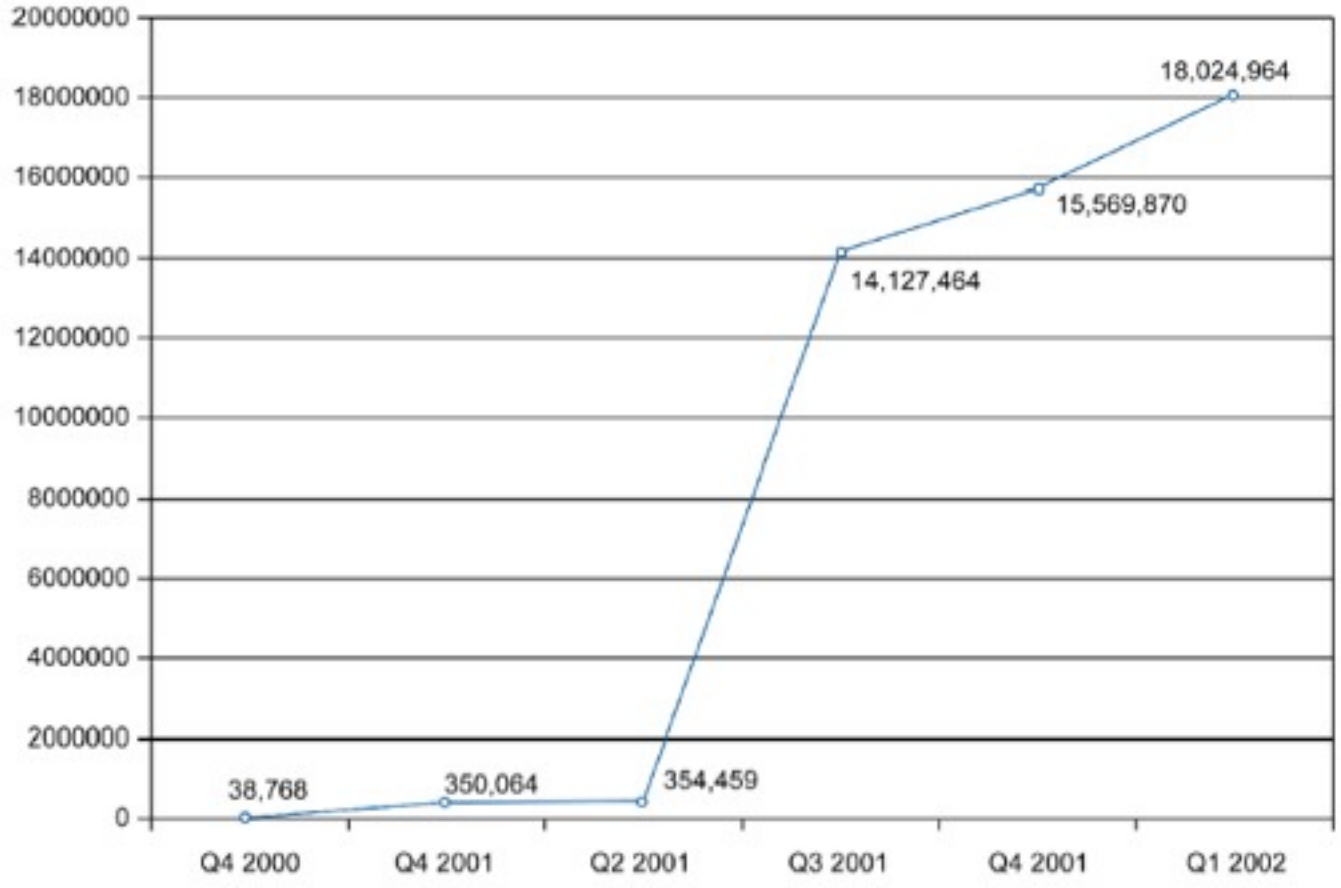


Figure 4: GEO submission statistics. Cumulative individual sample measurements submitted to GEO are shown. Data are presented by quarter since operations began on July 25, 2000.

Fall 2004: ~30,000 submissions, ~.5B measurements

Today (9/2010): ~472,929 samples

http://ncbi.nlm.nih.gov/geo/

Figure 4 from Edgar, Ron and Alex Lash. "Chapter 6 The Gene Expression Omnibus (GEO): A gene expression and hybridization repository." *The NCBI Handbook, National Library of Medicine*, 2003.

Where are the Phenotype and Environment-related Data?

Phenotype	= Genotype	+ Environment
Traits	Gene sequence	Diet, smoking, drugs, …
Diseases	SNP's	Insults and injuries
Behaviors	Expression data	Exposures
…	…	…

- Perform Controlled Experiments?
  - Unethical using human subjects!!!
  - OK on rats.

Experimental Subjects

Image by Randall McIlwaine on CartoonStock.com has been removed due to copyright restrictions. Researcher holding hat with Mickey Mouse ears says to another researcher, "We've run out of lab rats, Henderson... Put this on and come with us."

Image by DakotaPrarieNova on Flickr.

High-throughput phenotyping at Medical College of Wisconsin

Image of laboratory at Medical College of Wisconsin have been removed due to copyright restrictions.

Where are the Phenotype and Environment-related Data?

- Environment
  - (Hardest to get)
  - Questionnaires,
    - e.g., Nurses' Health Study, Framingham Heart Study
  - Monitoring
    - e.g., LDS hospital infectious disease monitors
- Phenotype
  - "Natural Experiments"
  - ∴ Clinical Data

The fantasy: Informatics for Integrating Biology & Bedside

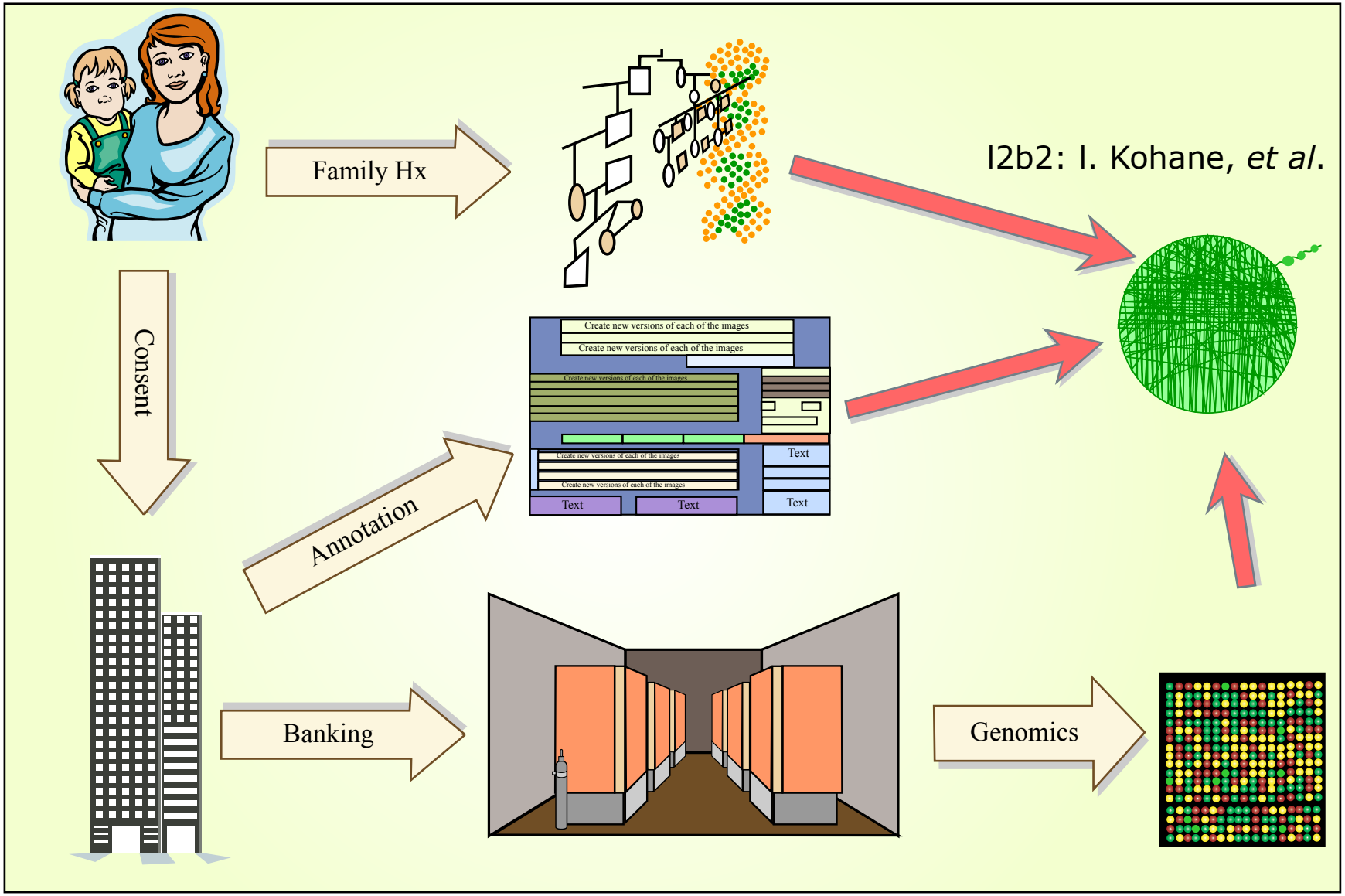
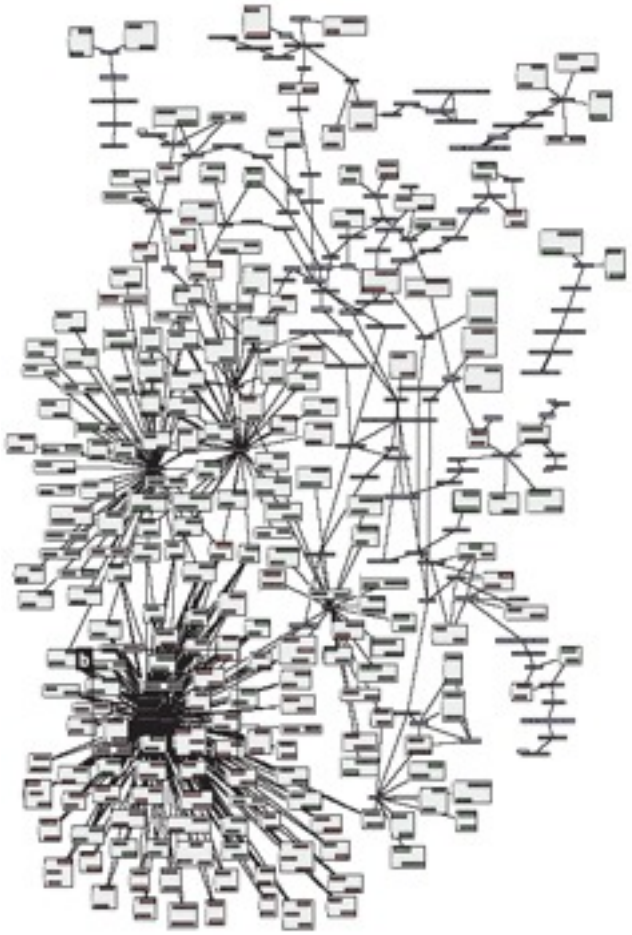


Image by MIT OpenCourseWare. Adapted from Peter Szolovits.

Plausibility

Butte & Kohane, *Nature Biotech* 2006

- Phenome-Genome Network
  - Gene Expression Omnibus
    - expression data
    - annotations: tissue, disease, expt. conditions, …
  - Interpret annotations to UMLS
  - Differential expression vs. condition
  - Interesting relations:
    - 11 genes & aging
    - DDX24 and leukemia
    - 2 genes & injury



Clinico-Genomic Research

- Identify a highly specific clinical population, and controls
- Gene-wide association studies (GWAS)
- Hope that notable differences appear between those with/those without disease
- Disease models:
  - Mendelian
  - Single-nucleotide polymorphisms
  - Private variation
  - ?

Time scale in medicine

- Cure—usually acute illness
- Manage—long-term, chronic illness
- Prevent
- Predict (especially based on genetics)

WHO Constitution defines "health"

"a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity"

- Physical
- Mental
- Social

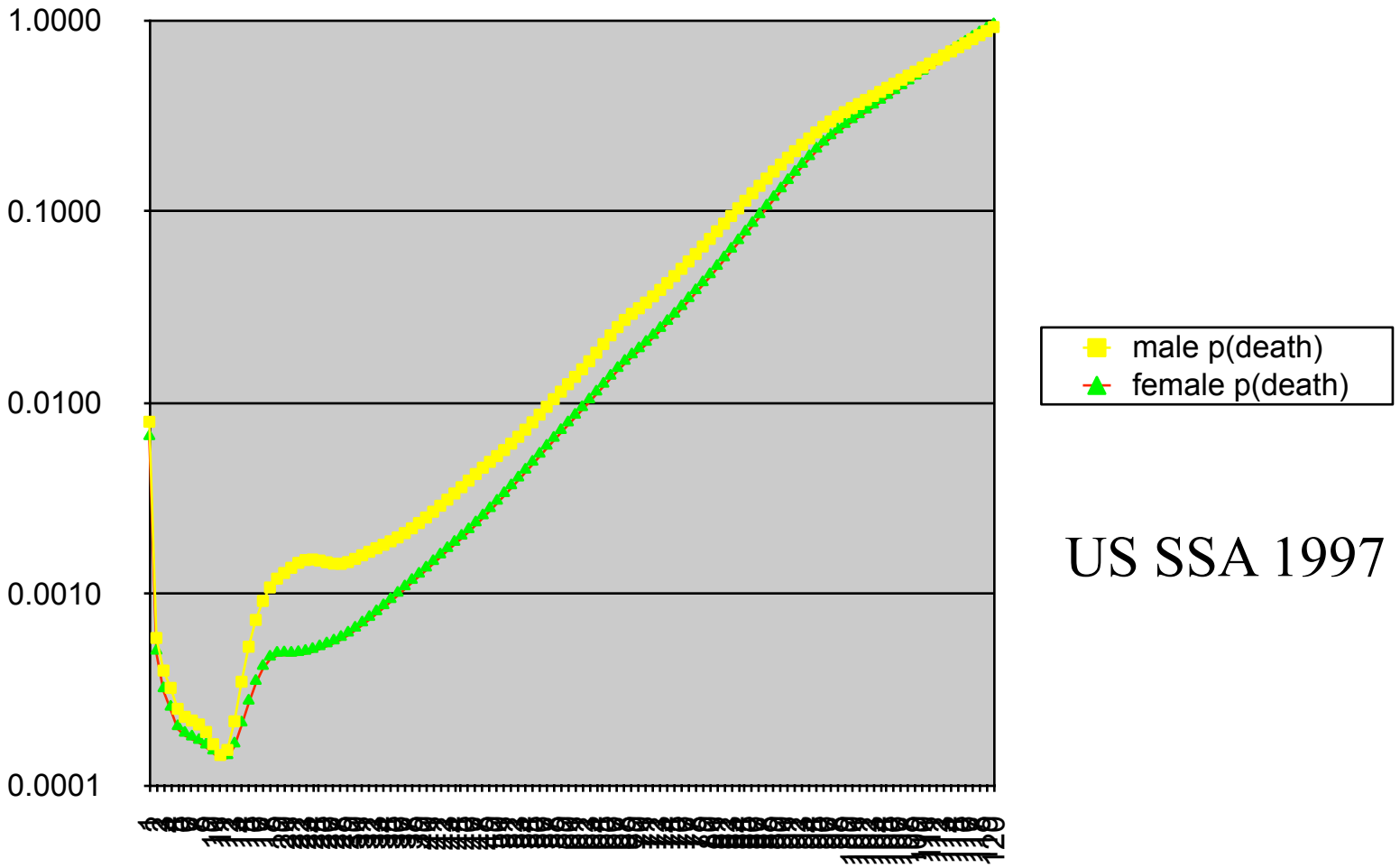
—very hard to measure

Distribution of Ages

- Life table
  deaths by year
  (Japan, 1989)

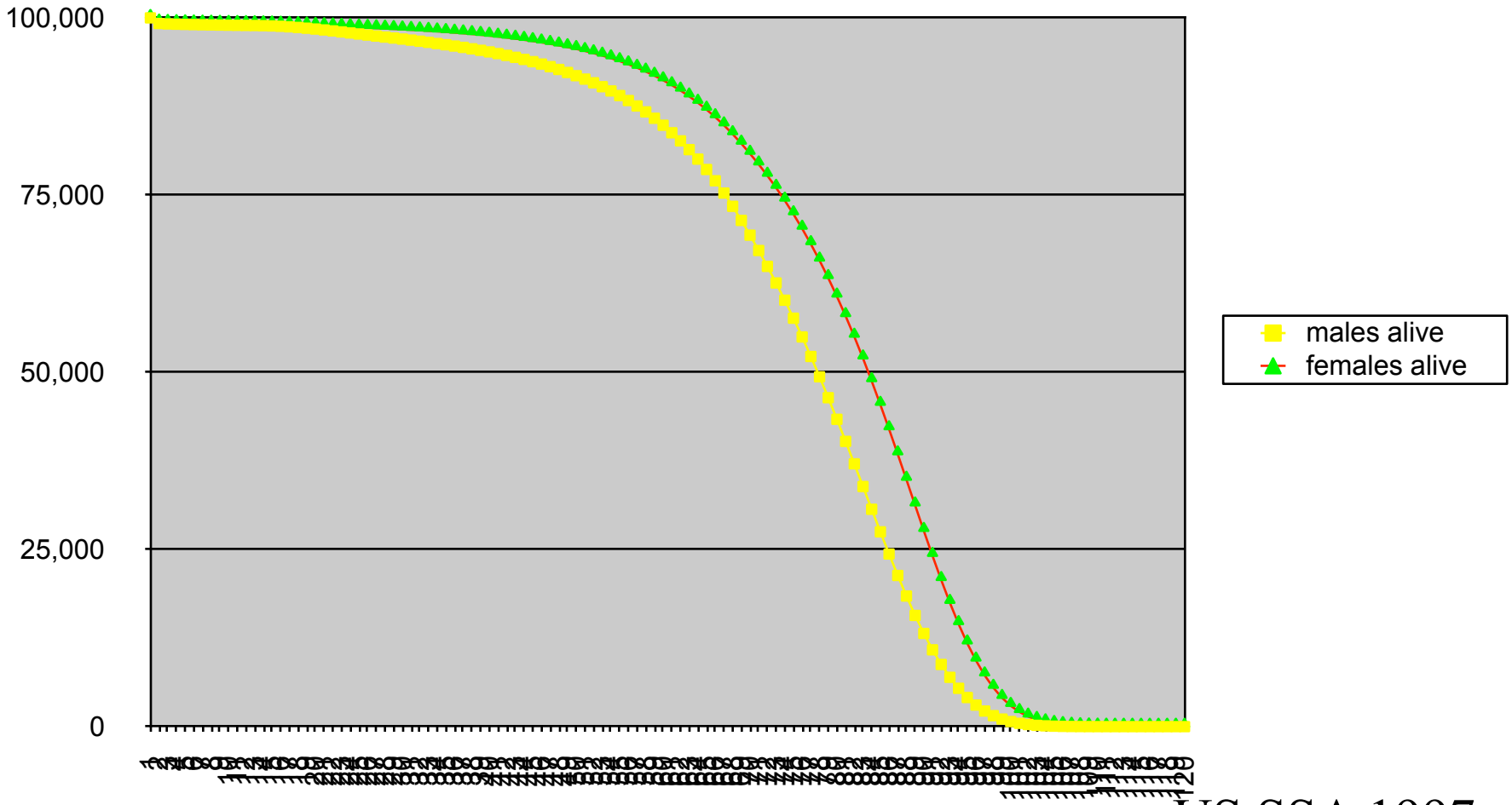
Graph showing distribution of ages in Japan has been removed due to copyright restrictions. The graph shows a far greater number of elderly people than younger people.

Life table death rates by age



US SSA 1997

Life table cohort survival



US SSA 1997

Measures of Health

- Longevity at birth (CIA World Fact Book, 2001)

Country	*Male*	*Female*
Rwanda	38.35	39.65
Kenya	46.57	48.44
South	47.64	48.56
Cambodia	54.62	59.12
Brazil	58.96	67.73
Russia	62.12	72.83
Albania	69.01	74.87
USA	74.37	80.05
Japan	77.62	84.15

Causes of death
(industrialized countries, 1989)

Circulatory system	48%
Malignant neoplasms	19%
Accidents	7%
Others	26%

Quality of life

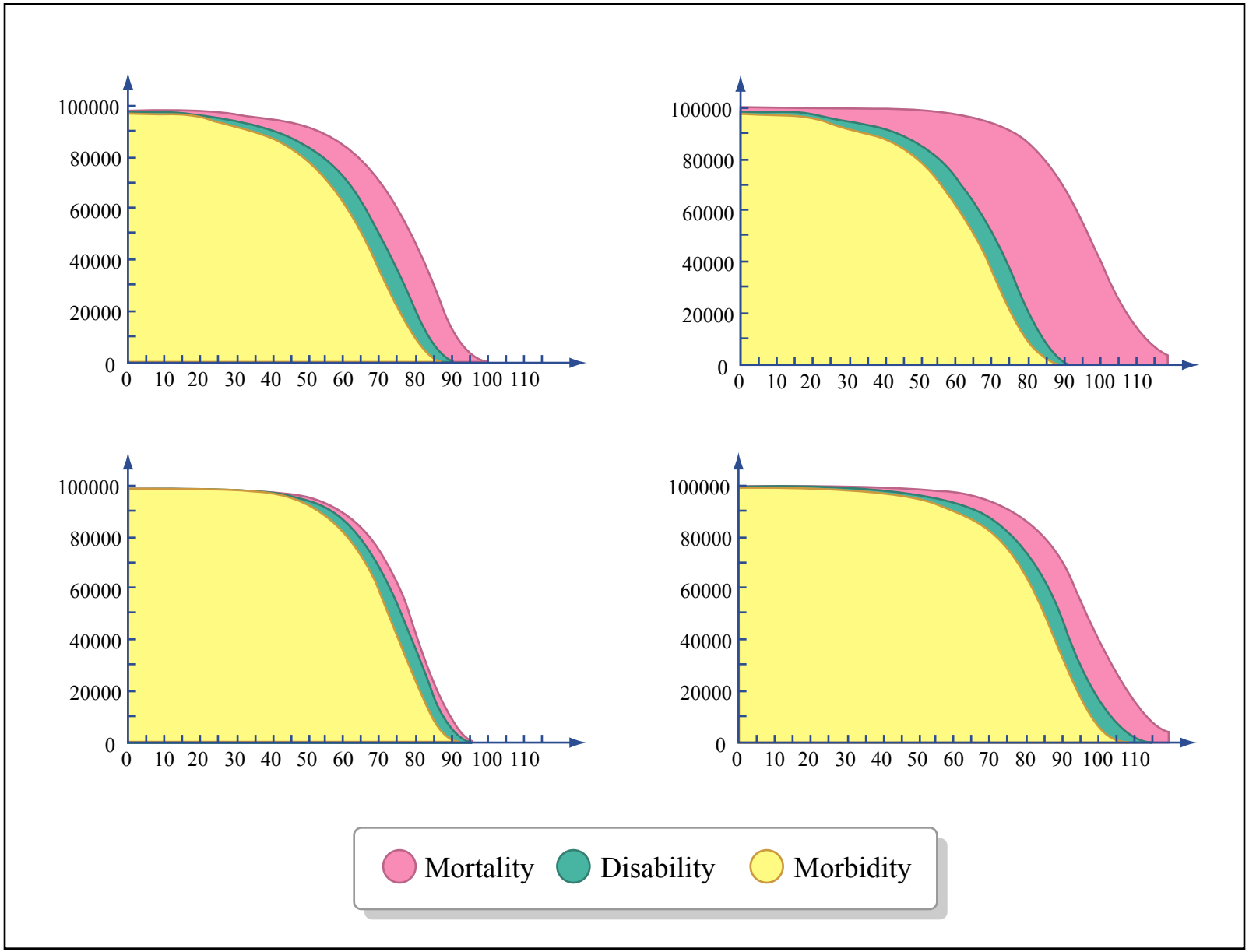
- Value of a total life depends on
  - Length (assume *now* is *N*)
  - Quality (*q*) over time
  - Discounts (*g*) for future or past (depends *very* much on what the value is to be used for)

$$V_N = \int_{t=0}^{T} q(t)g(t-N)\mathrm{d}t$$

Modeling life quality

Figure showing four hypothetical survival scenarios showing survival from death, onset of disease, and onset of disability has been removed due to copyright restrictions.

Mortality, Disability, Morbidity



Top 10 Chronic Conditions Persons aged ≥ 65

Condition	Both	Male	Female
Arthritis	49.6	40.7	55.7
Hypertension	39.0	33.0	43.2
Hearing impairment	30.0	35.2	26.3
Heart disease	25.7	26.9	24.9
Orthostatic impairment	16.8	15.7	17.8
Cataracts	15.5	11.3	18.4
Chronic sinusitis	15.2	13.7	16.2
Visual impairment	10.1	12.0	8.8
Genitourinary	9.9	11.3	8.9
Diabetes	8.9	7.8	9.7

U.S. Nat'l Ctr Health Stat, *Vital and Health Statistics*, 1985 (1982 data)

Societal quality of life

- Aggregation of individual qualities

+ Equity (distributions)

- Is more better? (Population control.)
- Is less better?
- How much to spend?

Who makes decisions?

"In those days there was no bureaucratic regimentation, there were few forms to fill out, malpractice premiums were affordable, and the overhead costs of running a practice were reasonable. Our bills were simple, spelled out so anybody could understand them without the use of codes. Patients usually paid their own bills, promptly too, for which an ordinary receipt was given. Hospital charges were set by the day, not by the aspirin. Medical care was affordable to the average person with rates set by the laws of the marketplace, and care was made available to all who requested it regardless of ability to pay. Doctors were well respected; rarely were we denigrated by a hostile press for political reasons. Yes, in the days before government intervention into the practice of medicine, doctor's fees were low, but the rewards were rich; those were truly the 'golden years' for medicine."

Edward Annis, past President of AMA

Code Blue, 1993

Aggregation

- Trend: social aggregation leads to decisions at a larger scale
  - Multi-specialty providers
  - Government guarantees and mandates
  - Risk sharing
  - Oregon-wide spending “optimization”;
  - British NHS

Changing Context of Health Care

- Fee-for-service
- HCFA (Health Care Financing Agency) pays for Medicare
- Capitation
  - HMO's (Health Maintenance Organizations) take overall responsibility to care for patient for fixed fee
  - Pushing risk down to the physician or group

Determining Factors:

$£€¥R

Exponentially growing expense of health care

- More healthcare than steel in GM cars
- Increased demand
  - Much more possible
  - Better tests, therapies
  - High human motivation
- No pushback
- Waste
  - Unnecessary procedures
    - ½ of health expenses in last year of life
  - Marginally useful procedures
    - Defensive medicine
  - Bad Medicine
    - IOM: 48-98K “unnecessary” deaths/year

Managed Care

"Decisions that were once the exclusive province of the doctor and patient now may be examined in advance by an external reviewer—someone accountable to an employer, insurer, health maintenance organization (HMO), or other entity responsible for all or most of the cost of care. Depending upon the circumstances, this outside party may be involved in discussions about where care will occur, how treatment will be provided, and even whether some treatments are appropriate at all."

Controlling Costs and Changing Patient Care IOM, 1989

How is care managed?

- Active case management:
  - Preadmission review
  - Continued-stay review
  - Second surgical opinion
- Selective case management—high-cost cohorts
- Institutional
  - Capitation
  - Institutional arrangements (referrals, hospitals, pharmacies, …)
  - Control “leakage”

Managed Care Scorecard

- “U.M. has helped to reduce inpatient hospital use and to limit inpatient costs…”
- “The impact of U.M. on net benefit costs is less clear. Savings on inpatient care have been partially offset by increased spending for outpatient care and program administration.”
- “U.M. … does not appear to have altered the long-term rate of increase in health care costs.”

IOM, 1989

Obama Proposals

- Universal coverage: everyone must get insurance
  - Employer
  - Insurance collaborative
  - Government (?) — rejected
- Insurance companies cannot deny insurance, cancel coverage, impose reimbursement limits based on illness, past or present
- Government assistance to poor people, small companies
- Health Information Technology (HIT) to smooth info flow
- Cost savings from avoiding billing disputes, ceasing to reimburse only procedures, evidence-based medicine.

Quality Improvement

- IOM Study: 96,000 US deaths/year from medical error (perhaps half preventable?)
- Information intervention *at the point of decision making* can improve decisions
- DPOE: Direct Physician Order Entry allows such intervention
- Leapfrog Group: Large employers ($$$) require DPOE from providers
- Patient Involvement: Indivo Health, Google Health, Microsoft Healthvault

Implications of Health Care Organization for Informatics

- Money determines much
  - Medicine spends 1-2% on IT, vs. 6-7% for business overall, vs. 10-12% for banking
  - “Bottom line” rules, therefore emphasis on
    - Billing
    - Cost control
    - Quality control, especially if demonstrable cost savings
    - Retention and satisfaction (maybe)
  - Management by accountants

Challenges

- Computerized Medical Records (EMR/ CPR/…)
- Usability of systems in the workflow of health care
- Large-scale “Engineering Systems” problem
- Genomic Medicine

HST.950J / 6.872 Biomedical Computing

Fall 2010