Building a Platform for Modeling Risk and Opportunities in Drug Development

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Agenda

- Basic Pharma Model
- Real World Issues
  - Real world medicine
  - Real world patients
- Designing the Platform
- Case Studies
  - Heart Failure
  - COPD
- Conclusions

What do these have in common with Pharma?

Movies

- Field of Dreams
- Pretty Woman
- Carnosaur
- The Cable Guy
- Save Me
- Gingerbread Man 3: Saturday Night Cleaver
- The Big Year
- Muppets from Space

TV

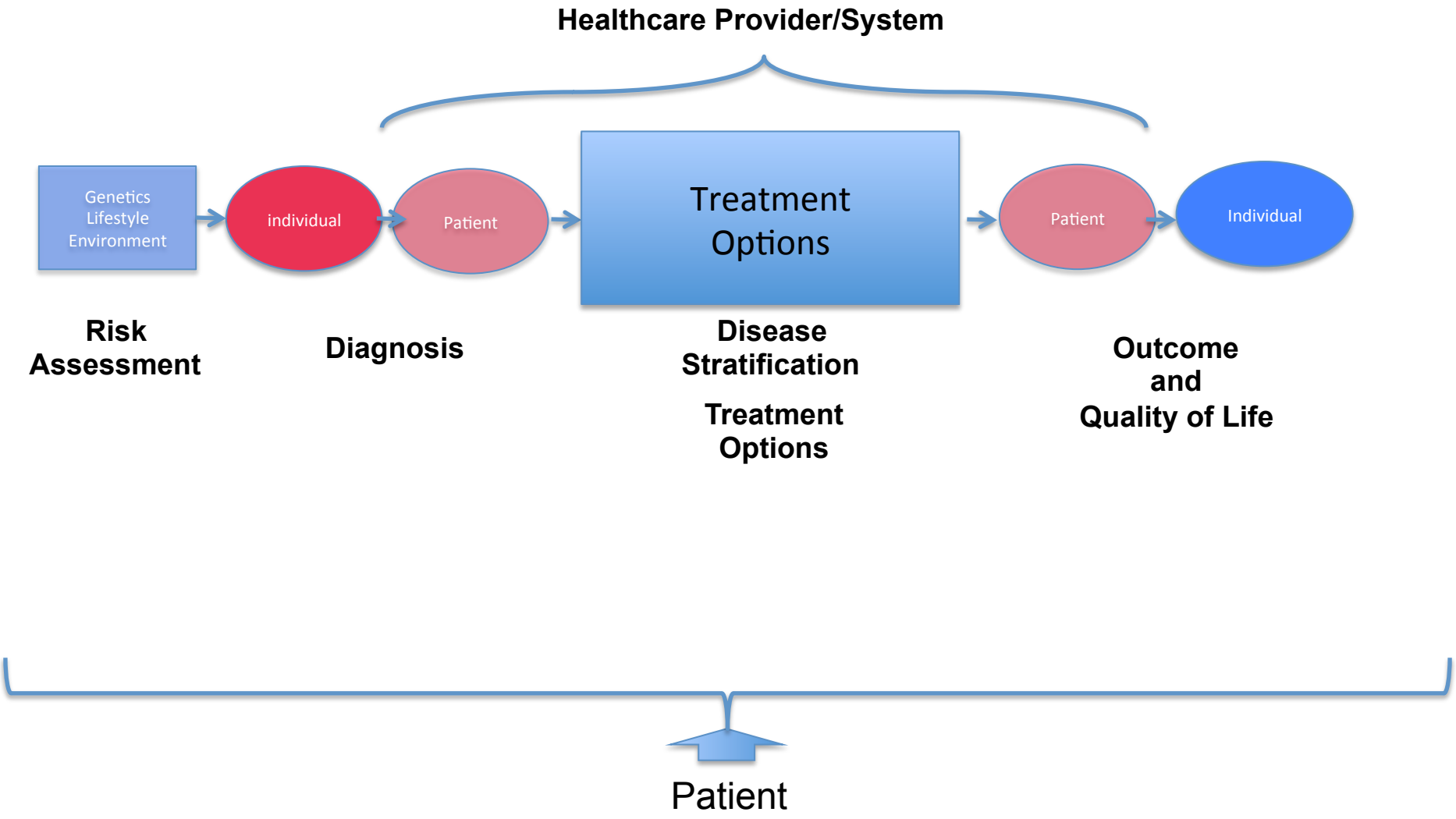
- Better Call Saul
- Bones
- Mystery Science Theater 300
- Married With Children
- The Nanny
- Law and Order
- Gilmore Girls
- Torchwood
- ER
- Brothers and Sisters

Pharma's Field of Dreams

- **"If you build it, they will come."**
  - Kevin Costner's in *Field of Dreams*

- **Why the Motto 'If You Build It, They Will Come' is B**(ia)**S**(ed)
  - David Donner Chait, Entrepeneur 2013

The Process of Disease



The Elephant in the Room is HUGEE!

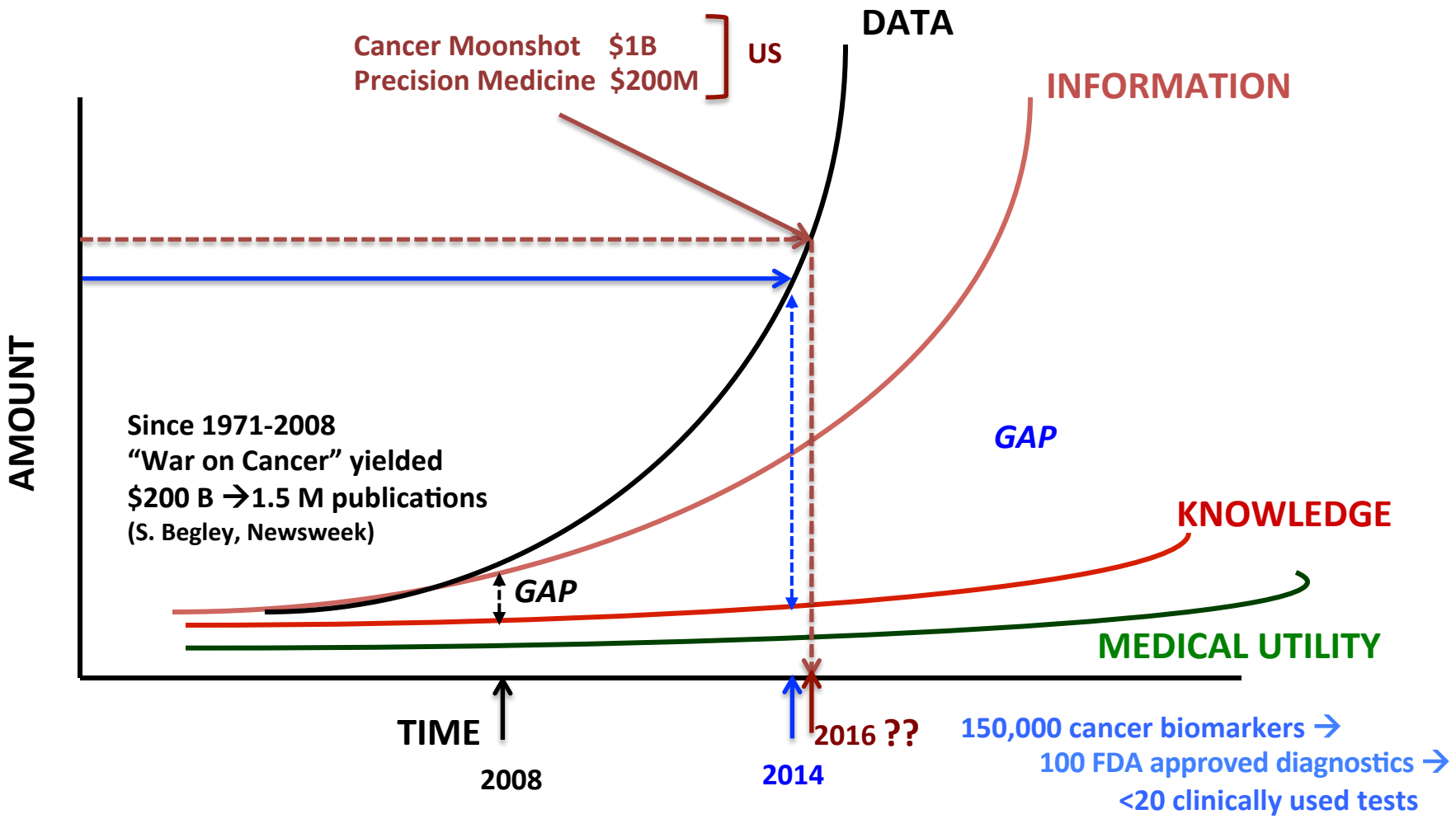
If the Physician doesn't prescribe it or the Patient doesn't take it, it's an "opportunity*", not a drug

*Opportunity = out-licensing, repurposing, etc

The Cost of non-adherence

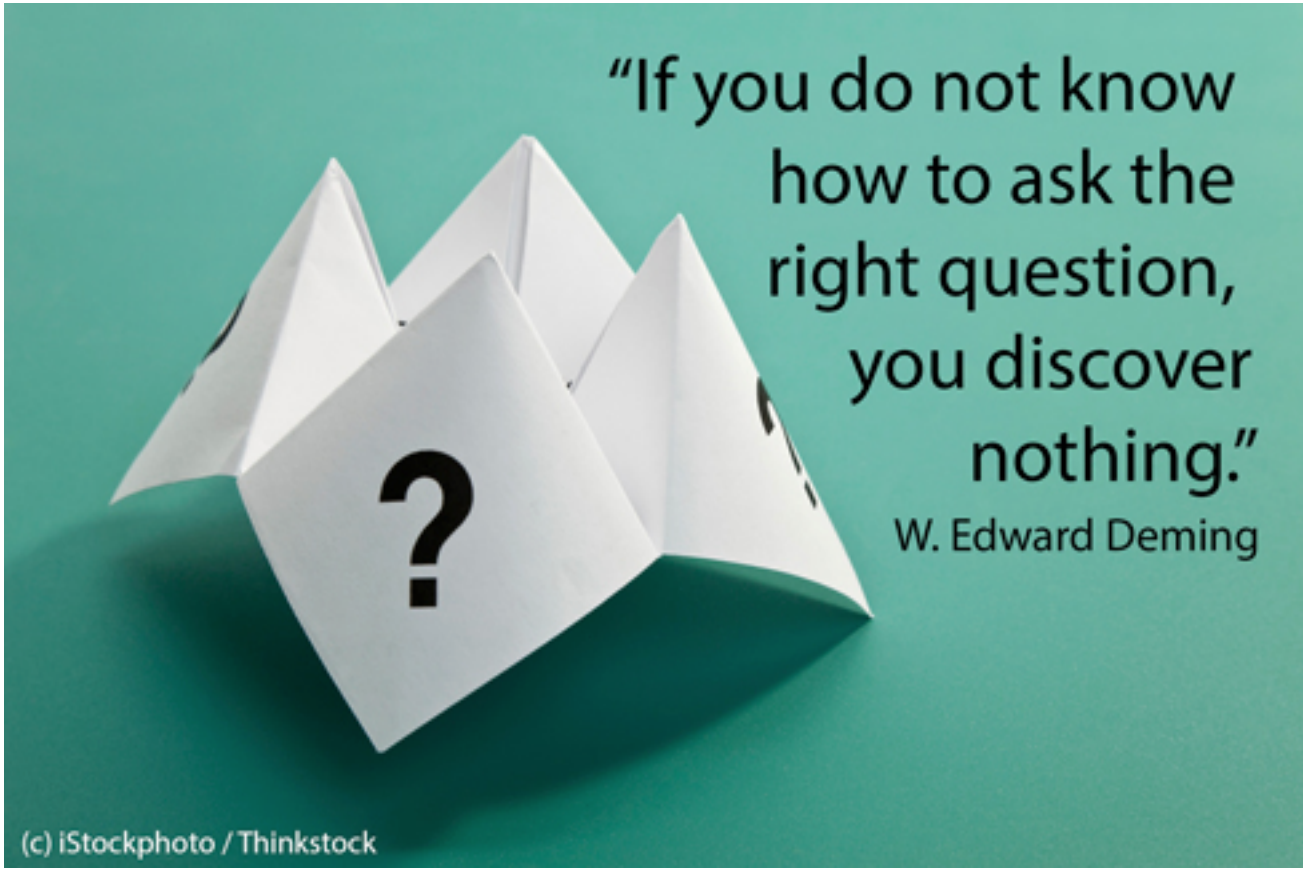
- According to a meta-analysis published in the *Annals of Internal Medicine*, Americans are failing to comply with medication prescriptions for a variety of reasons….and it's **costing them anywhere between $100 billion to $289 billion a year**
- A report by the Department of Health estimates that **unused medicines cost the NHS around £300 million** every year, with an estimated £110 million worth of medicine returned to pharmacies, £90 million worth of unused prescriptions being stored in homes and £50 million worth of medicines disposed of by Care Homes.

The Gap (2008-2014 and beyond)



ICD 10 is Not the Answer

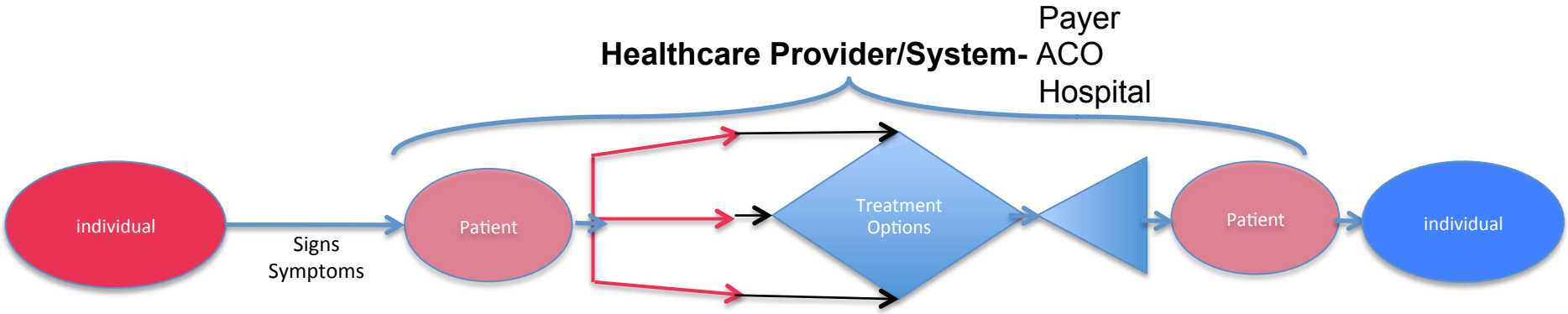
- W59.22XA Struck by a turtle
- W56.42XS Struck by a shark
- W55.12XD Struck by horse
- W53.81XA Bitten by other rodent
- W55.49XS Other contact with pig
- V90.37XD Drowning and submersion due to falling or jumping from crushed water-skis
- X71.3XXD Intentional self-harm by drowning and submersion in natural water


"If you do not know how to ask the right question, you discover nothing."
W. Edward Deming
?
(c) iStockphoto / Thinkstock

Clinical Needs

- **Unmet Clinical Need** reflects the degree to which there are existing treatments. A condition for which there is no effective treatment….significant unmet need, e.g. rare diseases, Alzheimer's disease, ALS
- **Unstated Unmet Clinical Need** reflects the gap in knowledge or adequacy of existing processes and procedures in clinical practice, e.g. diagnosis, disease stratification

Modeling the Disease Process



Risk Assessment
- -Family History
- -Genomic Profile
- -Lifestyle
- -Environment
- -in utero exposure
- -Clinical history

Diagnosis
- -Signs
- -Symptoms
- -Co-morbidities (active, inactive, undiagnosed)
- -Medications
- -Guidelines/Criteria
- -Biomarkers/Diagnostics
- -Disease Stage (direction, velocity)

Disease Stratification
- -Pre-Disease
- -Disease -subtypes
- -Advanced Disease
- -Prognosis

Treatment Options
- -Guidelines
- -Actual Practice
- -Off-label Use
- -Risk/Benefit Ratio

Physician Compliance

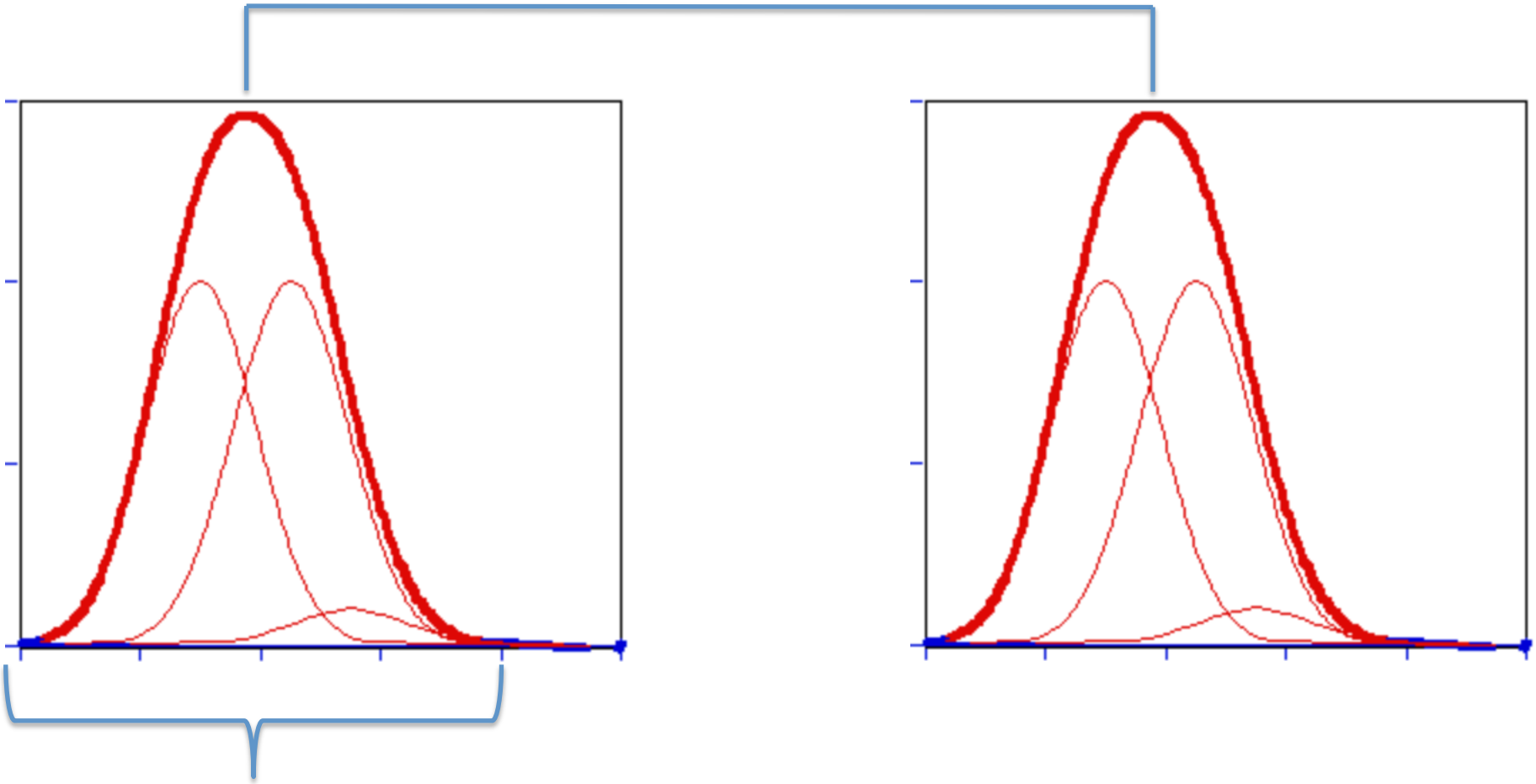
Patient Compliance
- -Perception of Risk (disease, treatment)
- -Adherence
- -Social and Community Networks
- -Cultural Background
- -Expectations

Outcome
- -Disease free Survival
- -Re-admission
- -Management vs Cure
- -Minimum residual disease
- -Complications

Patient

Error in Diagnosis

IOM 10% Error in Diagnosis



40-50% Error
in Disease Stratification

Syndrome

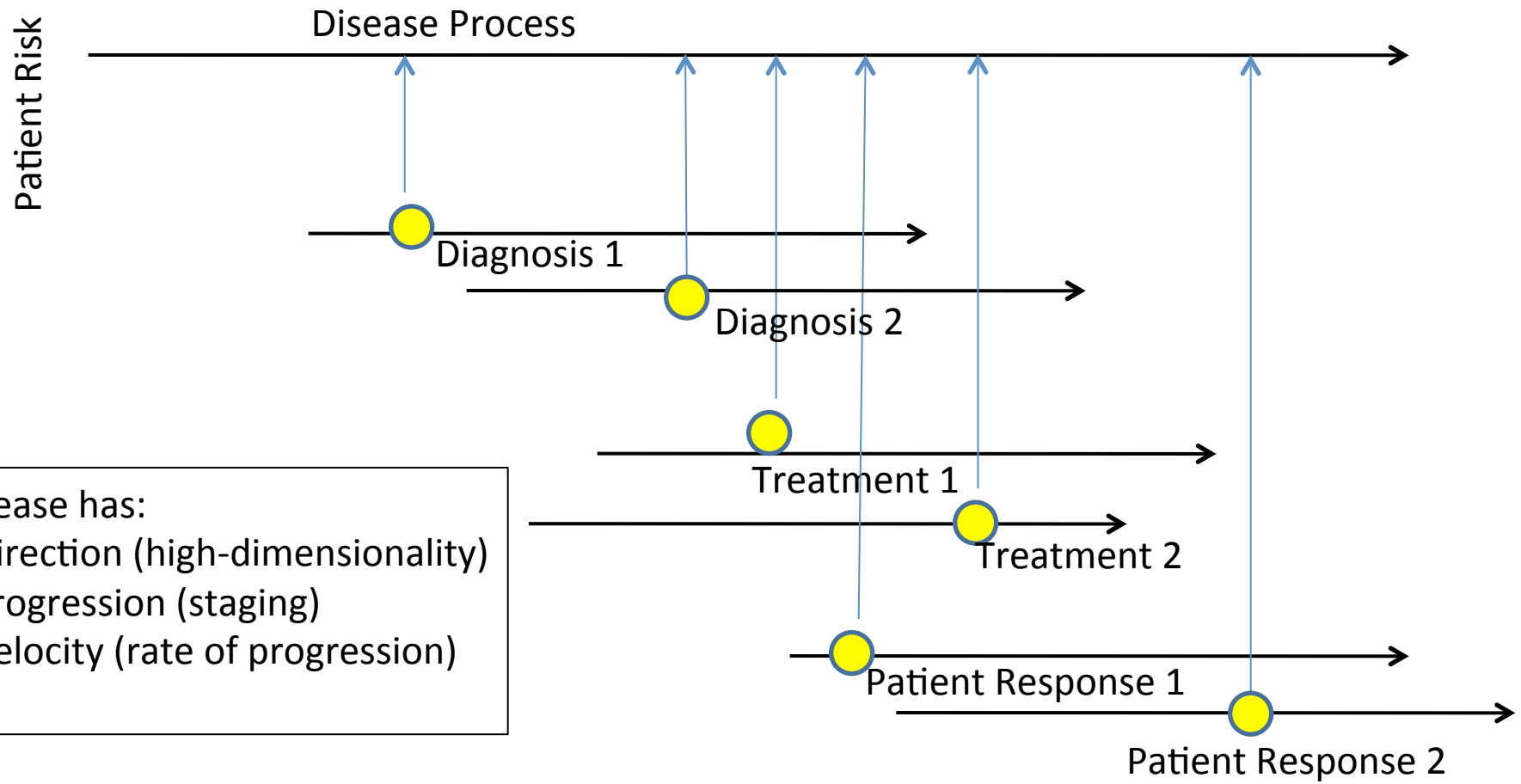
Patient 1 **"Diagnosis"**

- Symptom 1 pain
- Symptom 2 anemia
- Symptom 3 …
- Symptom 4 …
- Symptom 5 …
- Symptom 6 …
- Symptom 7 …
- Symptom 8 …
- Symptom 9 …
- Symptom 10 …

Patient 2 **"Diagnosis"**

- Symptom 1 pain
- Symptom 2 anemia
- Symptom 3 …
- Symptom 4 …
- Symptom 5 …
- Symptom 6 …
- Symptom 7 …
- Symptom 8 …
- Symptom 9 …
- Symptom 10 …

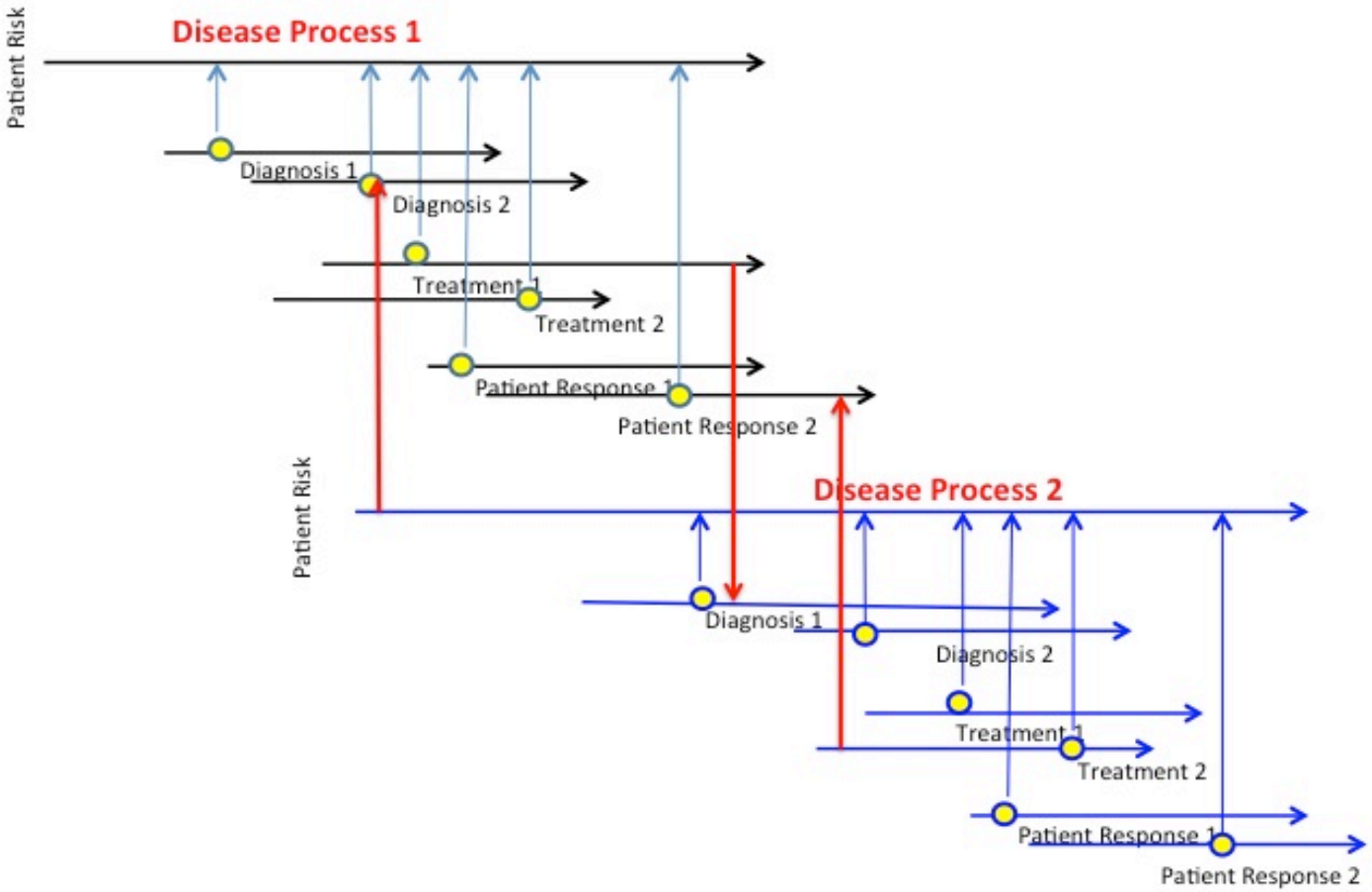
Disease is a Process, Not a State



A Disease has:

1. Direction (high-dimensionality)
2. Progression (staging)
3. Velocity (rate of progression)

Real World Patients: Multi-morbidities



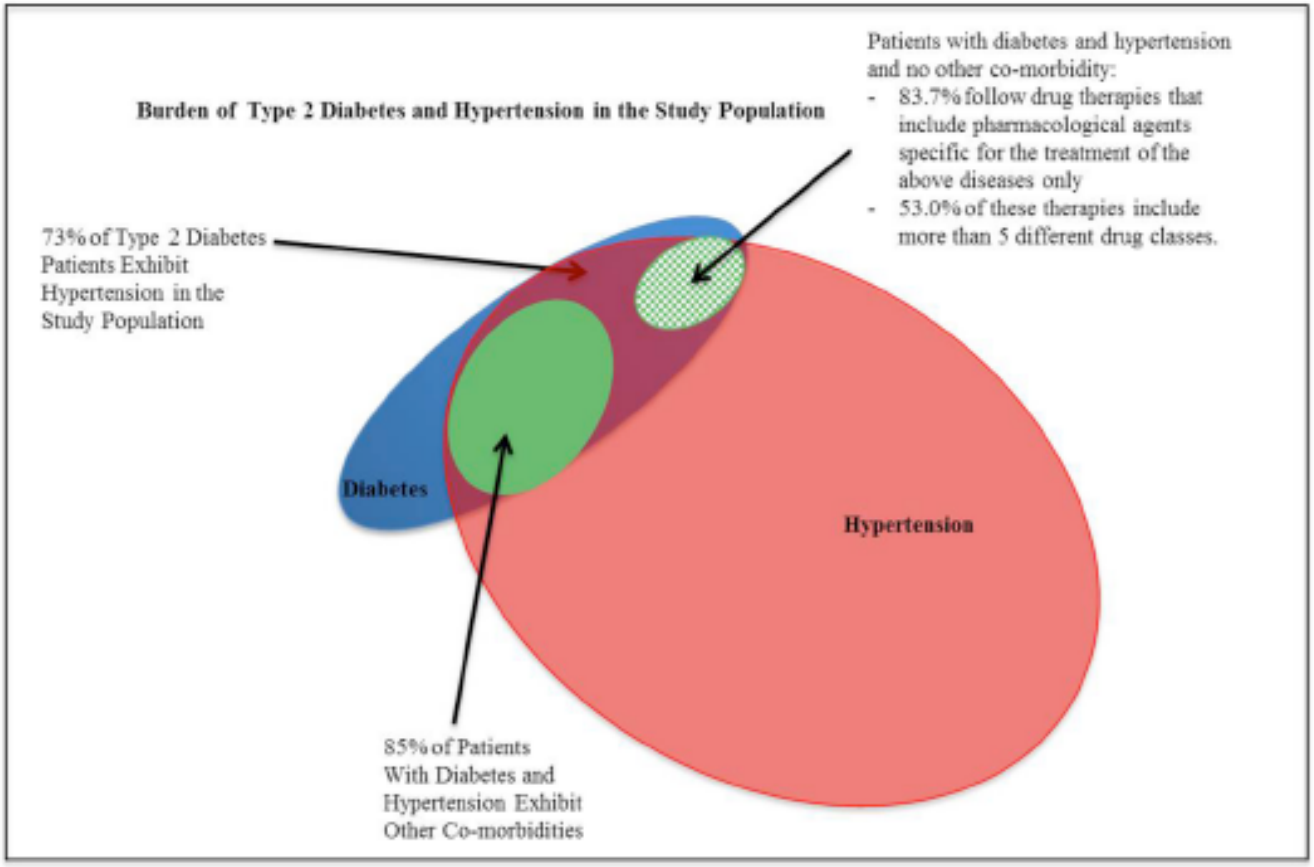


Fig. (6). Burden of type 2 diabetes and hypertension and co-morbidity rate in the study population. Prevalence of targeted drug therapies in patients having diabetes and hypertension only.

ipqanalytics

identify. prioritize. quantify.

PLATFORM DEMONSTRATION

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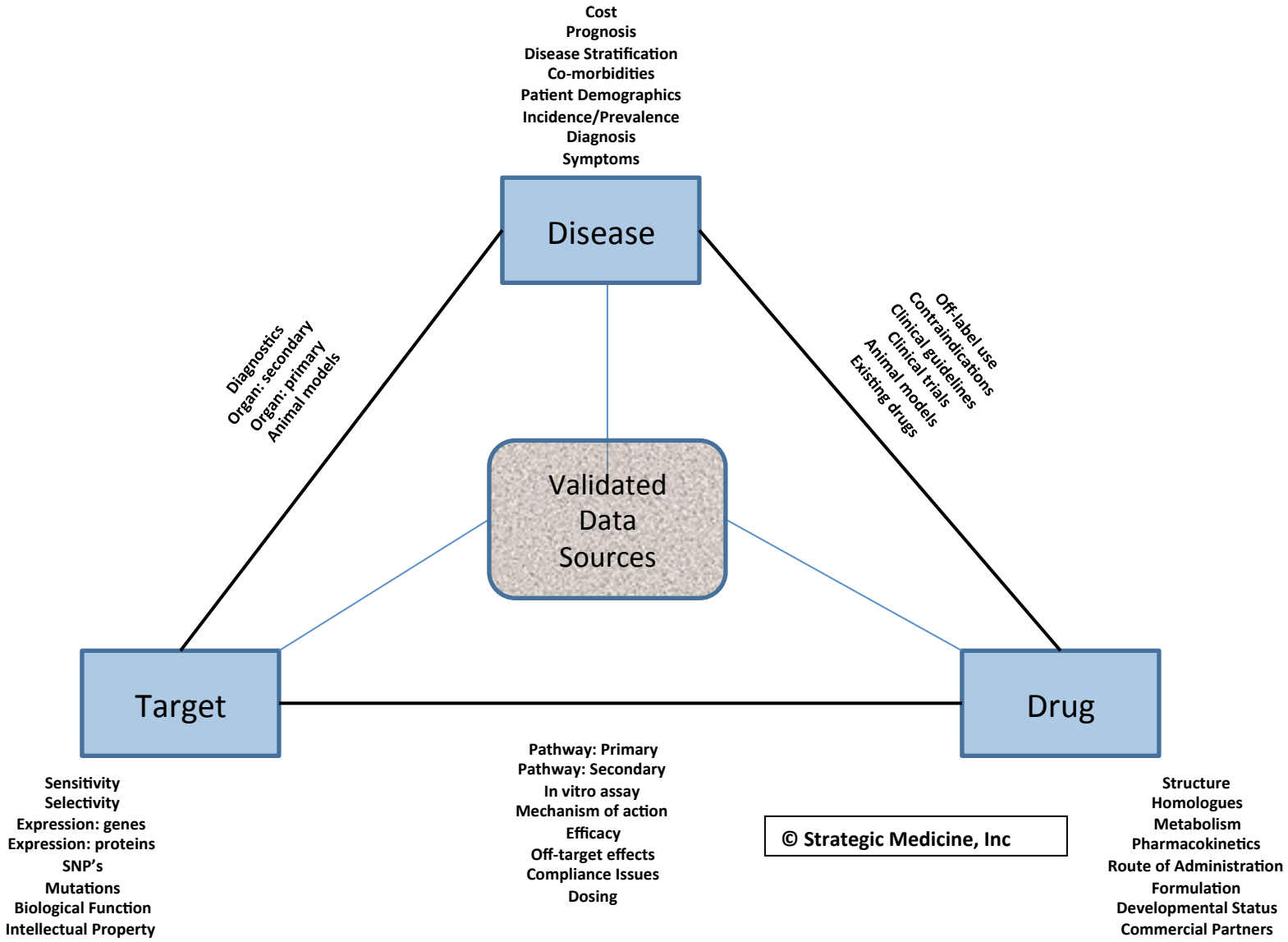
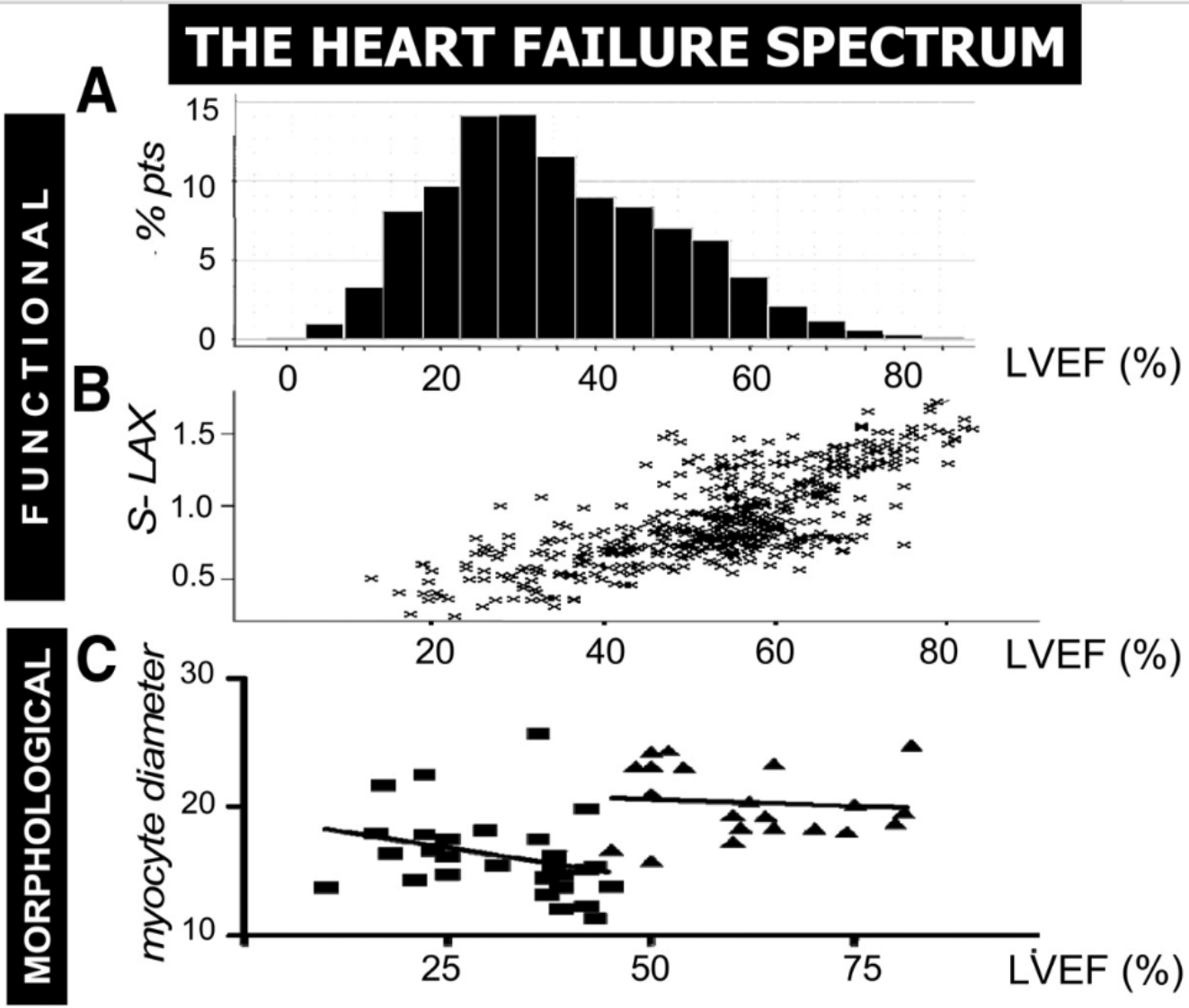
Kennett Square, PA


Cost
Prognosis
Disease Stratification
Co-morbidities
Patient Demographics
Incidence/Prevalence
Diagnosis
Symptoms
Disease
Diagnostics
Organ: secondary
Organ: primary
Animal models
Off-label use
Contraindications
Clinical guidelines
Clinical trials
Animal models
Existing drugs
Validated Data Sources
Target
Drug
Sensitivity
Selectivity
Expression: genes
Expression: proteins
SNP's
Mutations
Biological Function
Intellectual Property
Pathway: Primary
Pathway: Secondary
In vitro assay
Mechanism of action
Efficacy
Off-target effects
Compliance Issues
Dosing
© Strategic Medicine, Inc
Structure
Homologues
Metabolism
Pharmacokinetics
Route of Administration
Formulation
Developmental Status
Commercial Partners

Heart Failure

- Diagnostic Guidelines
  - Preserved vs Reduced Ejection Fraction
- Compound variables
- Functional diagnostics



The Heart Failure Spectrum: Time for a Phenotype-Oriented Approach
Gilles W. De Keulenaer and Dirk L. Brutsaert Circulation. 2009;119:3044-3046

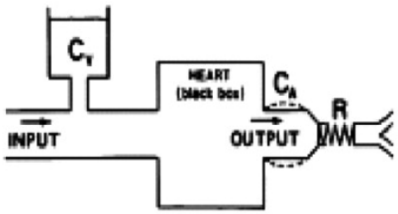
E_f is a compound variable!

E_f(%)= (1.00 – ESV/EDV) x 100

A patient who is 40/80 is not the same as one 75/150!!!

CONCEPTUAL - PHYSIOLOGICAL APPROACHES TO CARDIAC FUNCTION

A
HYDRODYNAMIC INPUT–OUTPUT SYSTEM



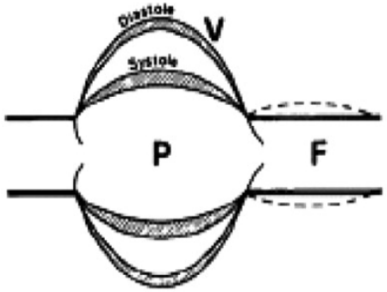
Cardiac output

Stroke volume

Peripheral resistence

Arterial pressure

B
HEMODYNAMIC COMPRESSION PUMP



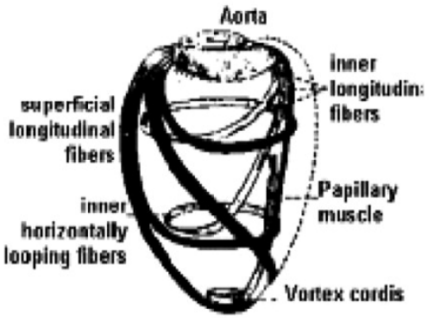
EJECTION FRACTION

Elastance (Emax)

Pressure-volume curve

Dp/dtmax

C
MUSCULAR PUMP



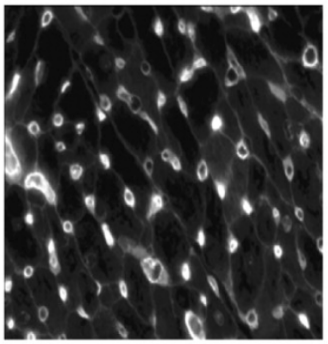
Contractility
Load dependent relaxation

Force-frequency

LV twisting/torsion,
LV untwisting and suction

Myocardial strain/strain rate

D
PLURI-CELLULAR TISSUE PUMP



Brain natriuretic peptide

Endothelin-1, nitric oxide, Neuregulin-1

Cytokines

The Heart Failure Spectrum: Time for a Phenotype-Oriented Approach
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Deconvolution of Echocardiogram

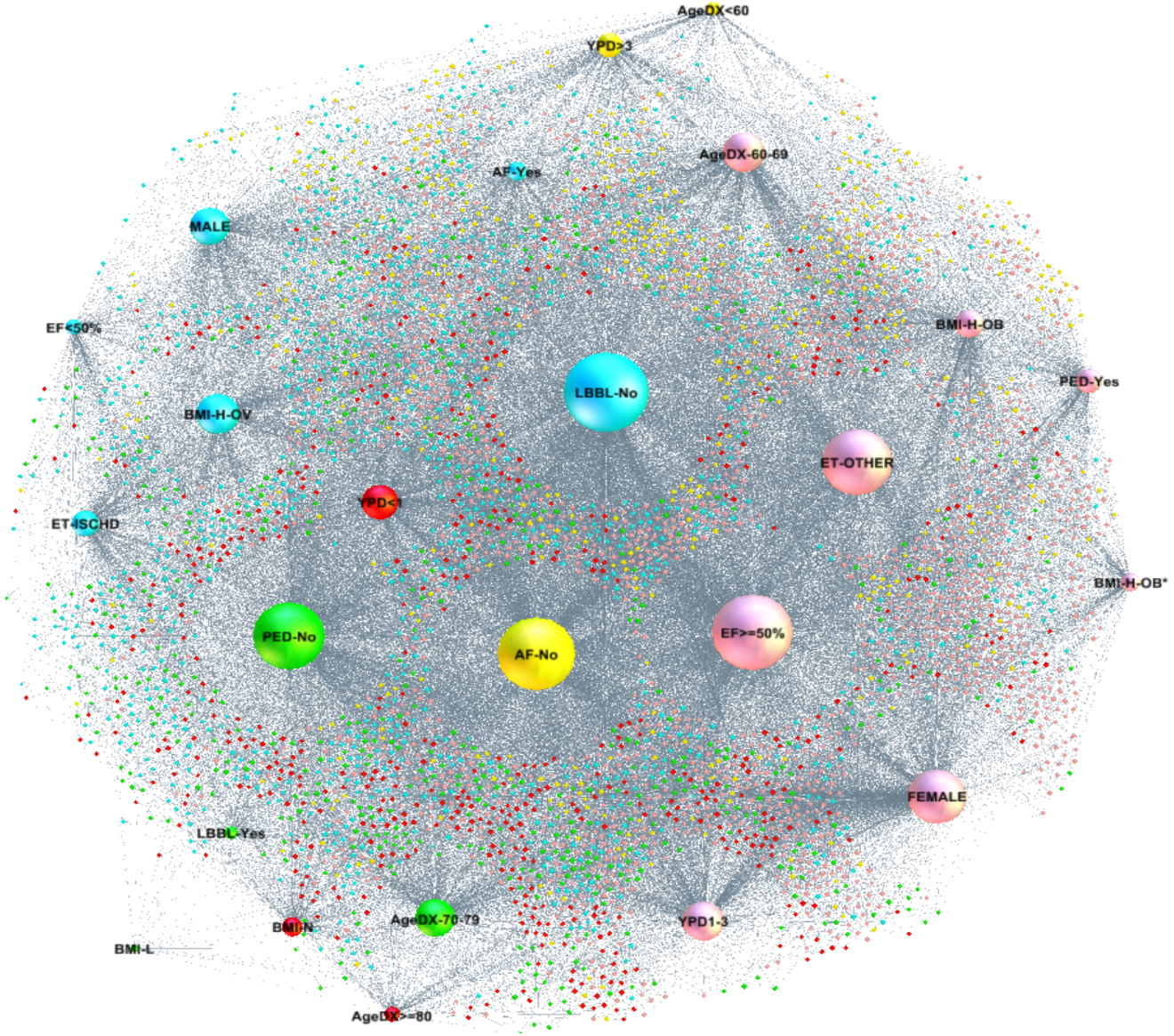
Functional domain	Variables
1) Left heart Structure	LV end-diastolic volume
	LV end-systolic volume
	LV end-diastolic dimension
	LV end-systolic dimension
	Septal wall thickness
	Posterior wall thickness
	LV mass
	Left atrial volume
	Left atrial volume
2) LV Systolic Function	LV ejection fraction
	Tissue Doppler velocity lateral
	Tissue Doppler velocity septal
3) LV diastolic function	Mitral inflow characteristics:
	E velocity
	A velocity
	E/A ratio
	E deceleration time
	IVRT
	Tissue Doppler characteristics:
	septal e' velocity
	lateral e' velocity
	septal a' velocity
	lateral a' velocity
	septal E/e' ratio
	lateral E/e' ratio
4) Hemodynamics	Stroke volume
	Cardiac output
	PA systolic pressure

IPQ Approach

- Strategy:
  - **Partition into clinical domains, e.g. history, demographics, panels, e.g. blood, liver, kidney, spleen**
  - Not necessarily mutually exclusive assignments
  - Analyze SNA's within domains using "normal population" data
  - Construct disease model and evaluate against literature
- Goal
  - **Results of analysis to be easily considered/adapted in current clinical practice and extend utility**

Standard Clinical Panels

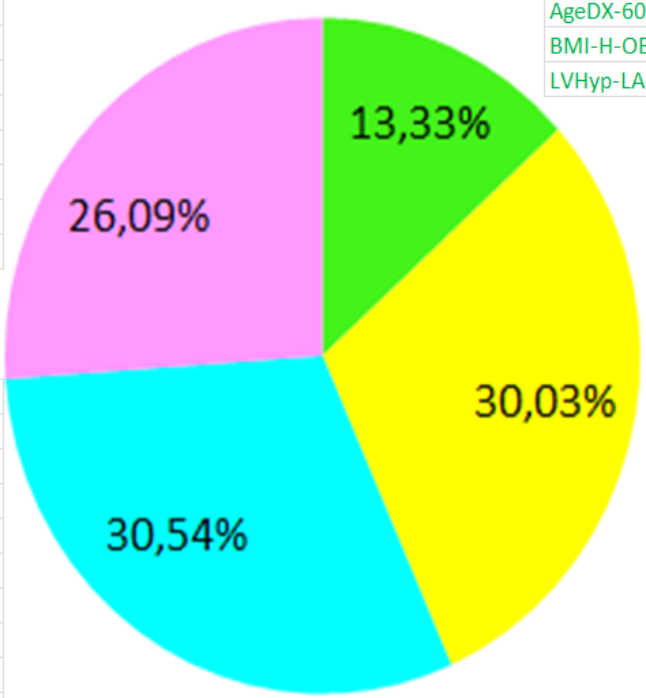
Blood	Liver	Kidney	Spleen
Age	Age	Age	Age
Gender	Gender	Gender	Gender
EOS - Eosinophils	ALB - Albumine	ALB - Albumine	ALT - Alanine Aminitransferase (or SGPT)
HCT – hematocrit	ALP - Alkaline phosphatase	ALP - Alkaline phosphatase	BILI - Total Bilirubin
HGB - Hemoglobin	ALT - Alanine Aminitransferase (or SGPT)	BICARB - Bicarbonate	HCT - hematocrit
LYM - lymphocytes	AST - Aspartate Aminotransferase (or GOT)	CL - Chloride	HGB - Hemoglobin
MONO - monocytes	BILI - Total Bilirubin	CREAT - Creatinine	PLAT - Platelets
PLAT - Platelets	GGT - Gamma glutamyl Transferase	PH	RBC - Red blood cell or Erythrocytes
RBC - Red blood cell or Erythrocytes	GLUC - Glucose	K - Potassium	SPLEENLEN - Numeric spleen length
NEUT - Neuthrophils		SODIUM	
		URATE	


AgeDX<60
YPD>3
AgeDX-60-69
AF-Yes
MALE
EF<50%
BMI-H-OB
PED-Yes
LBBL-No
BMI-H-OV
ET-OTHER
YPD<1
ET-SCHD
BMI-H-OB*
PED-No
AF-No
EF>=50%
FEMALE
LBBL-Yes
AgeDX-70-79
YPD1-3
BMI-N
BMI-L
AgeDX>=80

DM2 Communities distribution

PINK Community characteristics
COPD-No
LVHyp-LAEnl-Yes
FEMALE
DIAB-Yes
YPD>3
BMI-H-OB*
AgeDX<60
NYHA-Class4

GREEN Community characteristics
JVD-Abs
AgeDX-60-69
BMI-H-OB
LVHyp-LAEnl-No



YELLOW Community characteristics
NYHA-Class3
HF-Hosp6MM-No
BMI-H-OV
YPD1-3
AgeDX-70-79
LUN-OTHER
ATR-Yes
COPD-Yes
JVD-Pres

CYAN Community characteristics
DIAB-No
ATR-No
LUN-Clear
HF-Hosp6MM-Yes
MALE
YPD<1
NYHA-Class2
BMI-N
AgeDX>=80
BMI-L

COPD
Chronic Obstructive Pulmonary Disease

Diagnostic Guidelines
Asthma-COPD Overlap
Systems Biology
Disease Etiology

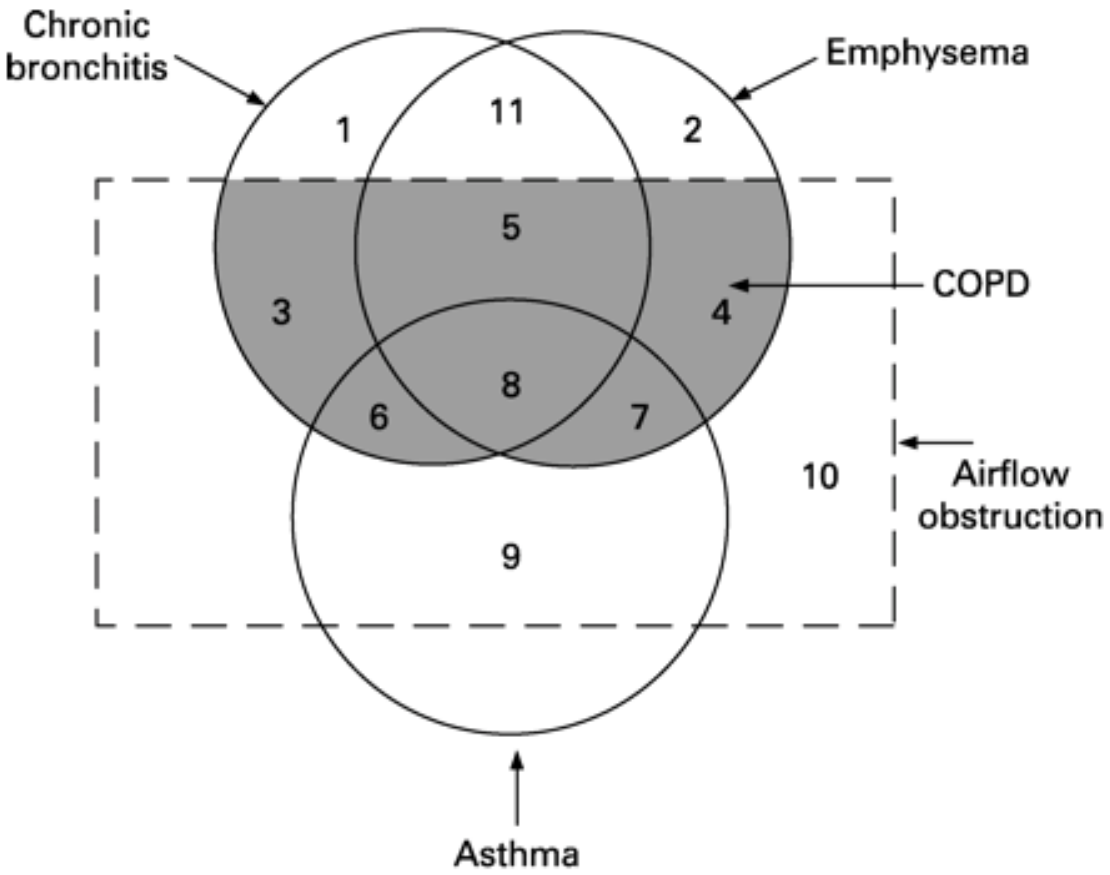
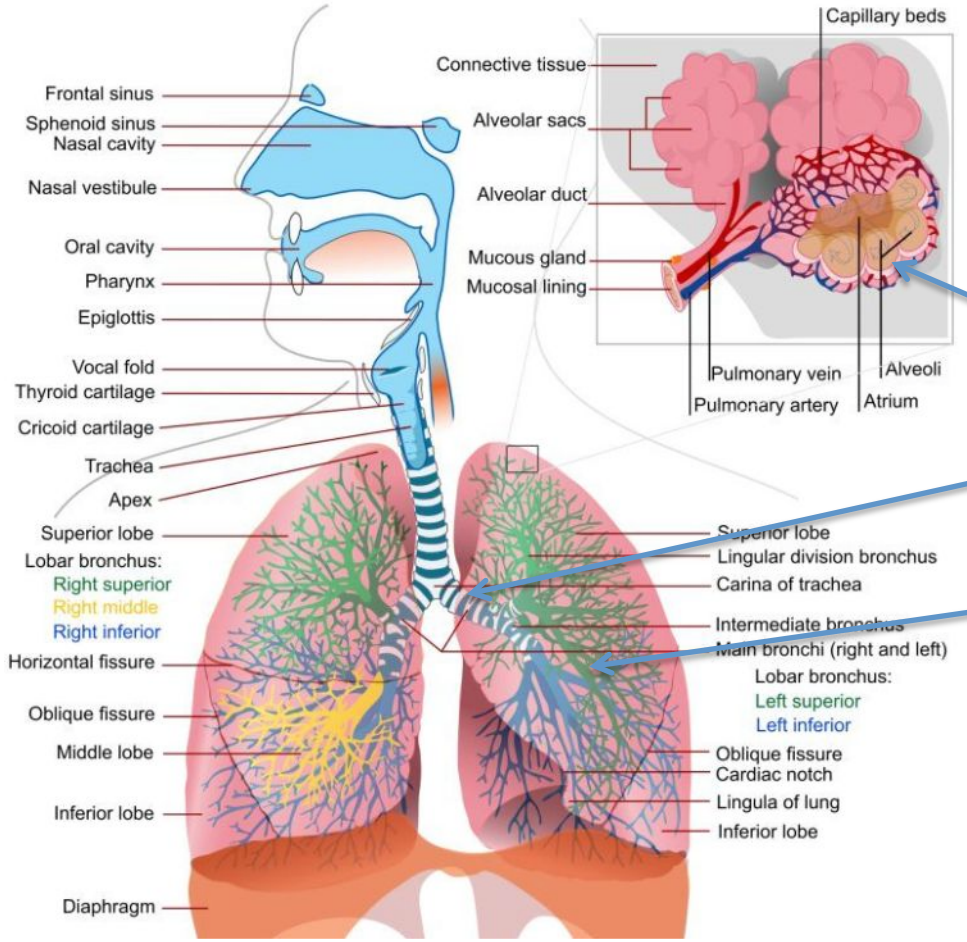


Figure 1

Non-proportional Venn diagram of chronic obstructive pulmonary disease (COPD) produced by the American Thoracic Society.4 The subsets comprising COPD are shaded. Subset areas are not proportional to the actual relative subset sizes. Asthma is by definition associated with reversible airflow obstruction although, in variant asthma, special manoeuvres may be necessary to make the obstruction evident. Patients with asthma whose airflow obstruction is completely reversible (subset 9) are not considered to have COPD. Because in many cases it is virtually impossible to differentiate patients with asthma whose airflow obstruction does not remit completely from persons with chronic bronchitis and emphysema who have partially reversible airflow obstruction with airway hyperreactivity, patients with unremitting asthma are classified as having COPD (subsets 6, 7 and 8). Chronic bronchitis and emphysema with airflow obstruction usually occur together (subset 5), and some patients may have asthma associated with these two disorders (subset 8). Individuals with asthma who have been exposed to chronic irritation, as from cigarette smoke, may develop chronic productive cough, which is a feature of chronic bronchitis (subset 6). Persons with chronic bronchitis and/or emphysema without airflow obstruction (subsets 1, 2 and 11) are not classified as having COPD. Patients with airway obstruction due to diseases with known aetiology or specific pathology such as cystic fibrosis or obliterative bronchiolitis (subset 10) are not included in this definition.

COPD Disease Indications



The main picture shows the majority of the respiratory system while the inset show detail of the alveoli.

Color coding enables the student to see divisions more clearly. The upper blue portion consists of the nose and nasal cavity, the pharynx, the larynx, and the trachea. The green branches of the lungs indicate the left and right superior bronchial lobes whereas the yellow and blue correspond to the middle and inferior bronchial lobes.

Emphysema

Chronic Bronchitis

Asthma (non-reversible)

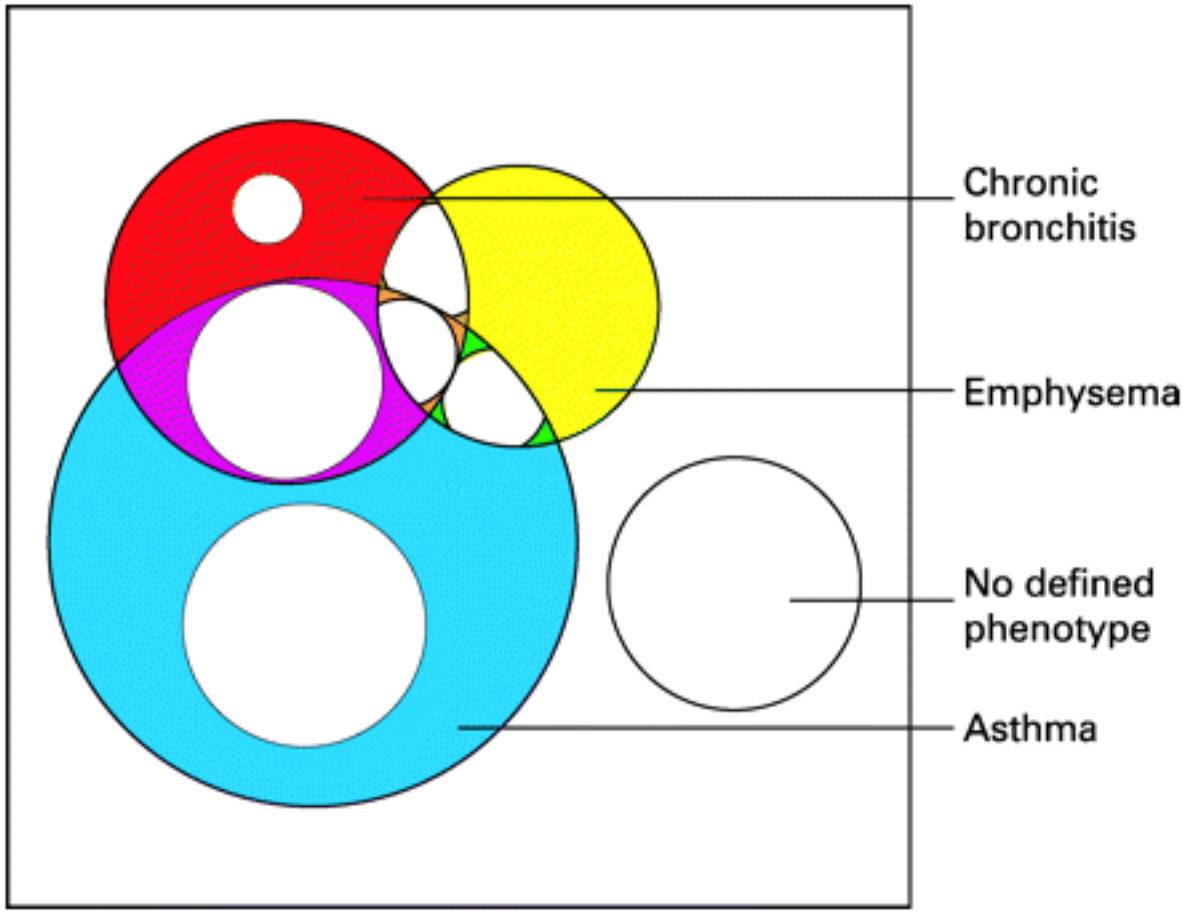
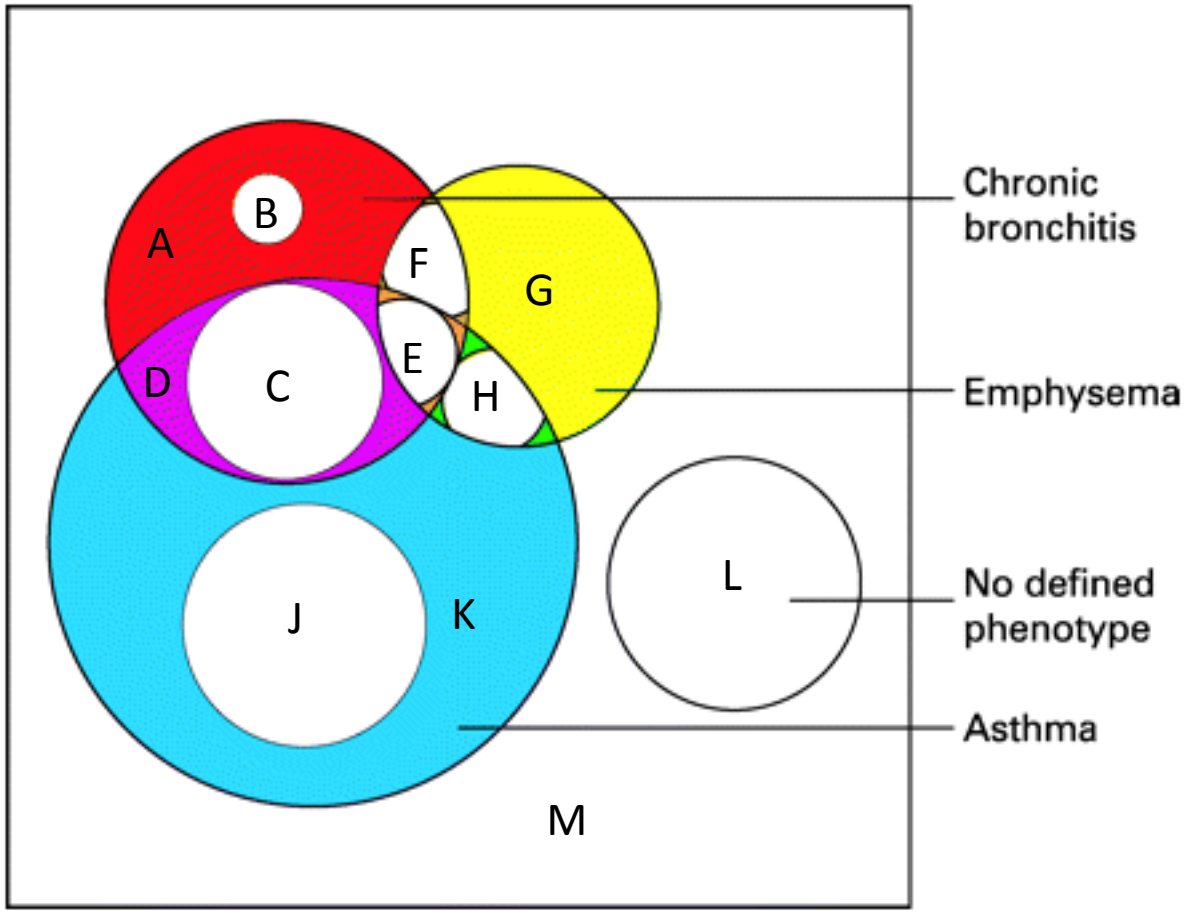


Figure 3

Proportional Venn diagram presenting the different phenotypes within the Wellington Respiratory Survey study population. The large black rectangle represents the full study group. The clear circles within each coloured area represent the proportion of subjects with COPD (post-bronchodilator forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) <0.7). The isolated clear circle represents subjects with COPD who did not have an additional defined phenotype of asthma, chronic bronchitis or emphysema.



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COPD co-morbidities (ATS designations vs Observed)

Patient	Chronic Bronchitis	Emphysema	Asthma	COPD	ATS designation	Wellington Survey
a	X			X	3	B
b		X		X	4	
c			X	X		J
d	X	X		X	5	F
e	X		X	X	6	C
f		X	X	X	7	H
g	X	X	X	X	8	E
h				X		L
i					10	M
j	X				1	A
k		X			2	G
l			X		9	K
m	X	X			11	
n	X		X			D
o		X	X			
p	X	X	X			

Table 1. Comparison of ATS Designations vs Wellington Survey Results (blue is discordance, red is non-observed and non-designated)

“All Complex Problems have a Simple Solution, that is Wrong”

A. Szent-Gyorgi

Nobel Prize in Medicine (1937)

Conclusions

- Drug development needs to look beyond clinical trials
  - Real World Physicians do not practice as they do in clinical trials, i.e. they do not follow guidelines
  - Real World Patients present complexities:
    co-morbidities, poly-pharmacy, environment/lifestyle
- Significant weaknesses need to be considered
  - Accuracy of the diagnosis; specificity of diagnostics
  - Limited understanding of actual disease processes and etiology
  - Inadequacy of patient data (EHR's): contents vs interoperability!!
  - Inadequacy of clinical practice guidelines
- Improvements in drug development require accepting these limitations and applying systematic, unbiased approaches to identify and quantify their potential impact

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