



*Understanding the
Development and
Progression of Disease.*

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Overview

- ❖ **Clinical Breast Care Project (CBCP)**
- ❖ **Windber Research Institute**
- ❖ **Data, Information and Knowledge**
- ❖ **Systems Biology**
- ❖ **Defining Translational Research**
- ❖ **Understanding the Question(s)**

Clinical Breast Care Project

❖ Creation of CBCP reference database

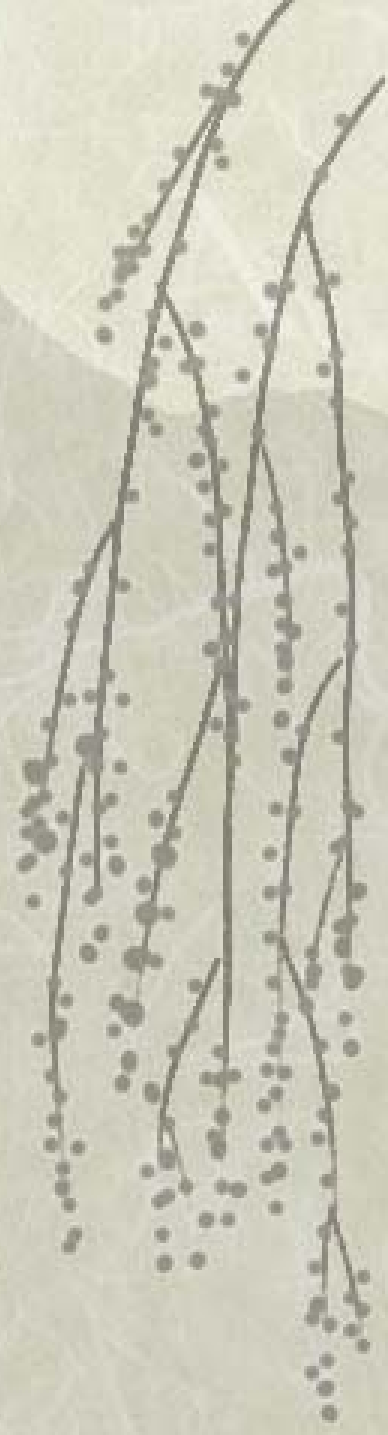
- **10,000 breast disease patients/year**
 - **Ethnic diversity; “transient**
 - **Equal access to health care for breast disease**
 - **All acquired under SINGLE PROTOCOL**
 - **All reviewed by a SINGLE PATHOLOGIST**
- **Tissue, serum, lymph nodes (>14,000 samples)**
- **patient data (500+data fields)**
- **mammograms, 4d-ultrasound, PET/CT, 3T MRI**
- **complementary genomics and proteomics, IHC**
- **Breast cancer vaccine program (her2/neu)**

Windber Research Institute

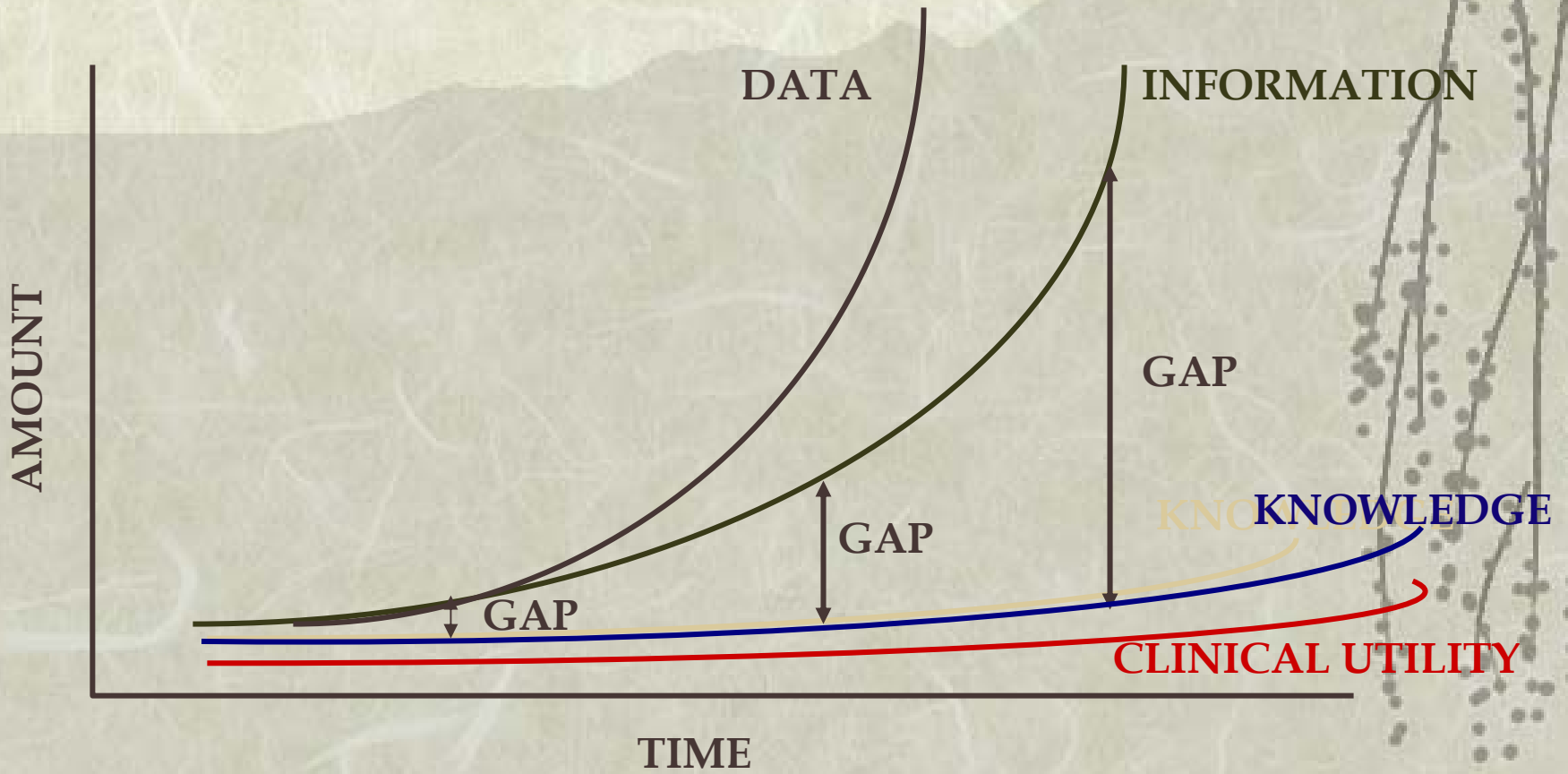
- ❖ Founded in 2001, 501(c) (3) corporation
- ❖ Genomic, proteomic and informatics collaboration with WRAMC
- ❖ 45 scientists (8 biomedical informaticians)
- ❖ 36,000 sq ft facility under construction
- ❖ Focus on Women's Health, Cardiovascular Disease, Processes of Aging

WRI's Mission

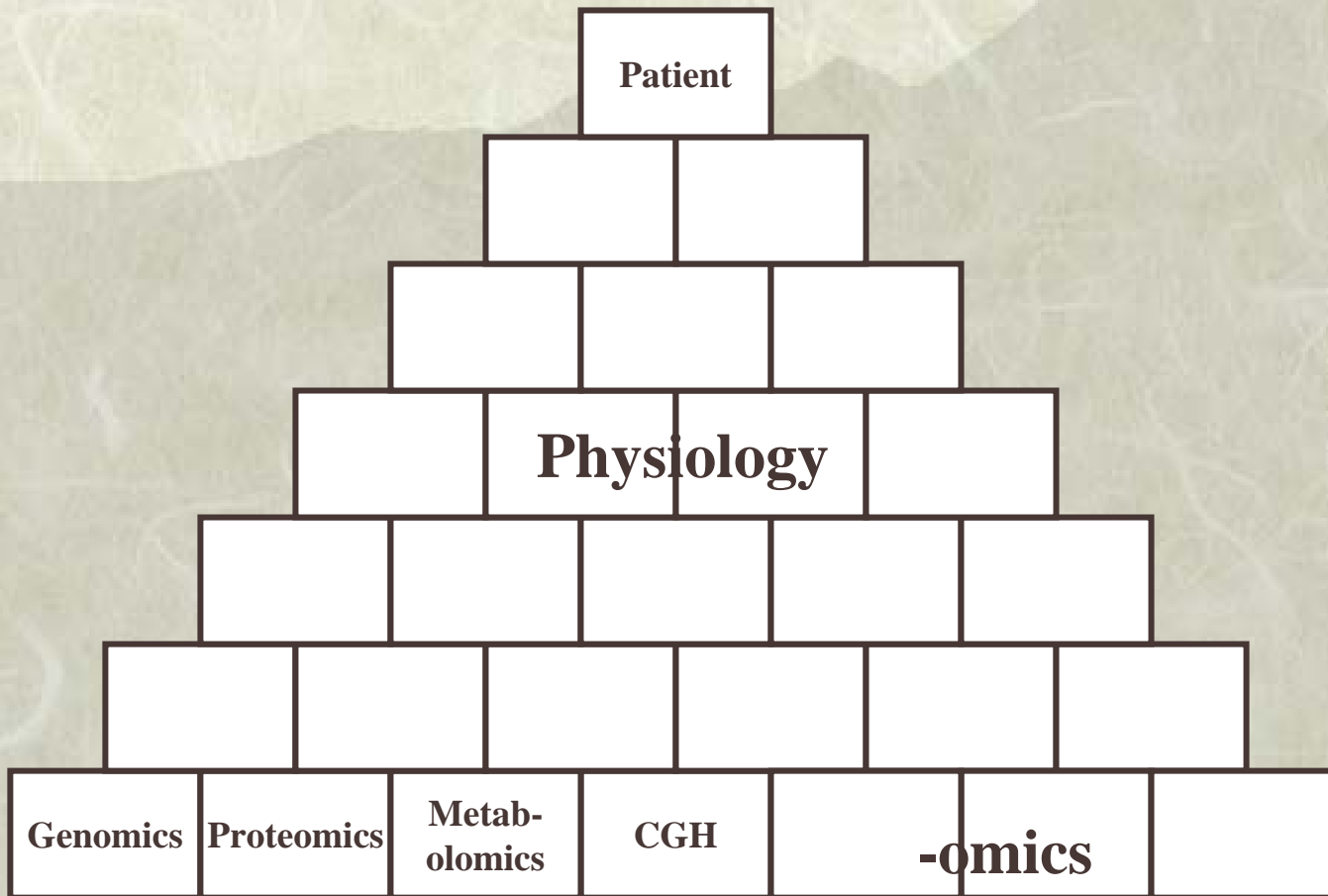
WRI intends to be a catalyst in the creation of the “next-generation” of medicine, integrating basic and clinical research with an emphasis on improving patient care and the quality of life for the patient and their family.



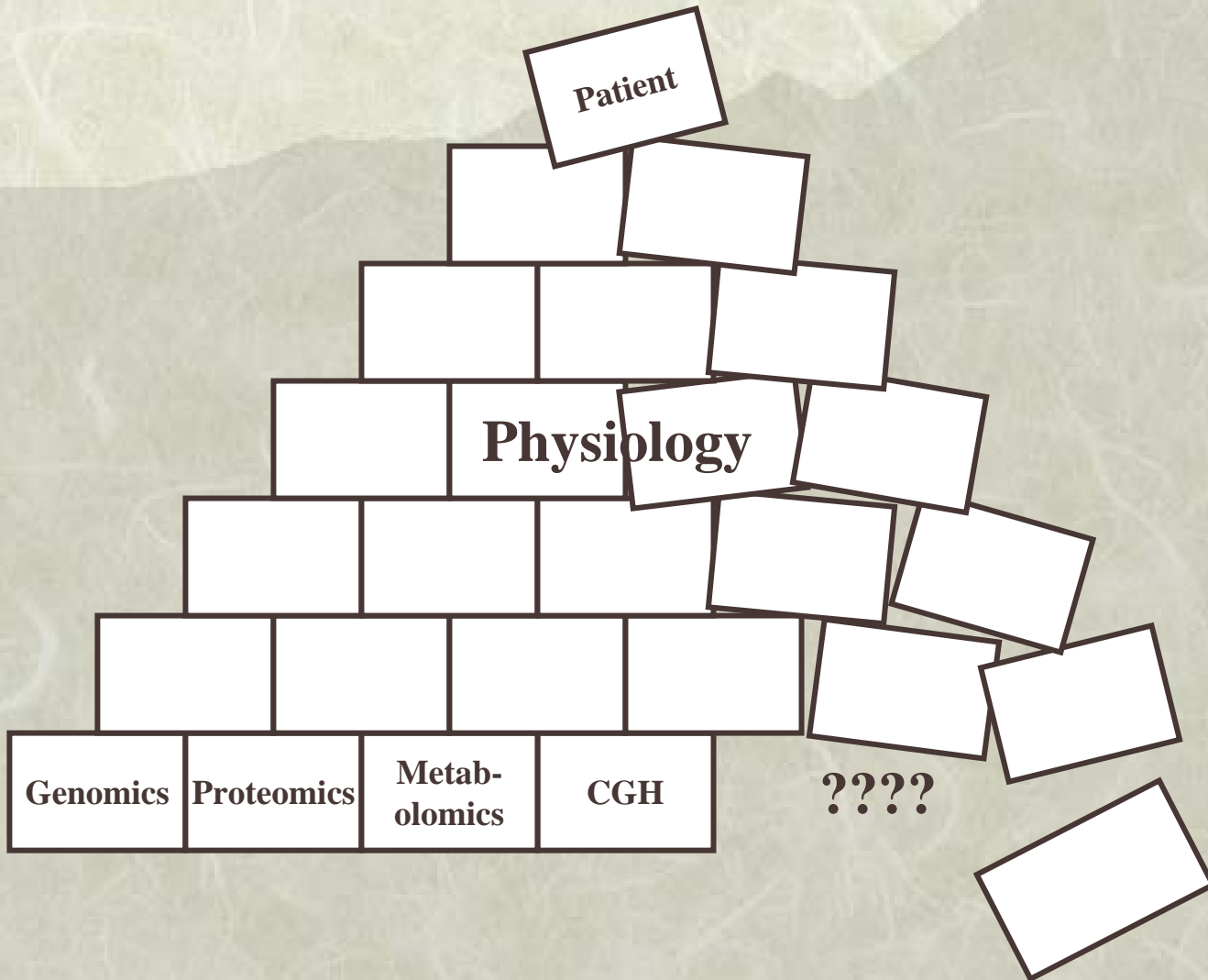
Gap



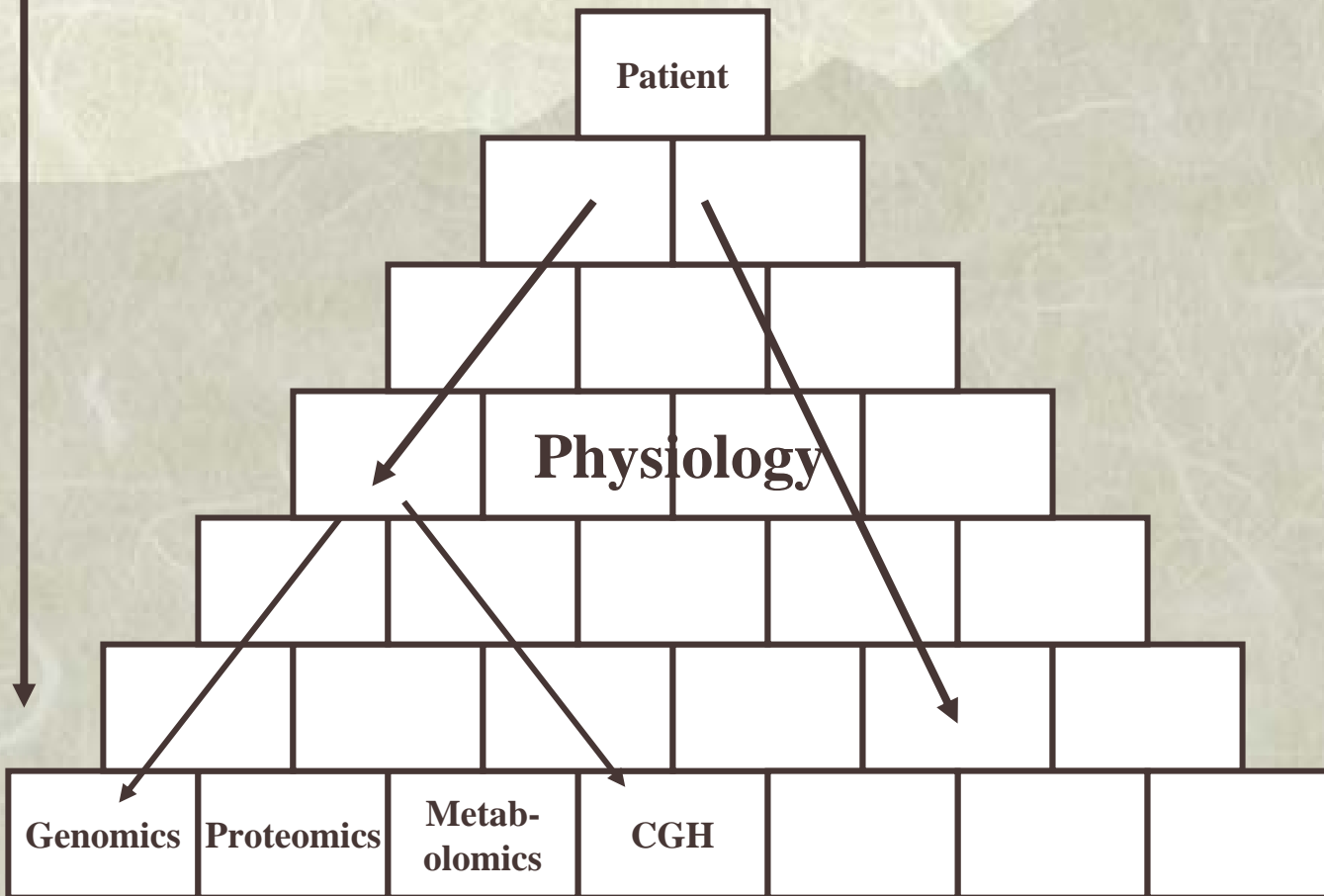
Systems Biology (Personalized Medicine)



Bottom Up Approach

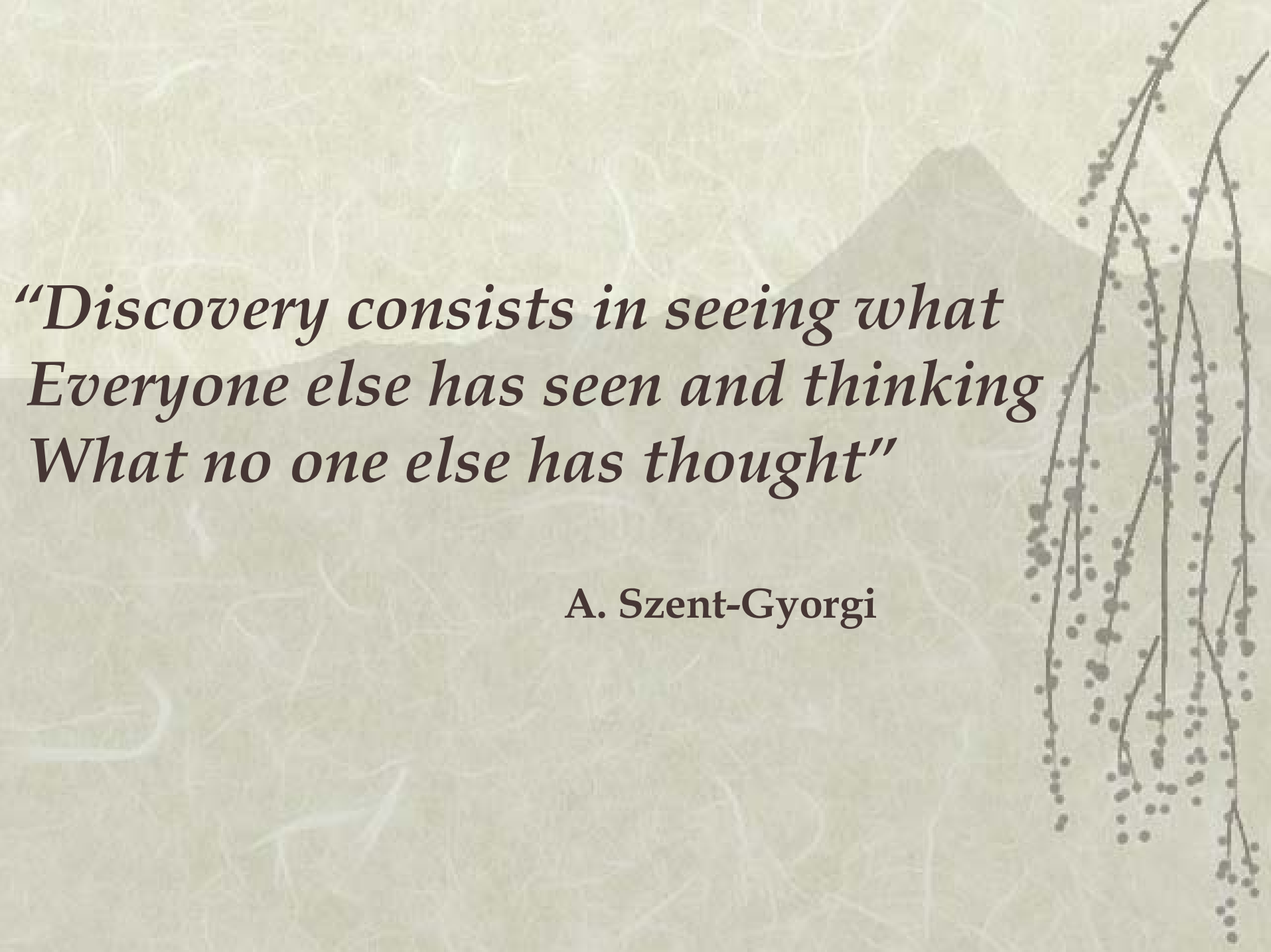


Top Down Approach (Personalized Disease)



Translational Medicine



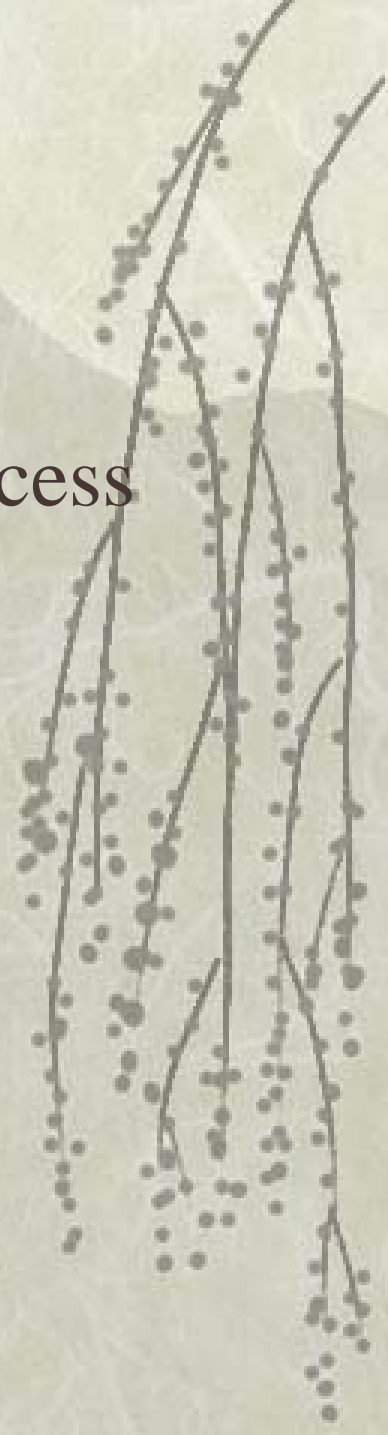
The background features a light beige, textured surface. A dark silhouette of a mountain peak is visible in the upper right quadrant. On the far right, a dark, thin branch of a willow tree hangs down, adorned with numerous small, dark, circular buds.

*“Discovery consists in seeing what
Everyone else has seen and thinking
What no one else has thought”*

A. Szent-Gyorgi

1. Modeling Disease

- ❖ Disease as a State vs Disease as a Process
- ❖ Bias of Perspective
- ❖ Temporal Perspective



Modeling Disease

{ Risk(s) }

{ Disease(s) }

Lifestyle + Environment = $F(t)$

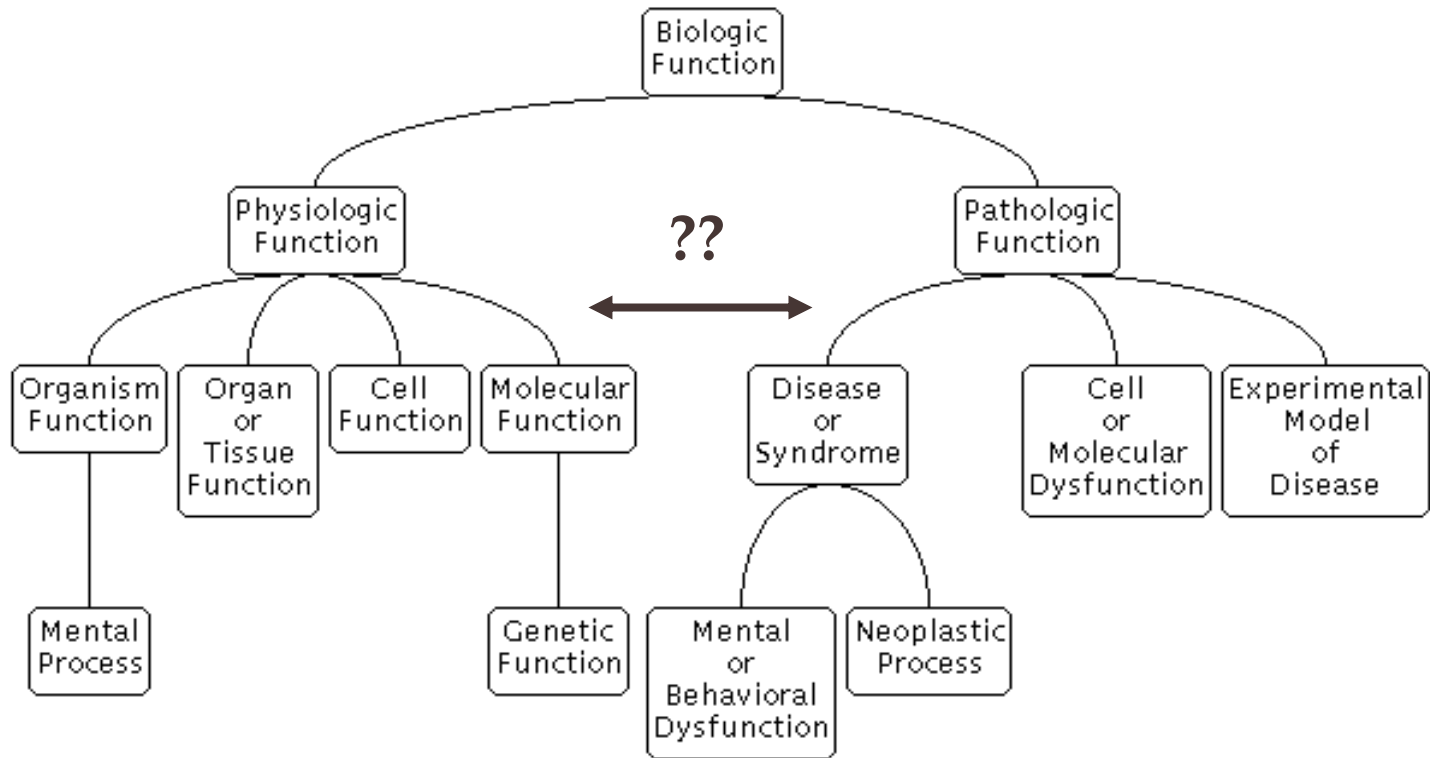
Genotype

Phenotype

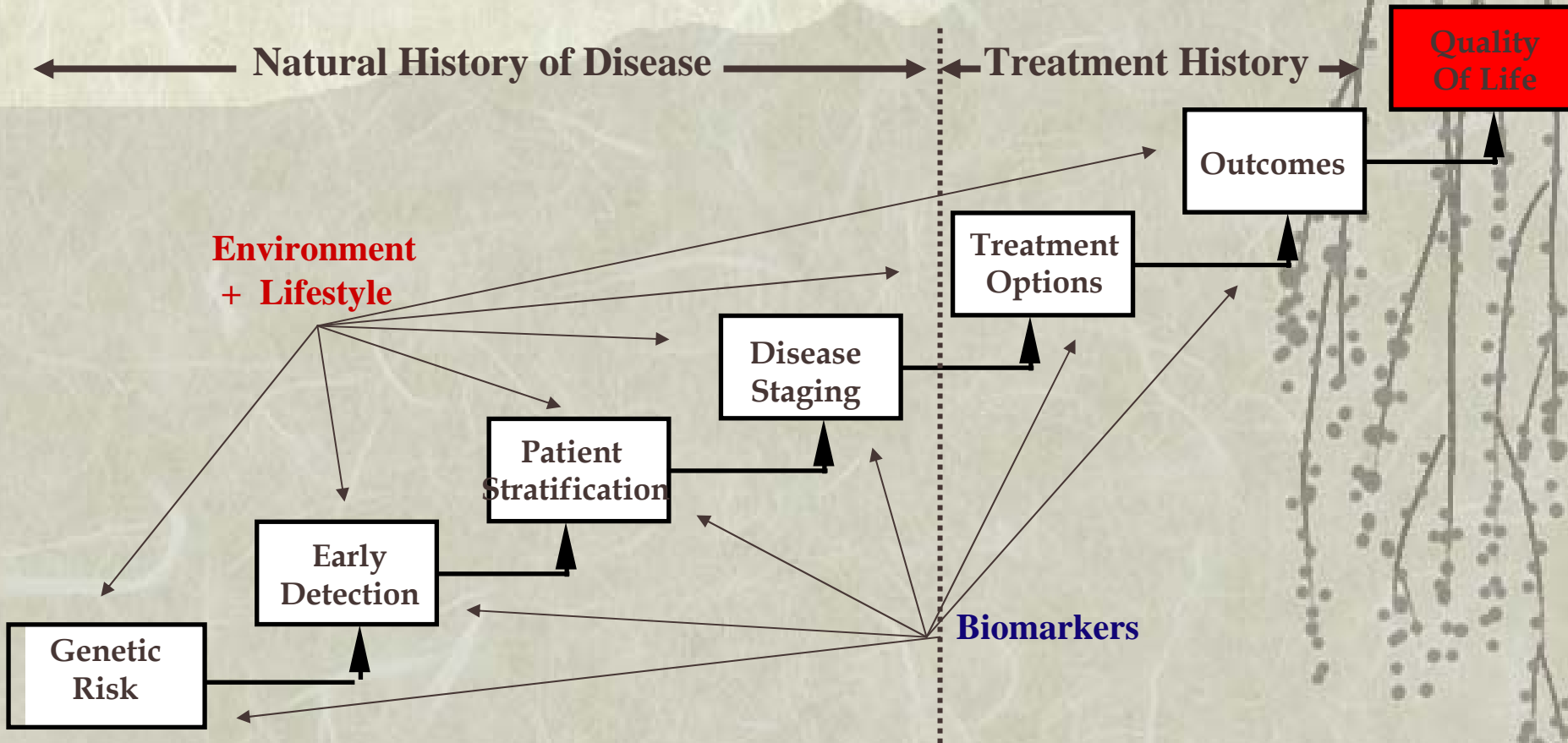
(SNP's, Expression Data)

(Clinical History and Data)

UMLS Semantic Network



Pathway of Disease



Phenotype

← **Genotype** →

Childhood Diseases

Smoking

Overweight

Menarche

Diabetes

Cardiovascular Disease

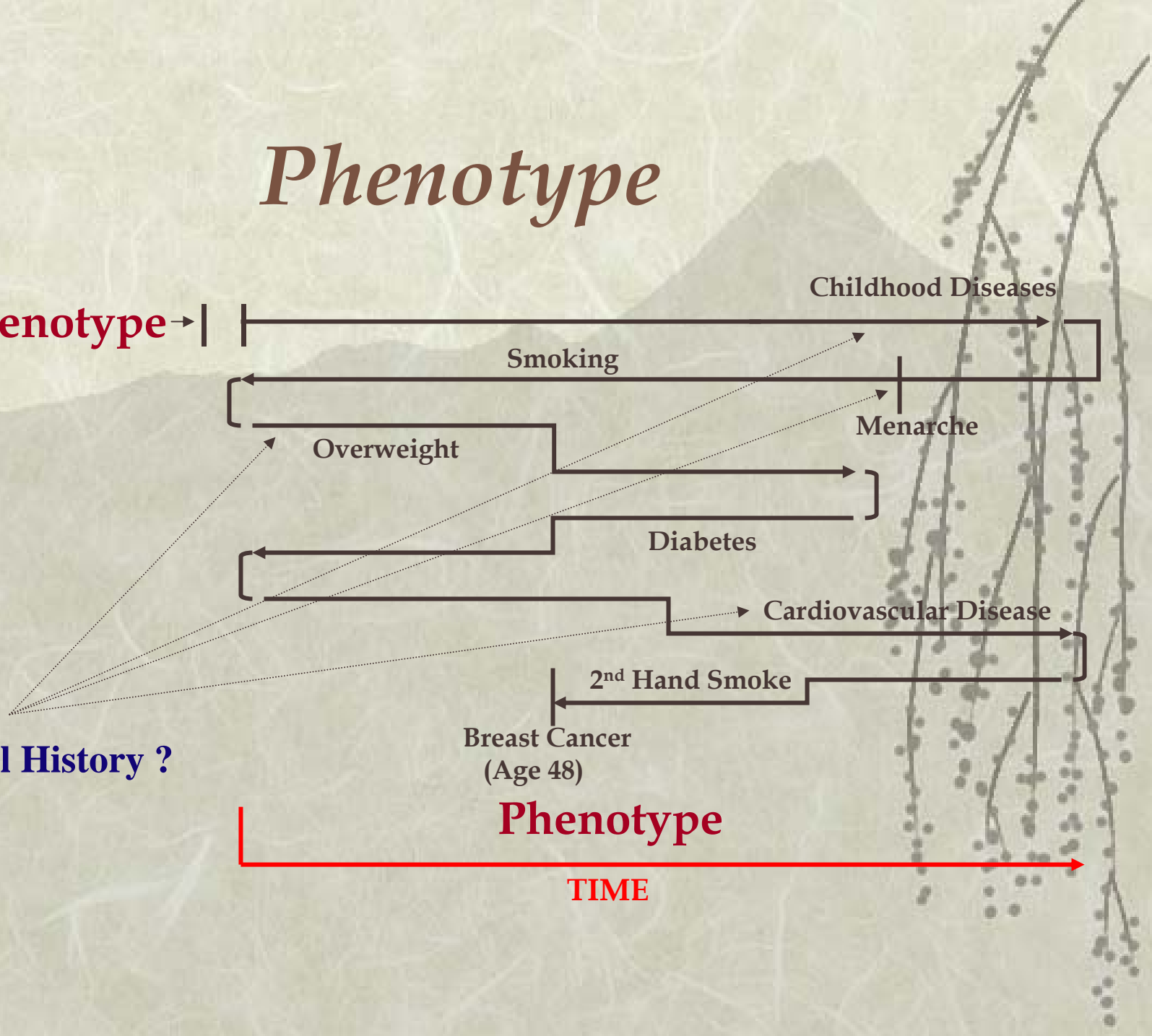
2nd Hand Smoke

Breast Cancer
(Age 48)

Natural History ?

Phenotype

TIME

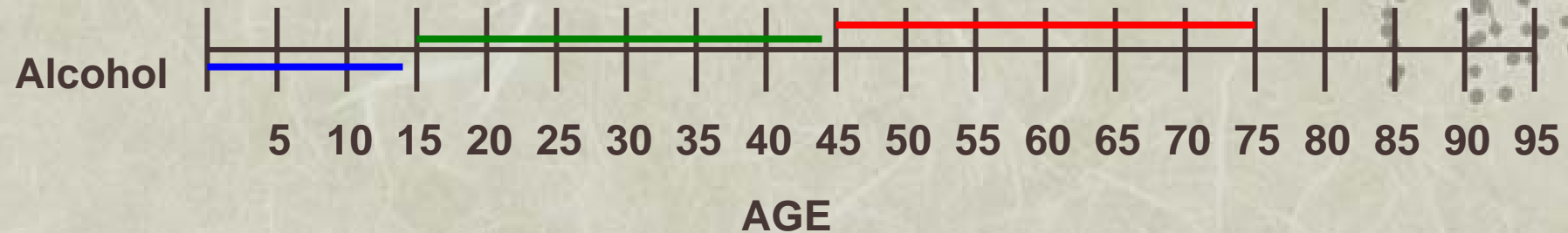
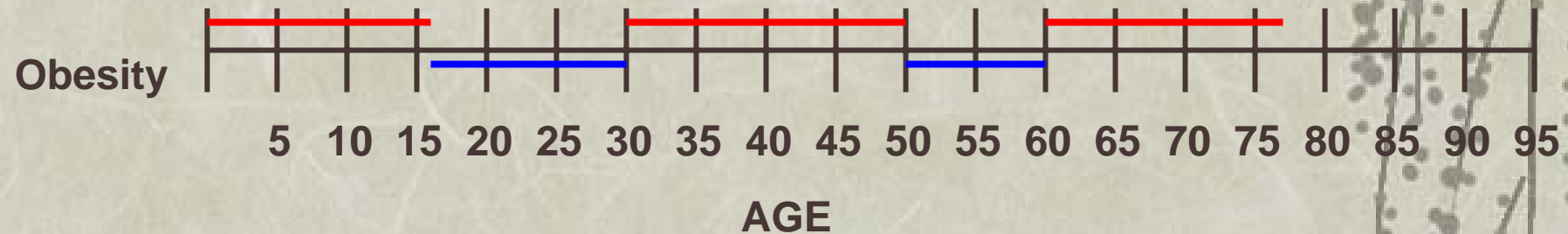
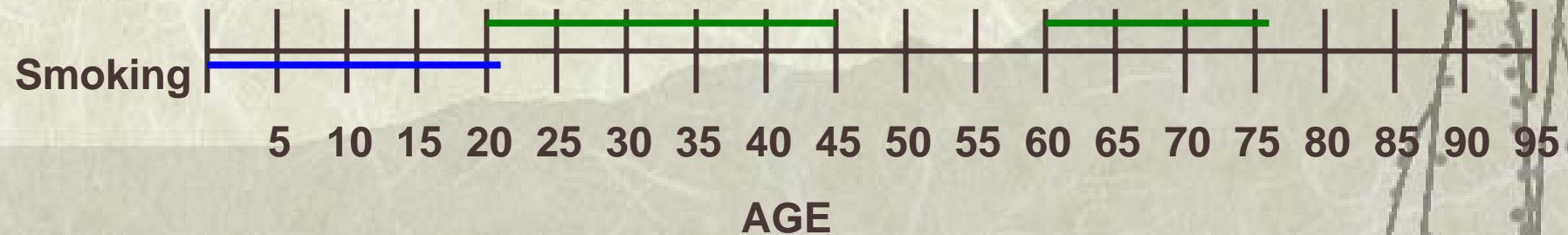


Longitudinal Interactions in Breast Cancer

- ❖ **Identify Environmental Factors**
- ❖ **Quantify Exposure**
 - When ?
 - How Long ?
 - How Much ?
- ❖ **Extract *Dosing* Model**
- ❖ **Compare with Stages of Biological Development**



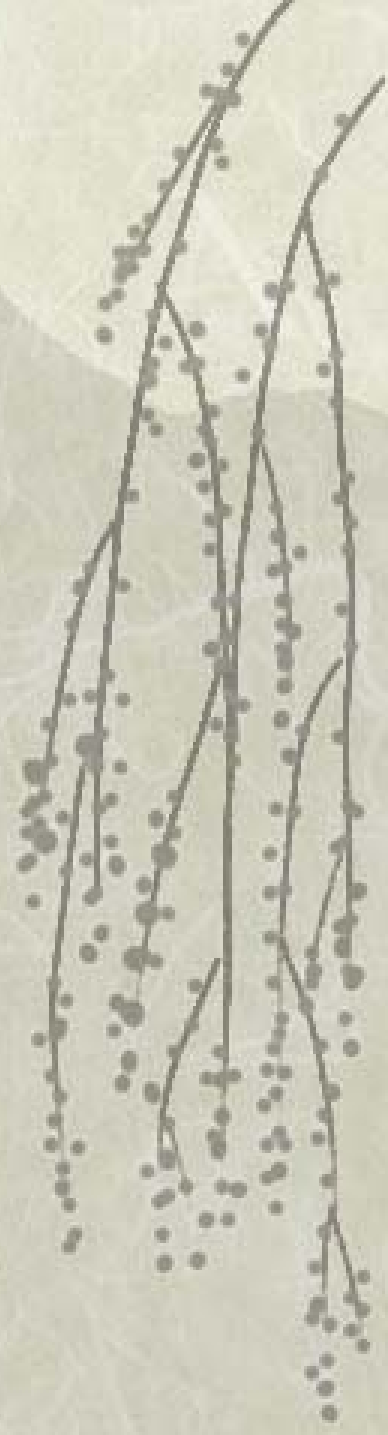
Lifestyle Factors



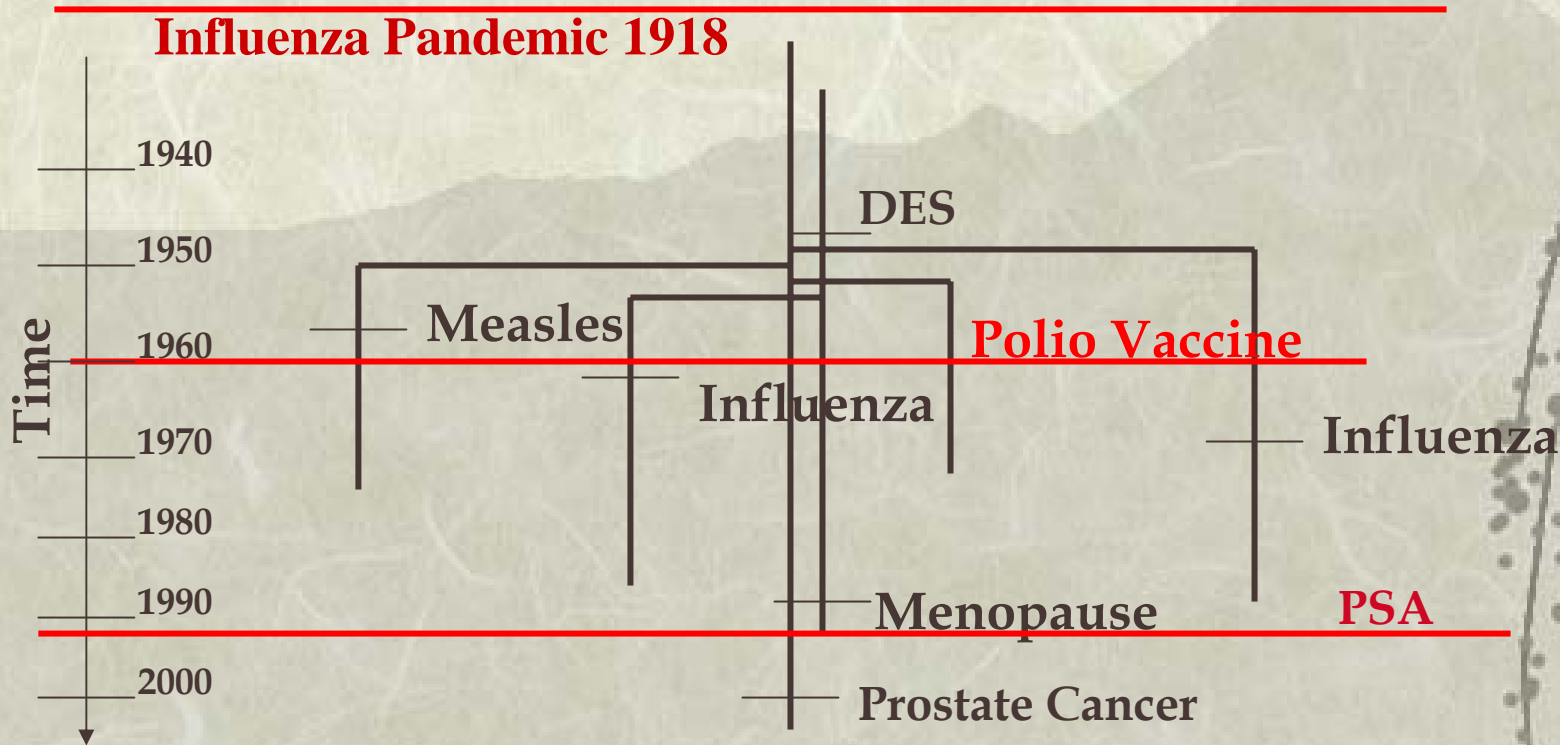
2. Genetics and Disease

❖ Genetic Pre-Disposition

- < 10 % of all breast cancers
- Not all BRCA1 and BRCA2 mutations result in breast cancer
- Modifier genes?
- Lifestyle or environmental factors?
- Pedigree Analysis

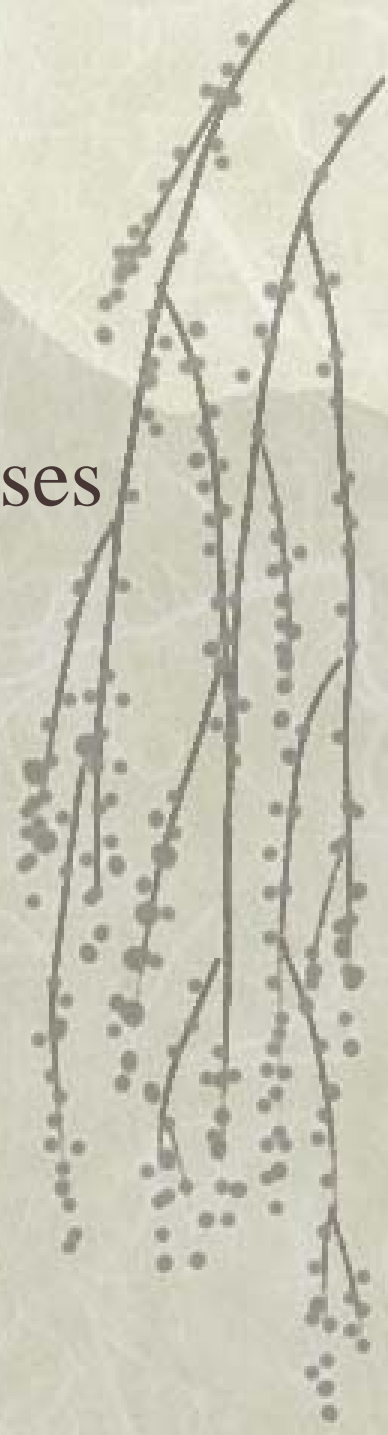


Pedigree (modified)

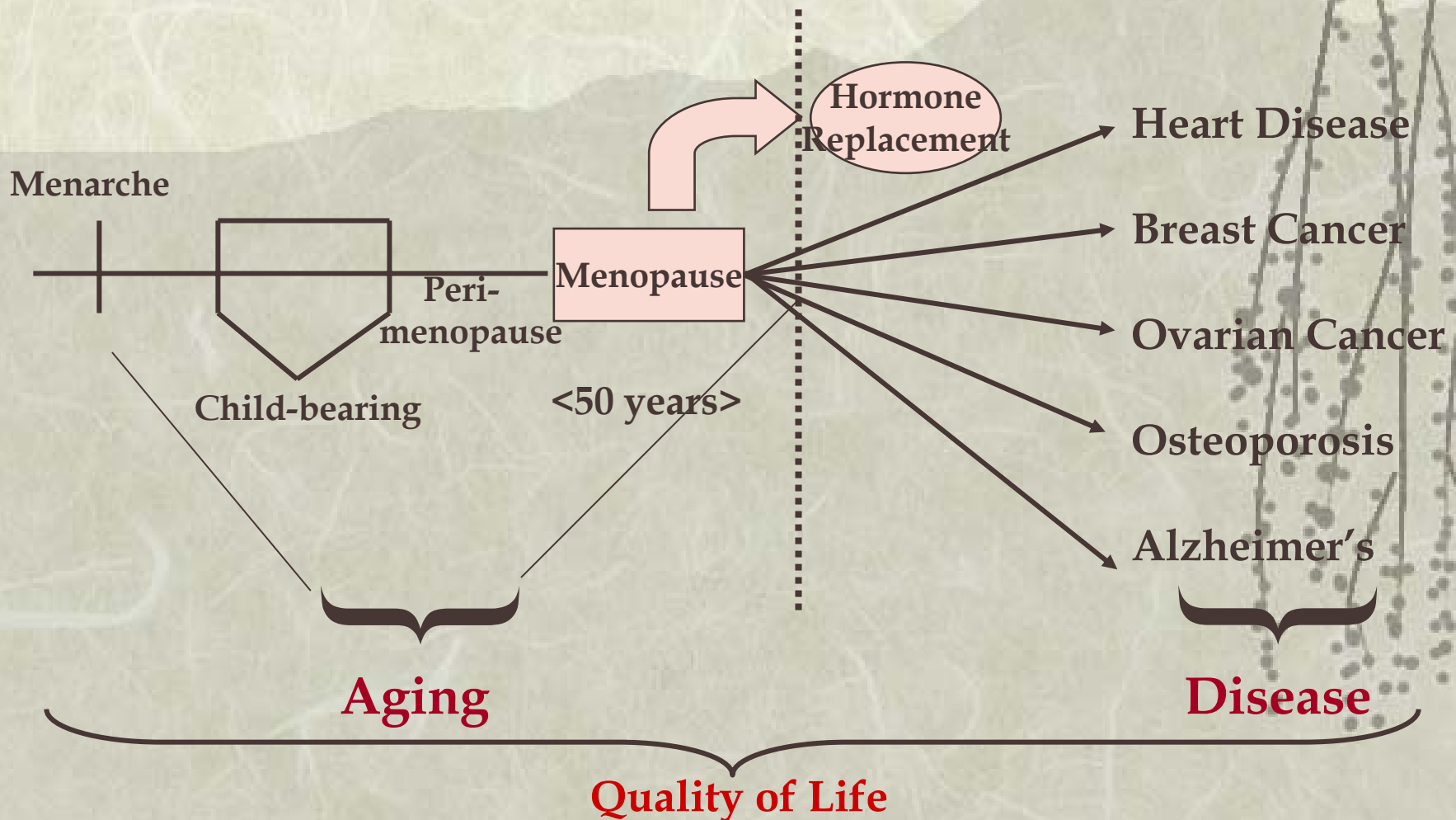


3. Aging and Disease

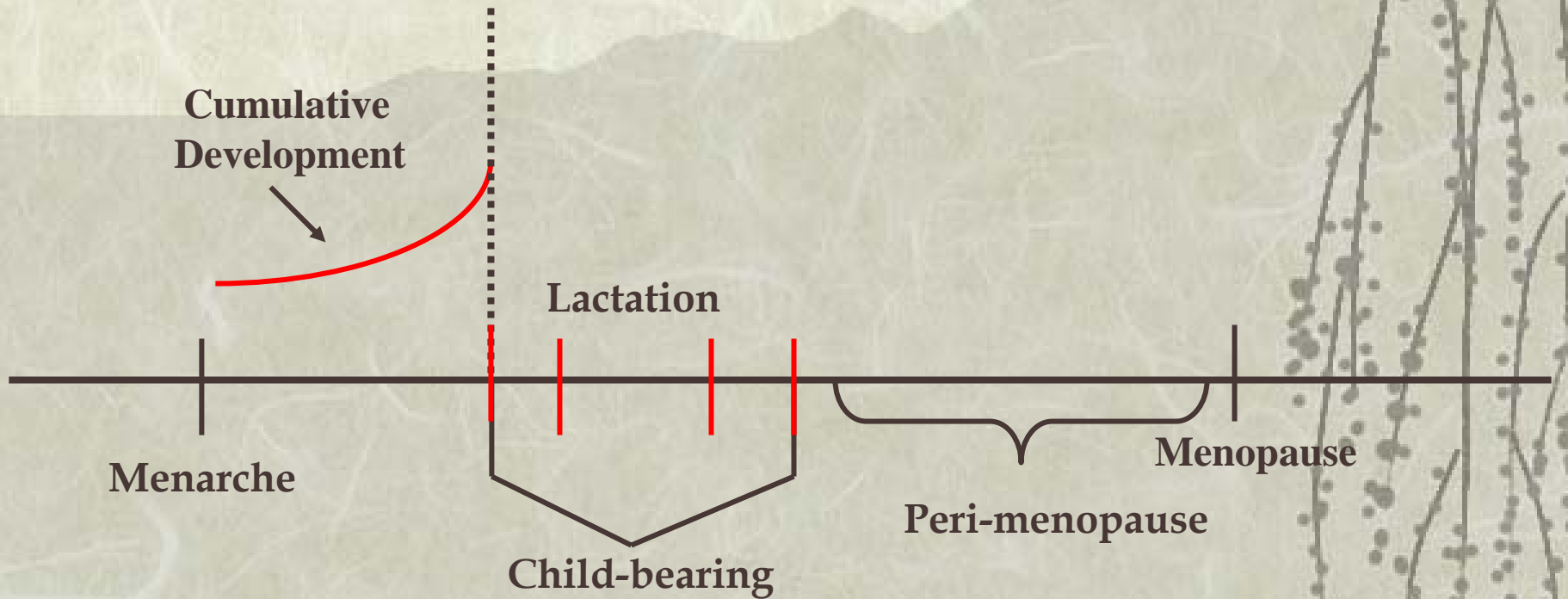
- ❖ Processes of Aging vs Disease Processes
- ❖ Ongoing Breast Development
- ❖ Same Disease : Different Host?
- ❖ Text Data-mining Approaches



Disease vs Aging



Breast Development



Ontology: Breast Development

Parous

Terminal Buds

Buds

Lobes

Ducts

Puberty

Neo-natal → Menarche → Pregnancy → Lactation → Peri-menop → Menop → Post-Menop

Buds

Lobes

Terminal Buds

Human Mouse?

NulliParous

SPSS - LexiMine and Clementine

Query Map Help

Trends Agents Admin

Keywords

breast cancer

Refine

Base LifeSciences2

Mine Search

Concepts

- breast cancer
- advanced breast cancer
- advanced breast cancer patier
- cancer of the breast
- cases of breast cancer
- causes of breast cancer
- contralateral breast cancer
- developed breast cancer
- development of breast cancer
- early breast cancer
- elderly breast cancer patients
- history of breast cancer
- human breast cancer
- international breast cancer con
- lower breast cancer risk
- management of breast cancer
- metastatic breast cancer
- national cancer institute-design
- negative breast cancer
- new breast cancer information
- operable breast cancer
- recurrent breast cancer
- recurrent breast cancer patient:
- refractory metastatic breast car

14
9
7
6

breast cancer NEAR middle age NEAR puberty

Types: Term Person Organization Product Location My Category Unknown

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Puberty:

- Two hormones – estrogen and progesterone signal the development of the glandular breast tissue.
- In female estrogen acts on mesenchymal cells to stimulate further development.
- The gland increases in size due to deposition of interlobular fat.
- The ducts extend and branch into the expanding stroma.
- The epithelial cell proliferation and basement membrane remodeling is controlled by interactions between the epithelium and the intra-lobular hormone sensitive zone of fibroblasts.
- The smallest ducts, the intra-lobular ducts, end in the epithelial buds which are the prospective secretory alveoli.
- Breast ducts begin to grow and this growth continues until menstruation begins.

→ Production of: Stroma, mesenchymal cells, epithelial cells

Reality of Disease

DNA RNA Amino Acids

Genes

Proteins

Enzymes Substrates Co-Factors

Pathways

Tissues Cells Organelles

Processes: Tissue generation; Inflammation....

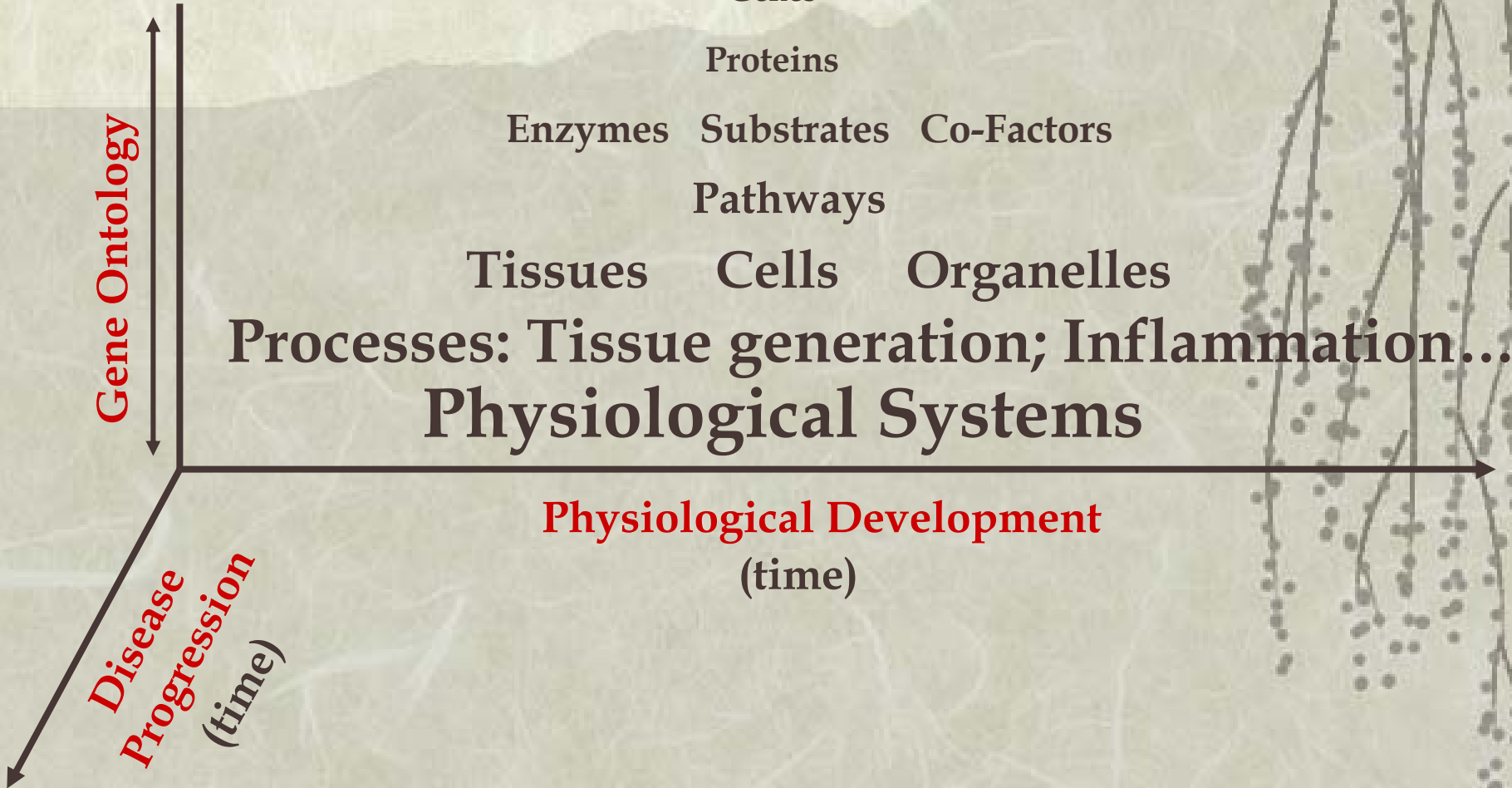
Physiological Systems

Physiological Development

(time)

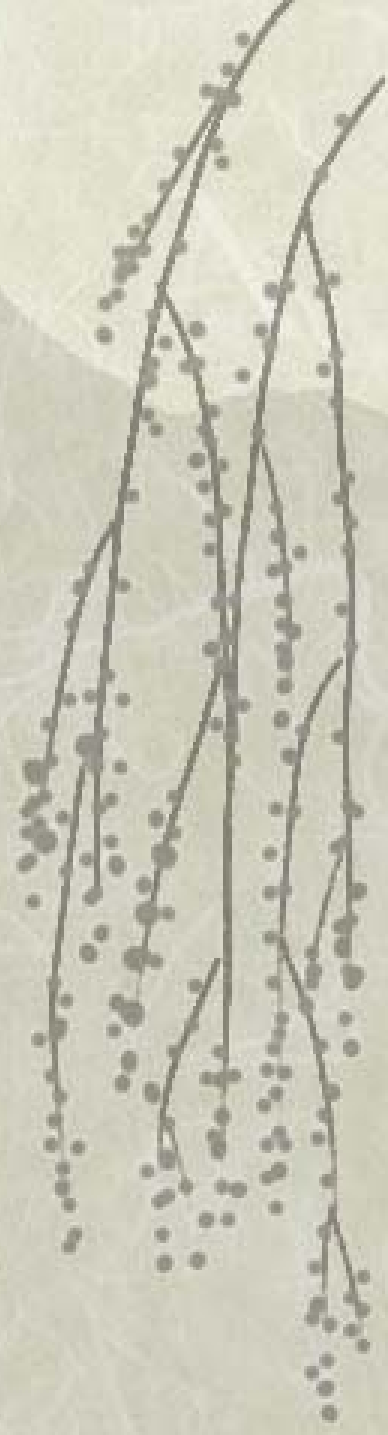
Gene Ontology

Disease
Progression
(time)



4. Stratifying Disease

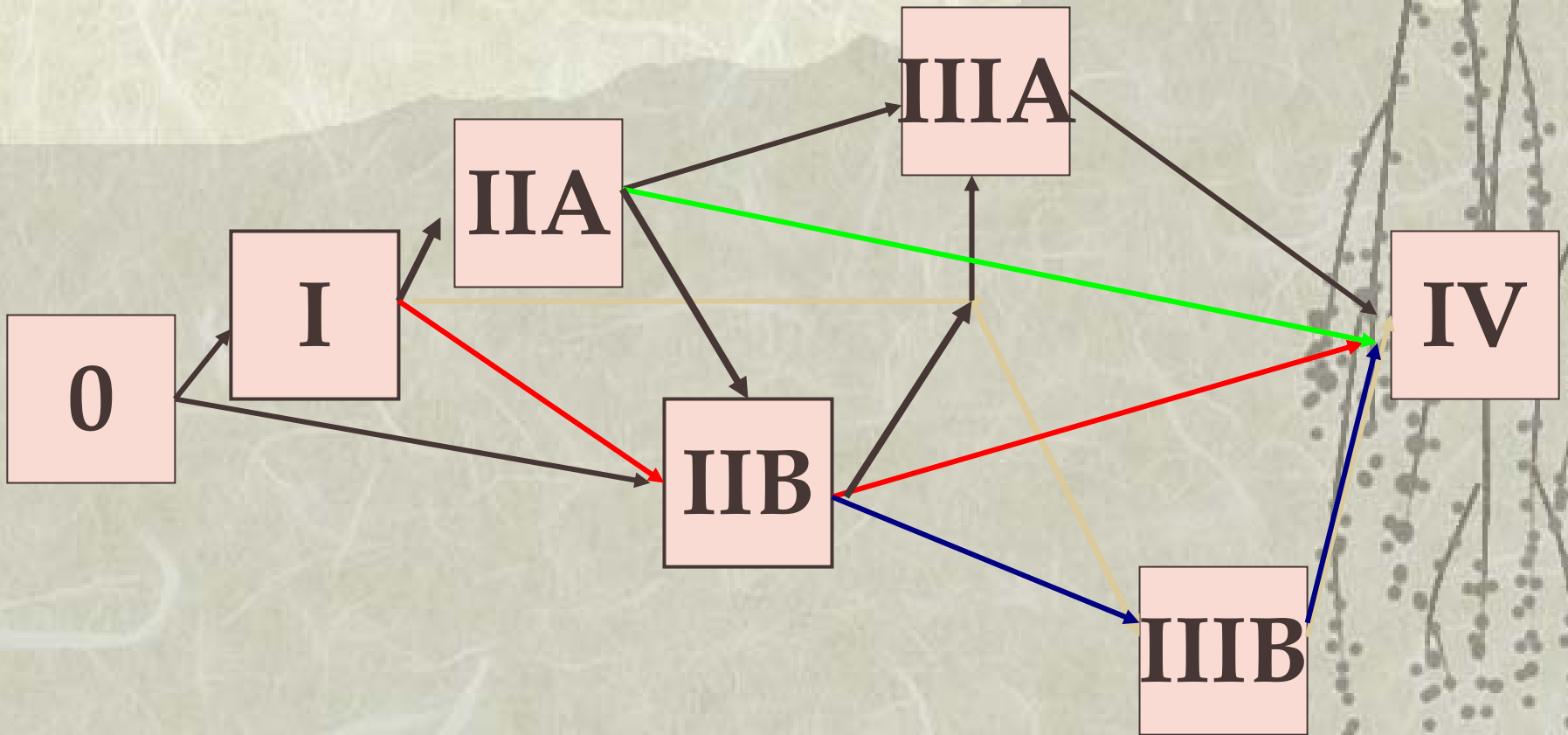
- ❖ Tumor Staging
- ❖ T,M,N tumor scoring
- ❖ Analysis of Outcomes



Cancer Progression



Tumor Progression



Tumor Staging

Stage 0

(Tis, N0, M0)

Stage I

(T1, * N0, M0) ; [*T1 includes T1mic]

Stage IIA

(T0, N1, M0) ; (T1, * N1, ** M0); (T2, N0, M0) [*T1 includes T1mic]

[**The prognosis of patients with pN1a disease is similar to that of patients with pN0 disease]

Stage IIB

(T2, N1, M0) ; (T3, N0, M0)

Stage IIIA

(T0, N2, M0); (T1, * N2, M0); (T2, N2, M0); (T3, N1, M0); (T3, N2, M0)

[*T1 includes T1mic]

Stage IIIB

(T4, Any N, M0) ; (Any T, N3, M0)

Stage IV

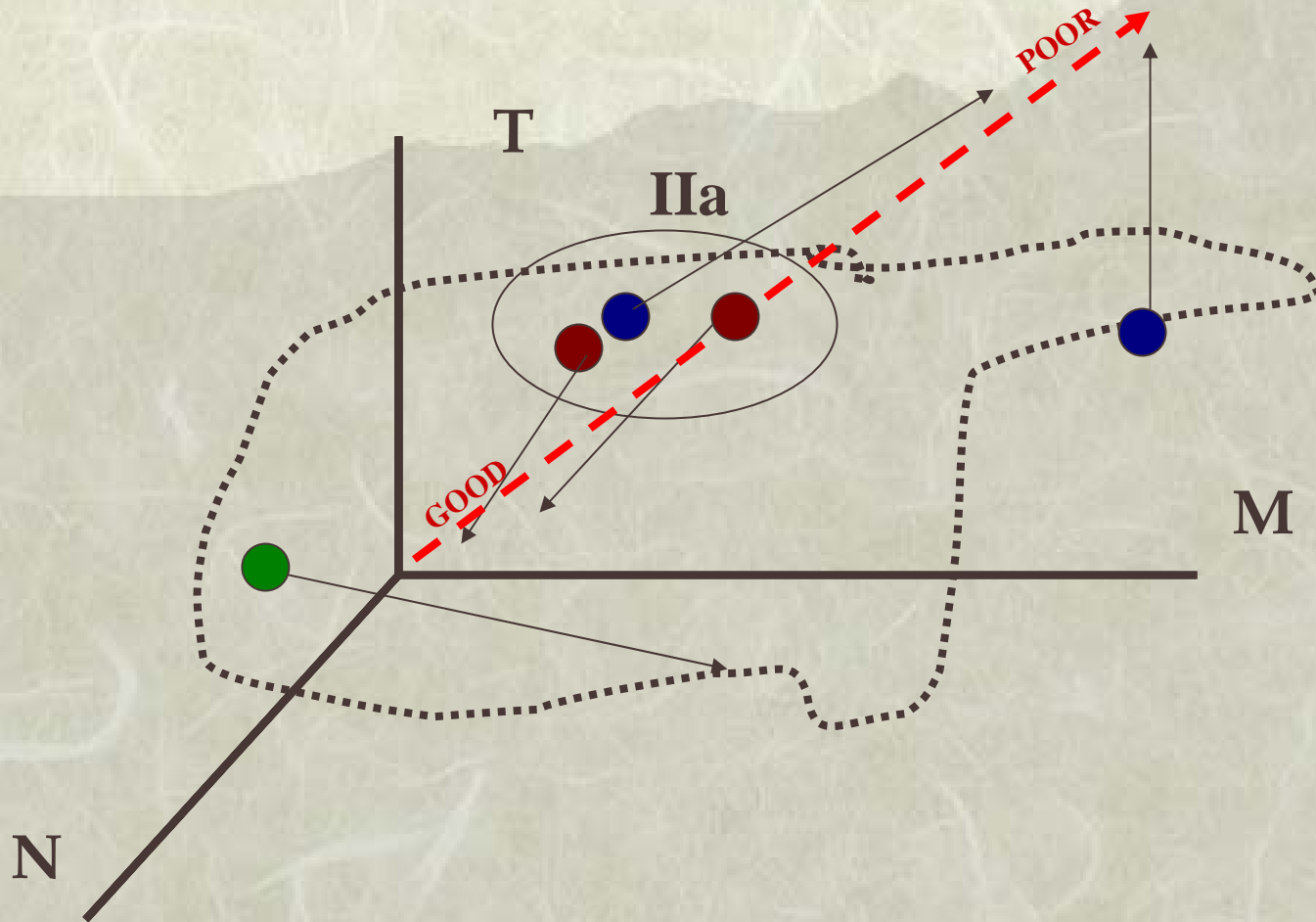
(Any T, Any N, M1)

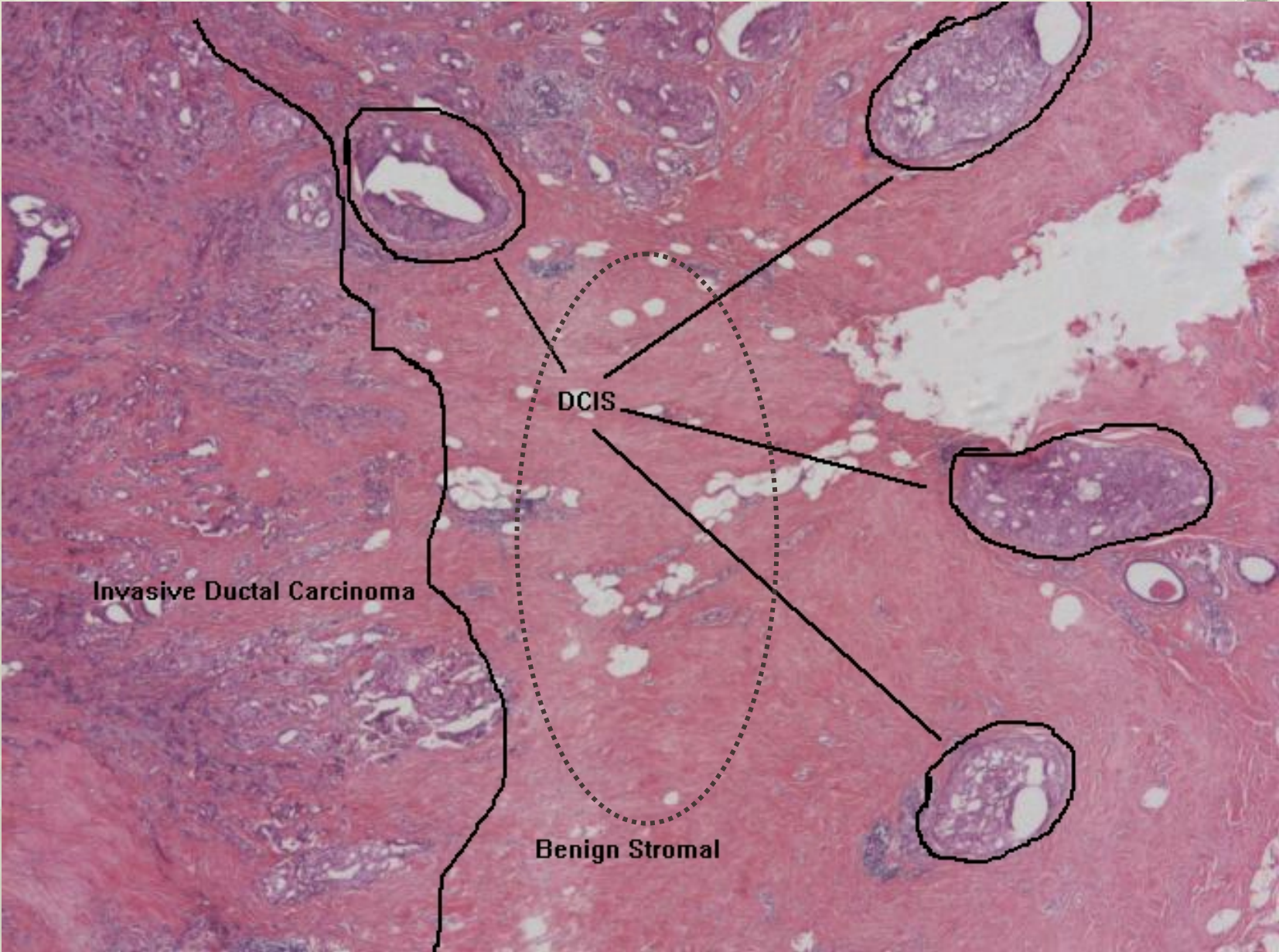
Stage IIIC

(Any T, N3, Any M)

10/10/02

(T, M, N) Information Content





Data Integration

- ❖ Data Warehouse Model
 - Teradata → Oracle
- ❖ Cimarron's Sierra LIMS
 - Amersham LWS
- ❖ Creation of CLWS

A Patient is:



A Patient is a Mother, Sister, Wife, Daughter.....

Modular Data Model

- ❖ **Socio-demographics(SD)**
- ❖ **Reproductive History(RH)**
- ❖ **Family History (FH)**
- ❖ **Lifestyle/exposures (LE)**
- ❖ **Clinical history (CH)**
- ❖ **Pathology report (P)**
- ❖ **Tissue/sample repository (T/S)**
- ❖ **Outcomes (O)**
- ❖ **Genomics (G)**
- ❖ **Biomarkers (B)**
- ❖ **Co-morbidities (C)**
- ❖ **Proteomics (Pr)**

Swappable based on Disease

Conclusions

- ❖ **Personalized Disease will improve Patient Care, Today; Personalized Medicine, Tomorrow**
- ❖ **Disease is a Process, not a State**
- ❖ **Translational Medicine must be both:**
 - **Bedside-to-bench, and**
 - **Bench-to-bedside**
- ❖ **The processes of aging are critical:**
 - **For accurate diagnosis of the patient**
 - **For converting breast cancer to a chronic disease**

Acknowledgements

- ❖ Windber Research Institute
- ❖ Joyce Murtha Breast Care Center
- ❖ Walter Reed Army Medical Center
- ❖ Immunology Research Center
- ❖ Malcolm Grow Medical Center
- ❖ Landstuhl Medical Center
- ❖ Henry Jackson Foundation
- ❖ USUHS
- ❖ MRMC-TATRC
- ❖ Military Cancer Institute

Patients, Personnel and Family!

The background features a stylized illustration of a mountain range in shades of brown and tan, set against a textured, light-colored paper-like background. On the right side, there is a detailed drawing of a willow tree with dark, thin branches and clusters of small, dark buds or leaves.

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