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)**

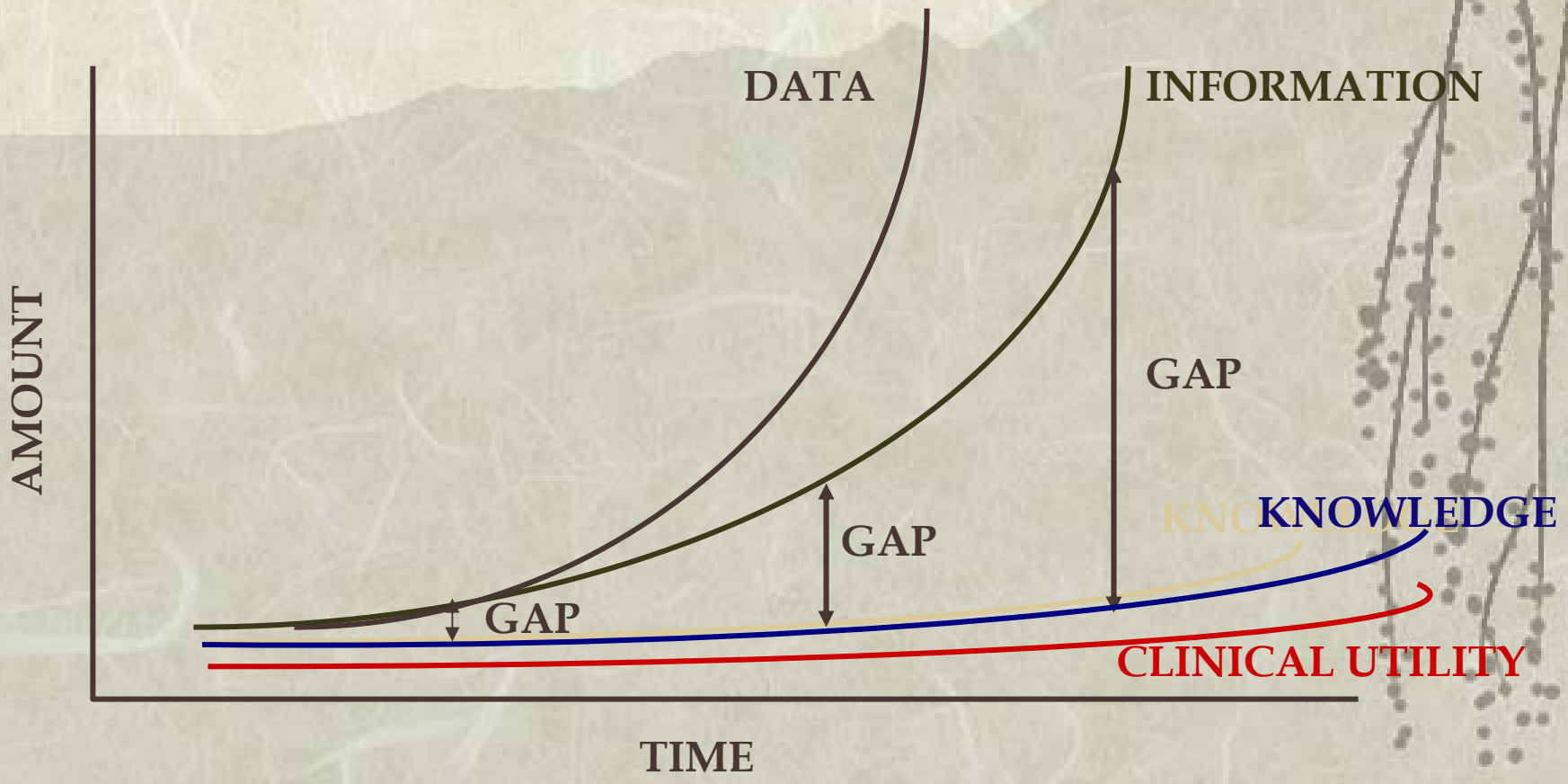
Windber Research Institute

- 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

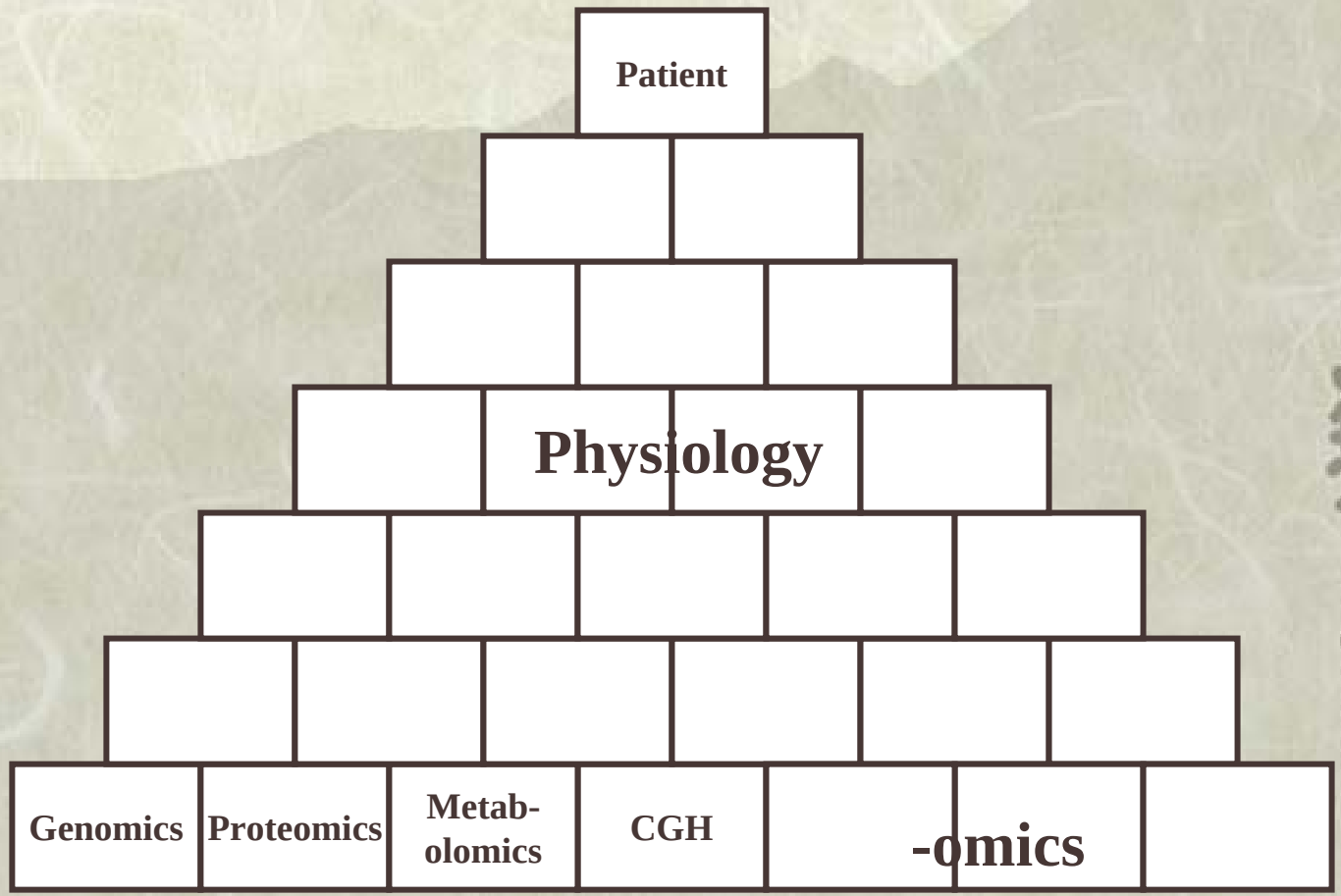
WRI's Mission

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.

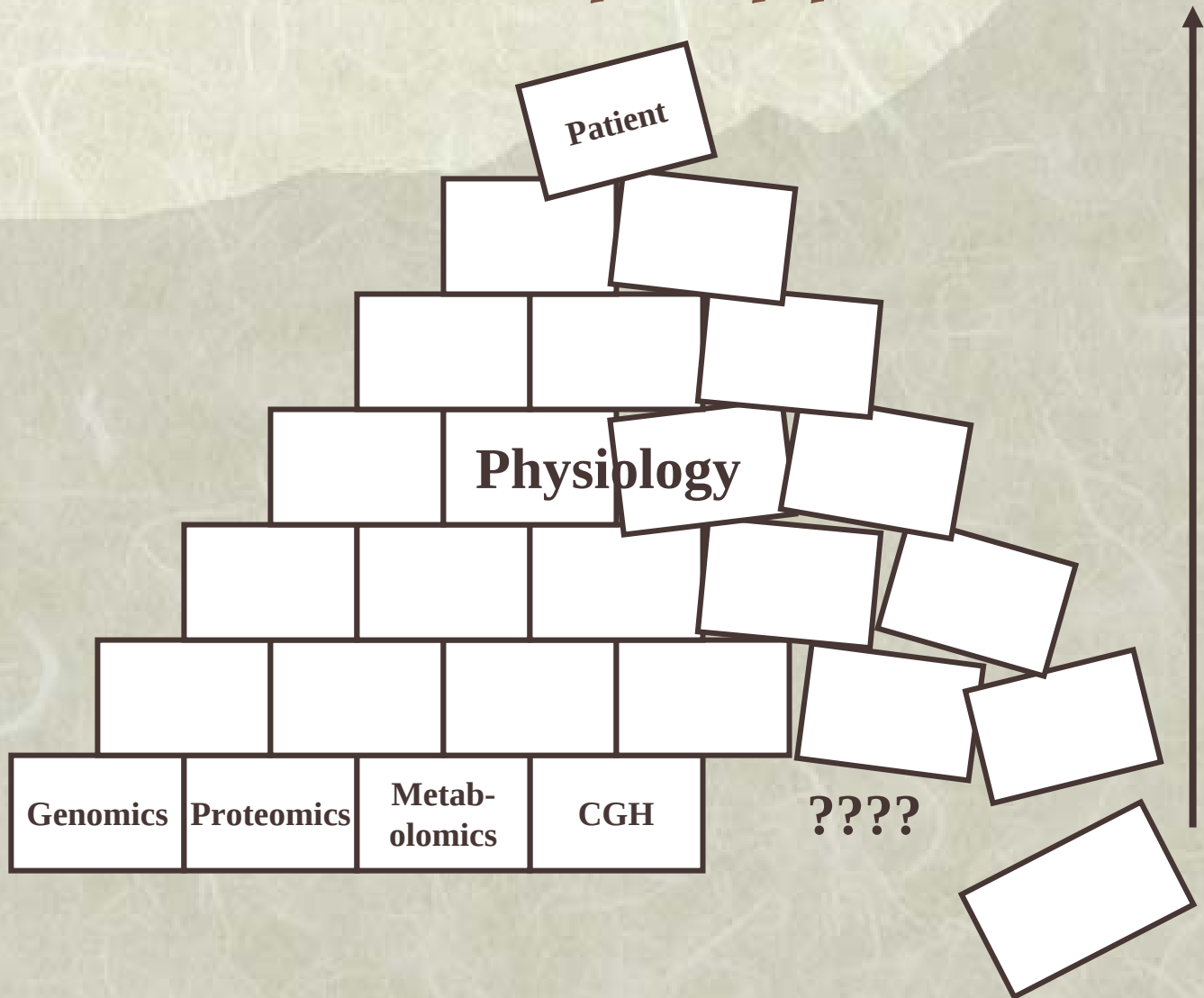
Gap


DATA
INFORMATION
GAP
GAP
GAP
KNOWLEDGE
CLINICAL UTILITY
AMOUNT
TIME

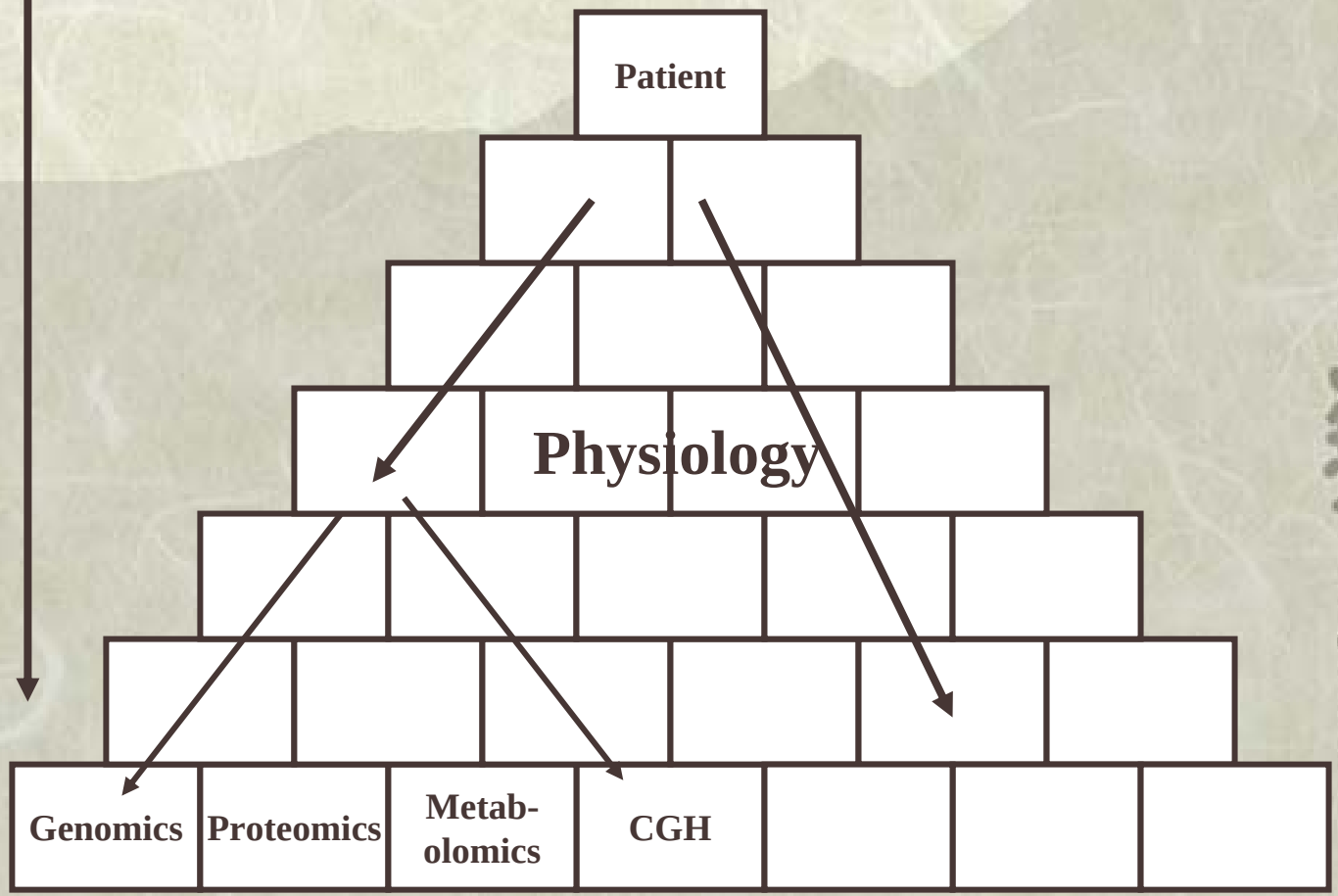
Systems Biology (Personalized Medicine)



Bottom Up Approach



Top Down Approach (Personalized Disease)



Translational Medicine

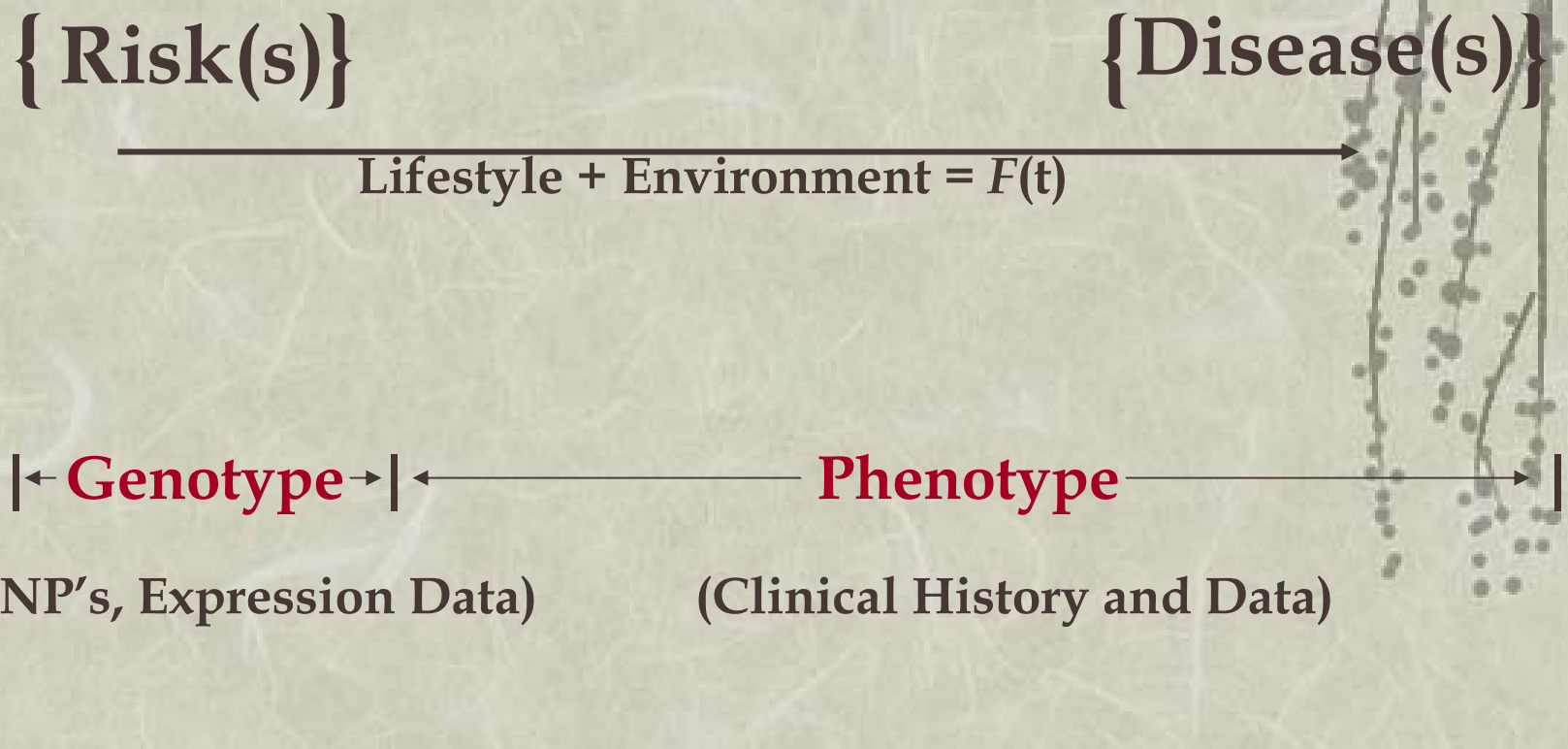
"Discovery consists in seeing what Everyone else has seen and thinking What no one else has thought"

A. Szent-Gyorgi

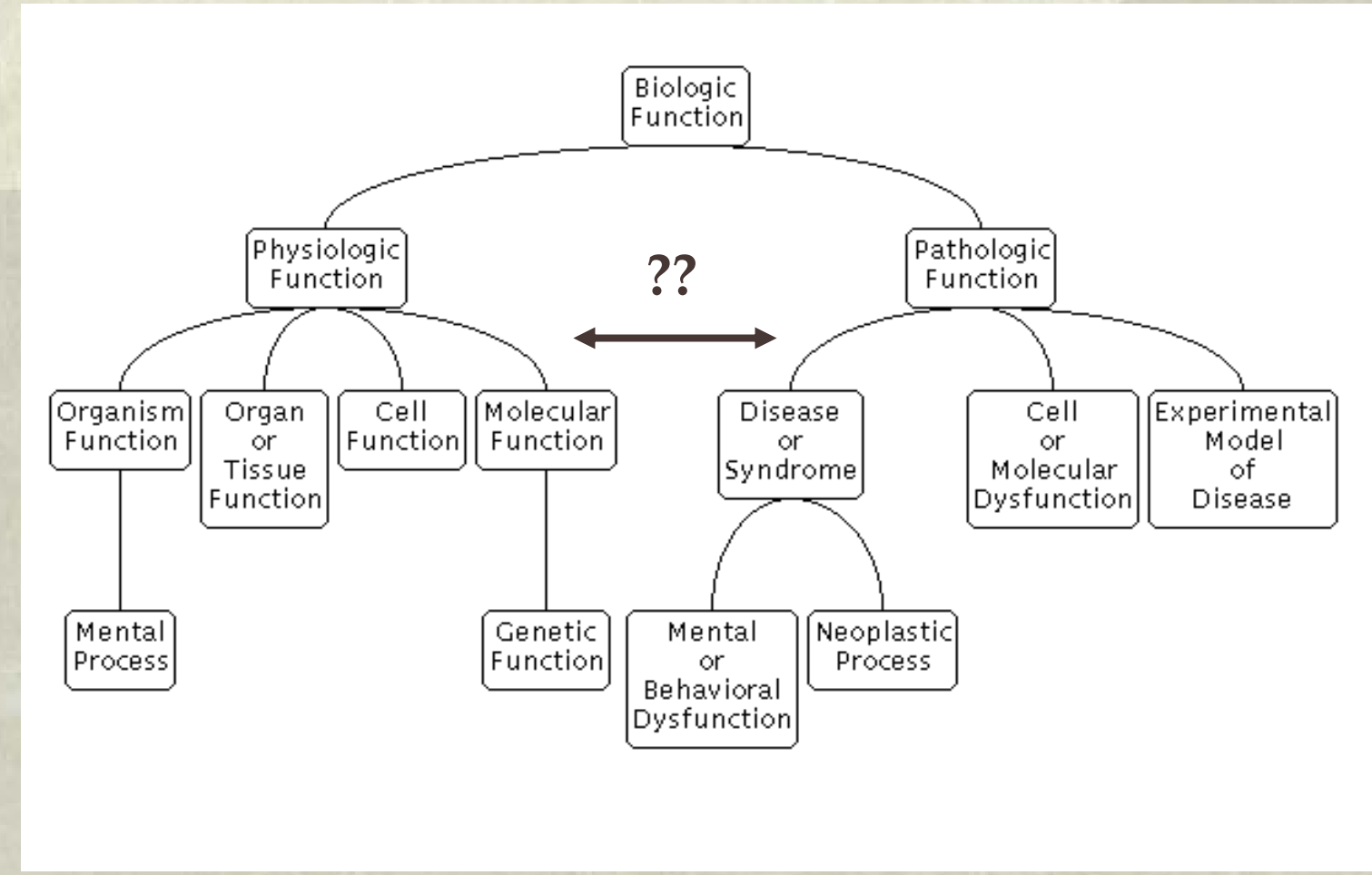
1. Modeling Disease

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

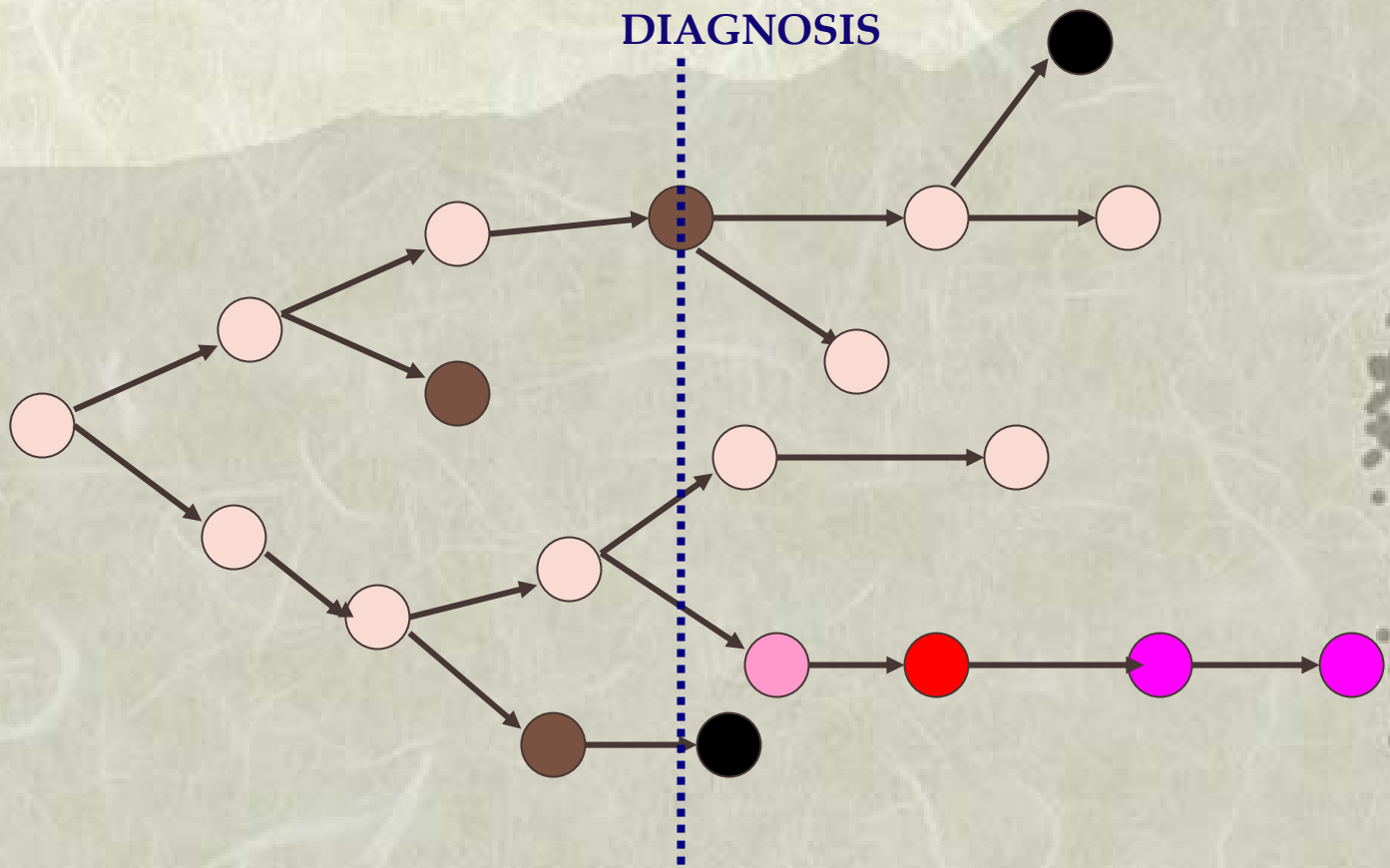
Modeling Disease



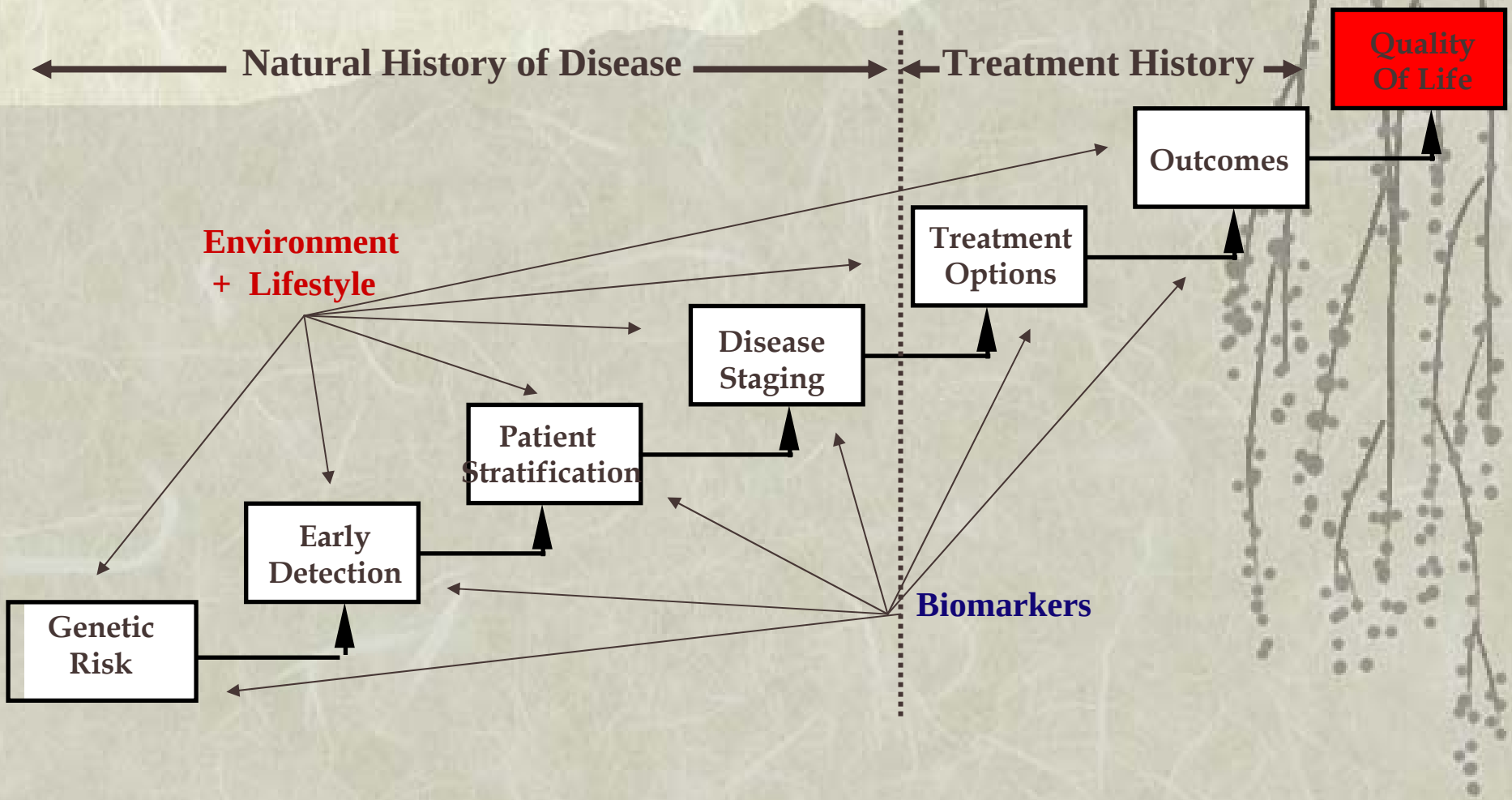
UMLS Semantic Network



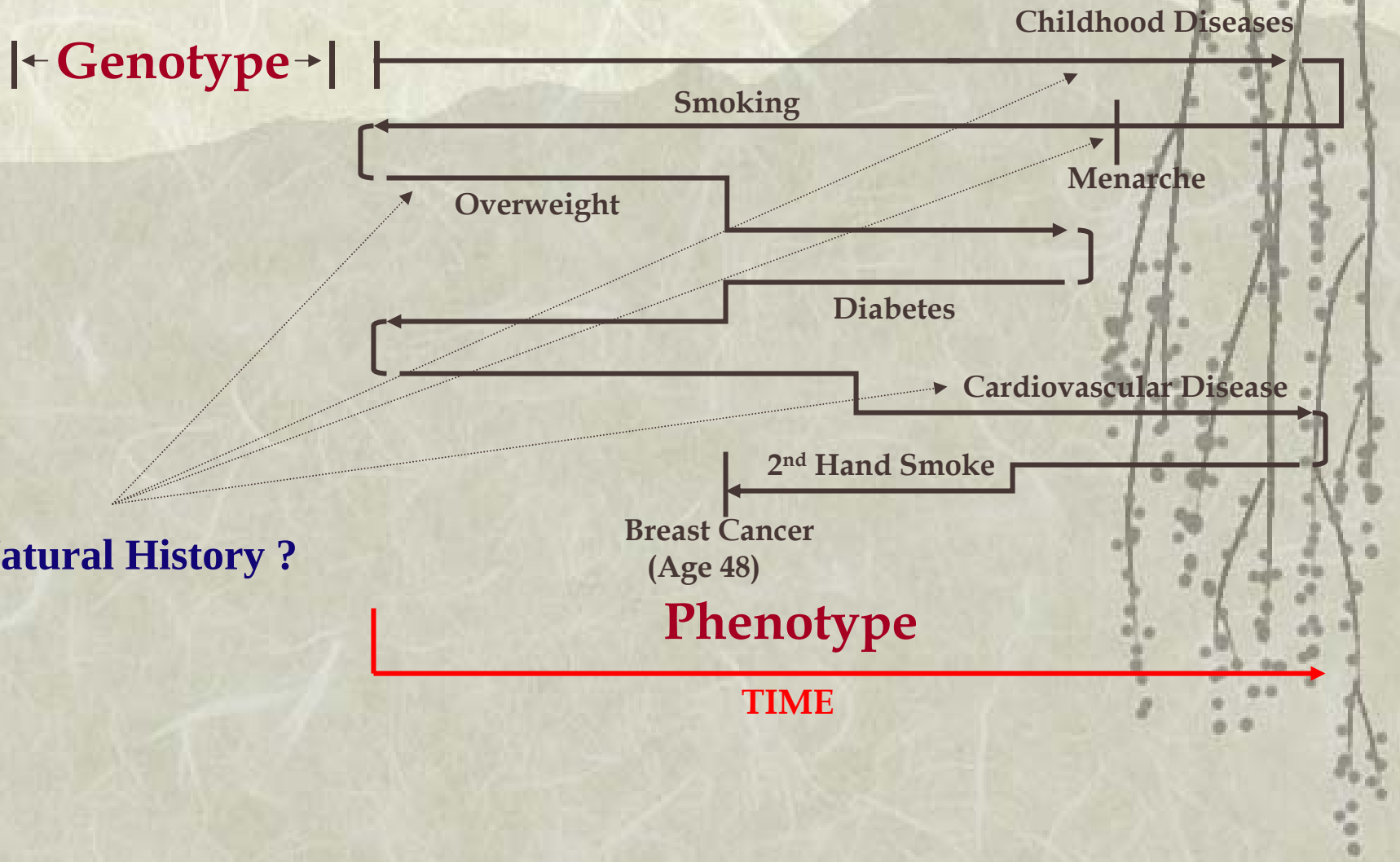
Disease Etiology



Pathway of Disease



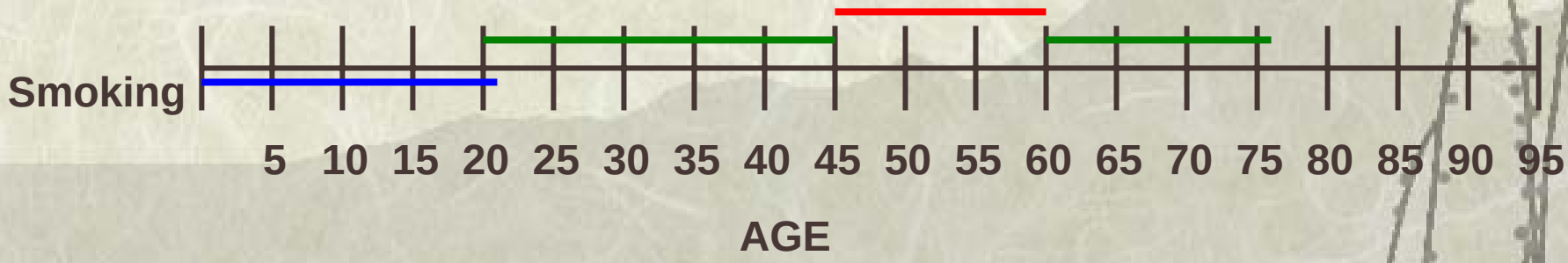
Phenotype

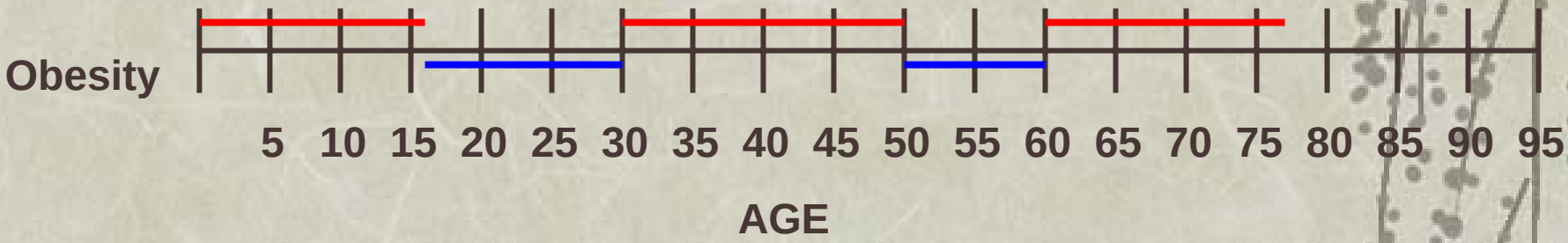

Genotype
Childhood Diseases
Smoking
Menarche
Overweight
Diabetes
Cardiovascular Disease
2nd Hand Smoke
Breast Cancer
(Age 48)
Natural History ?
Phenotype
TIME

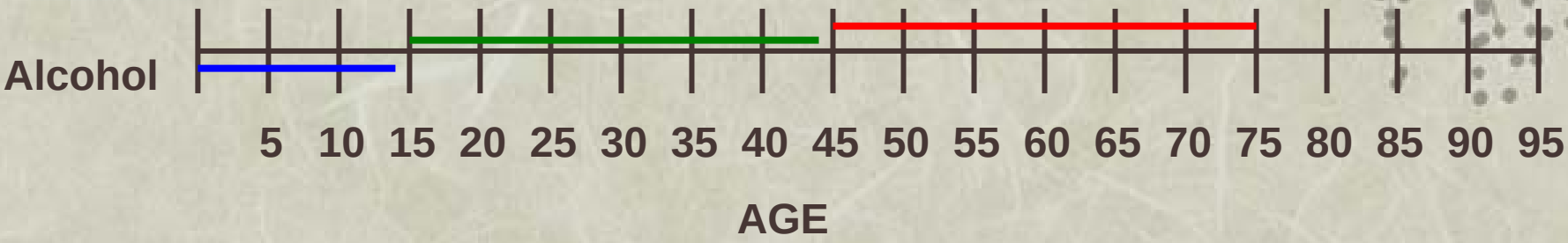
Longitudinal Interactions in Breast Cancer

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

Lifestyle Factors



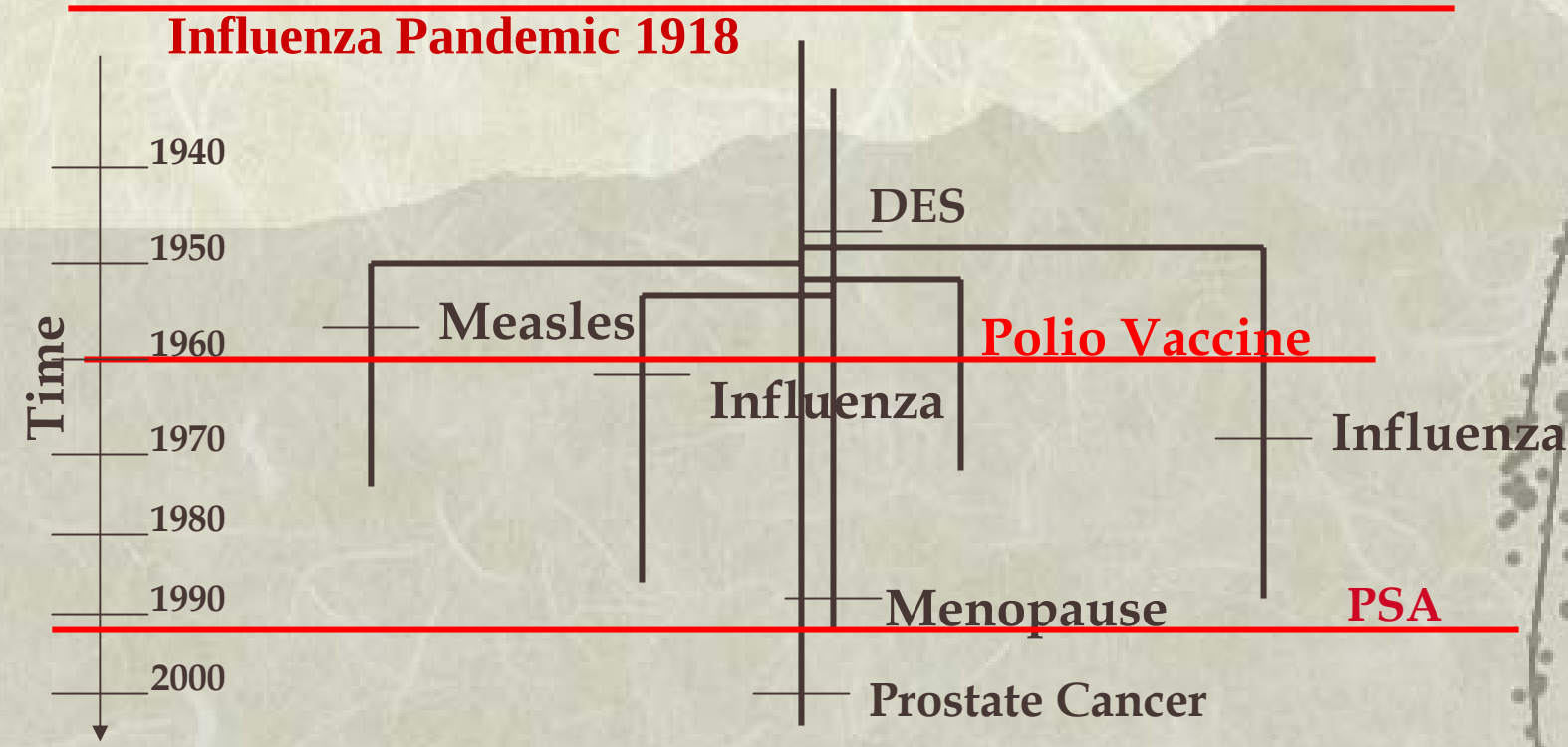




2. Genetics and Disease

- 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

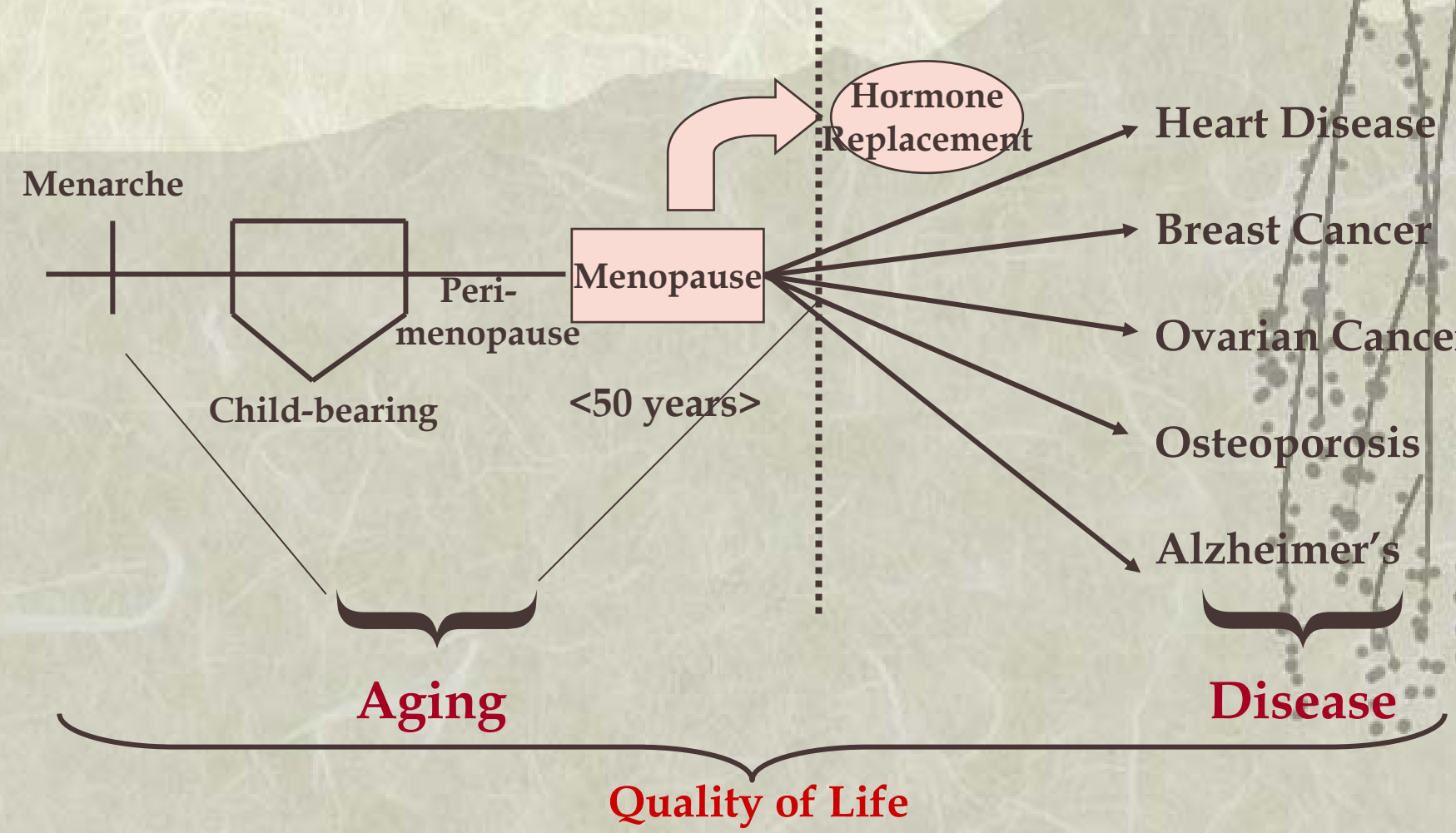
Pedigree (modified)



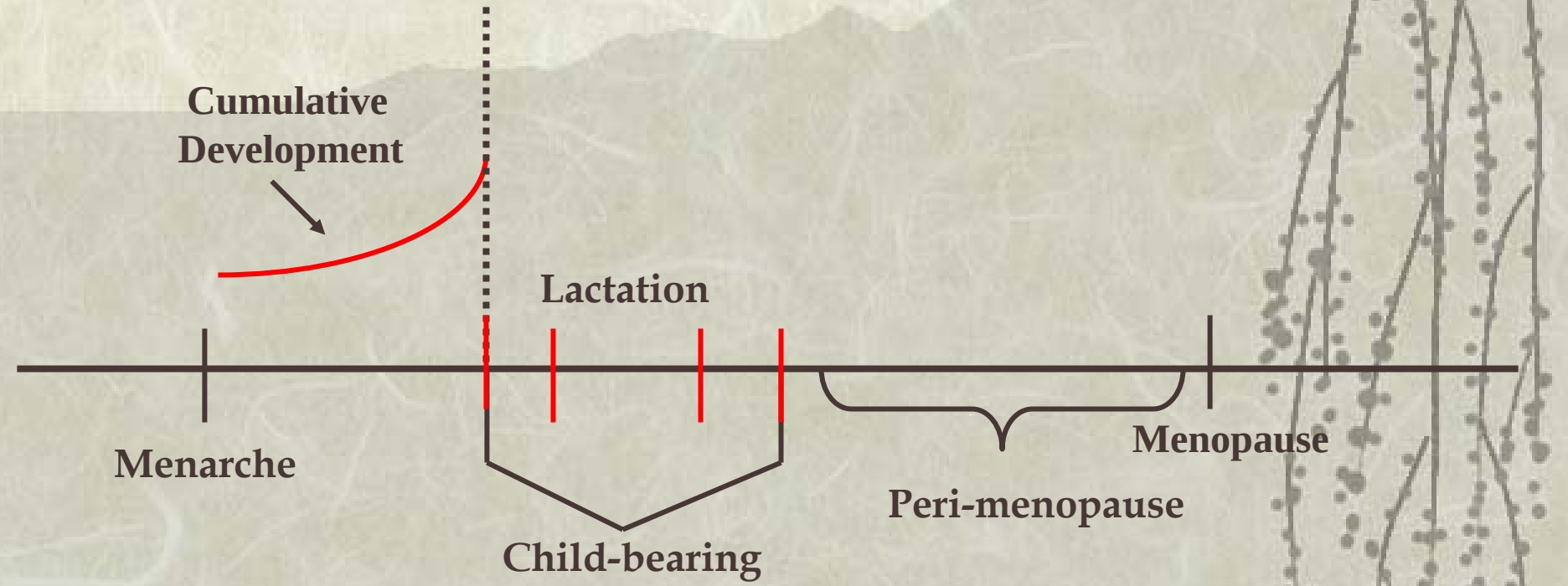
3. Aging and Disease

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

Disease vs Aging

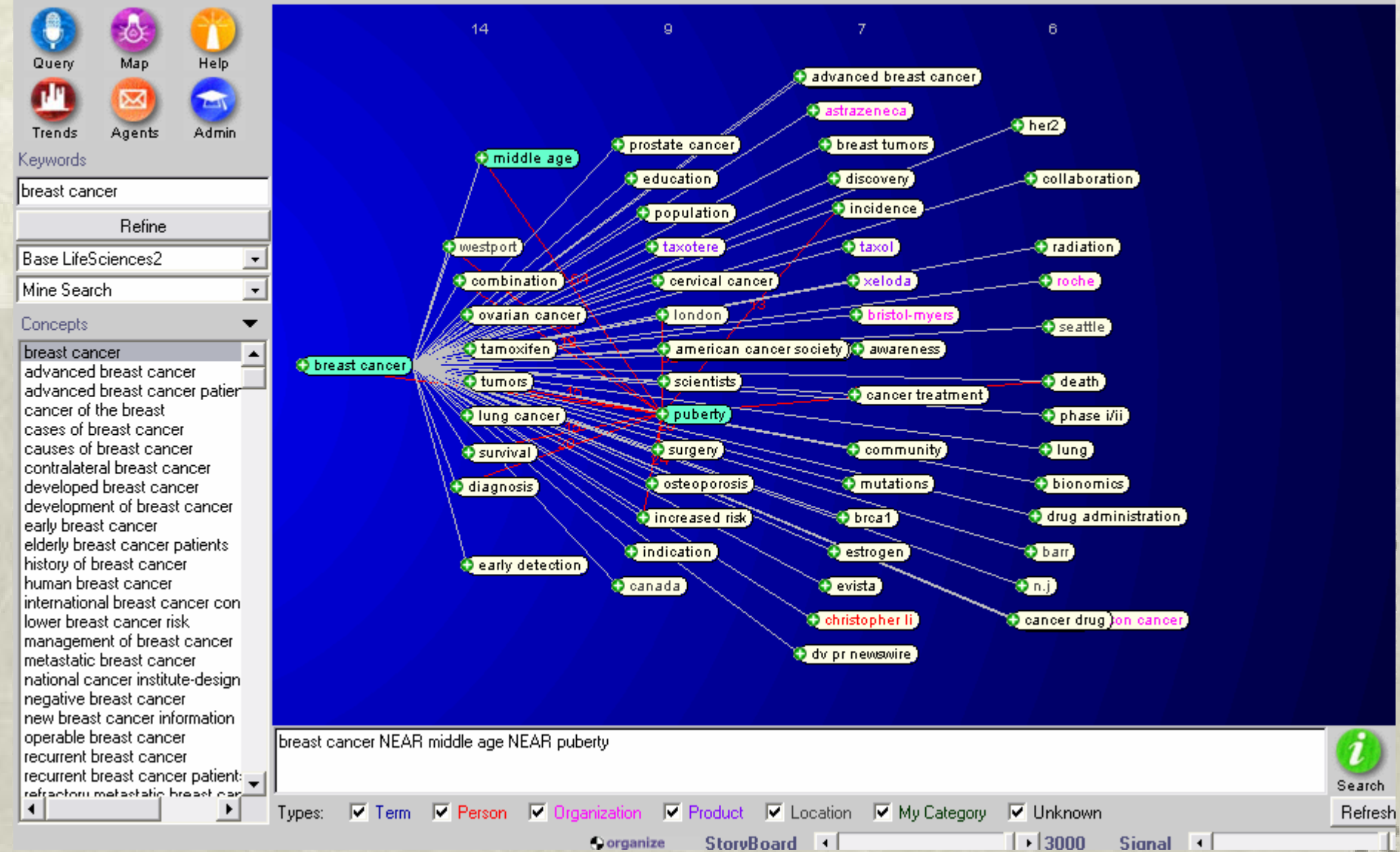


Breast Development



Ontology: Breast Development

SPSS – LexiMine and Clementine

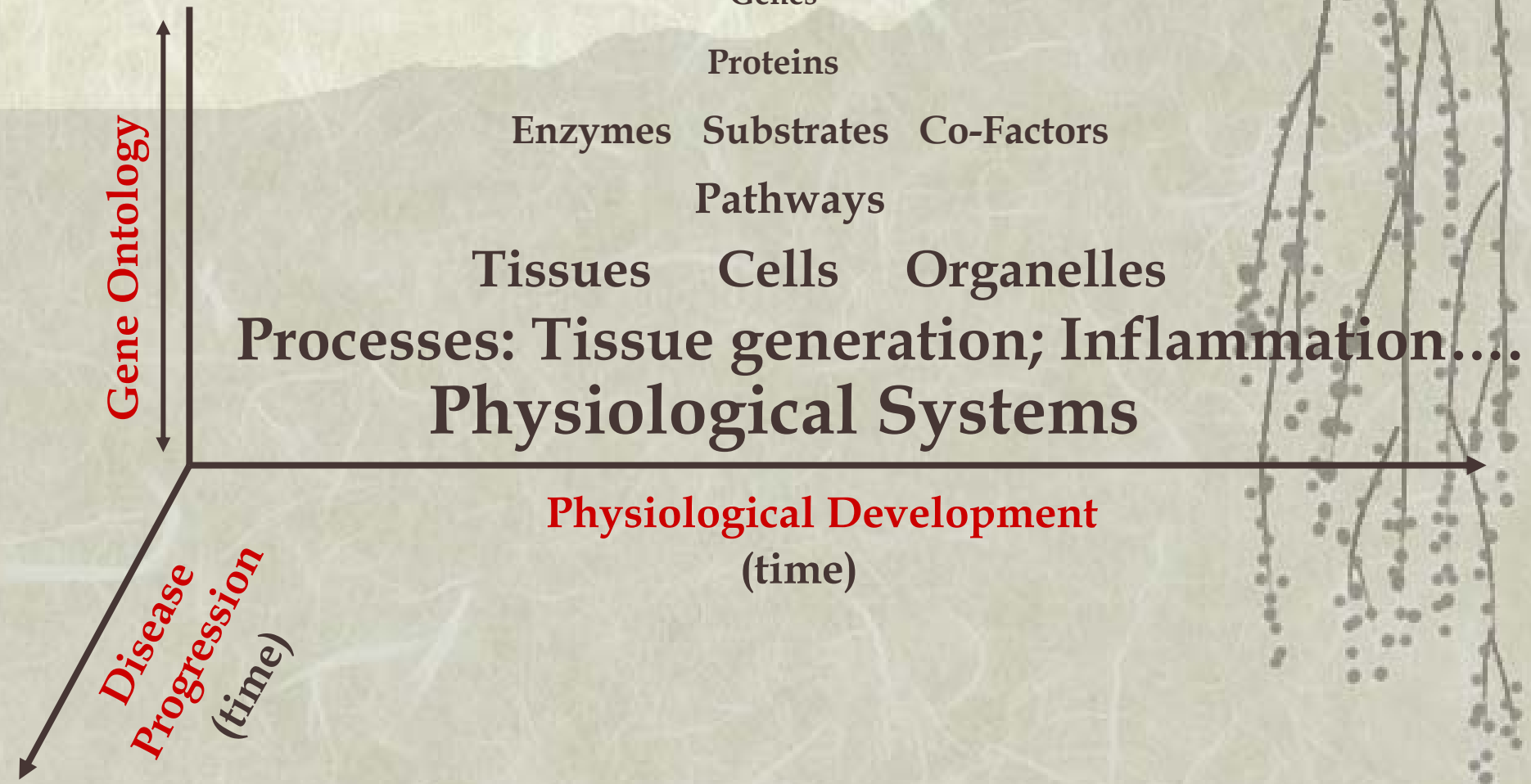


Puberty:

- 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

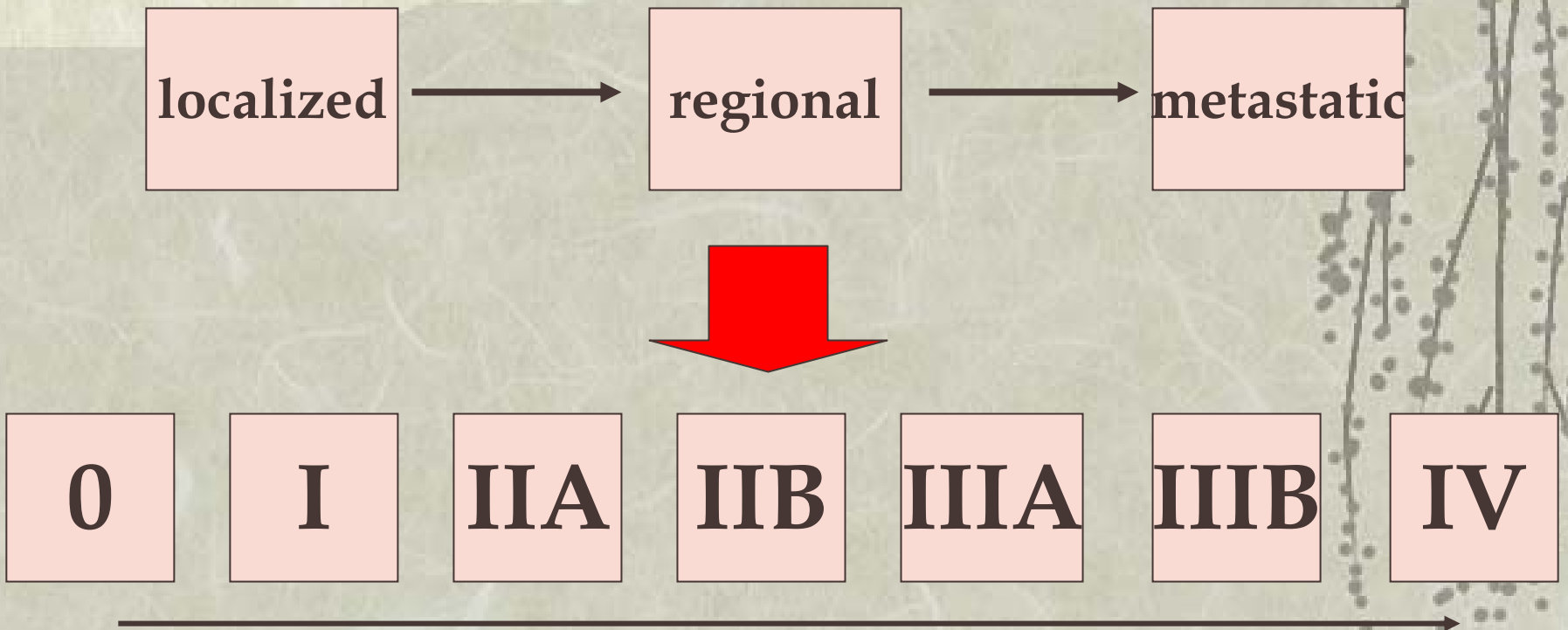
Reality of Disease



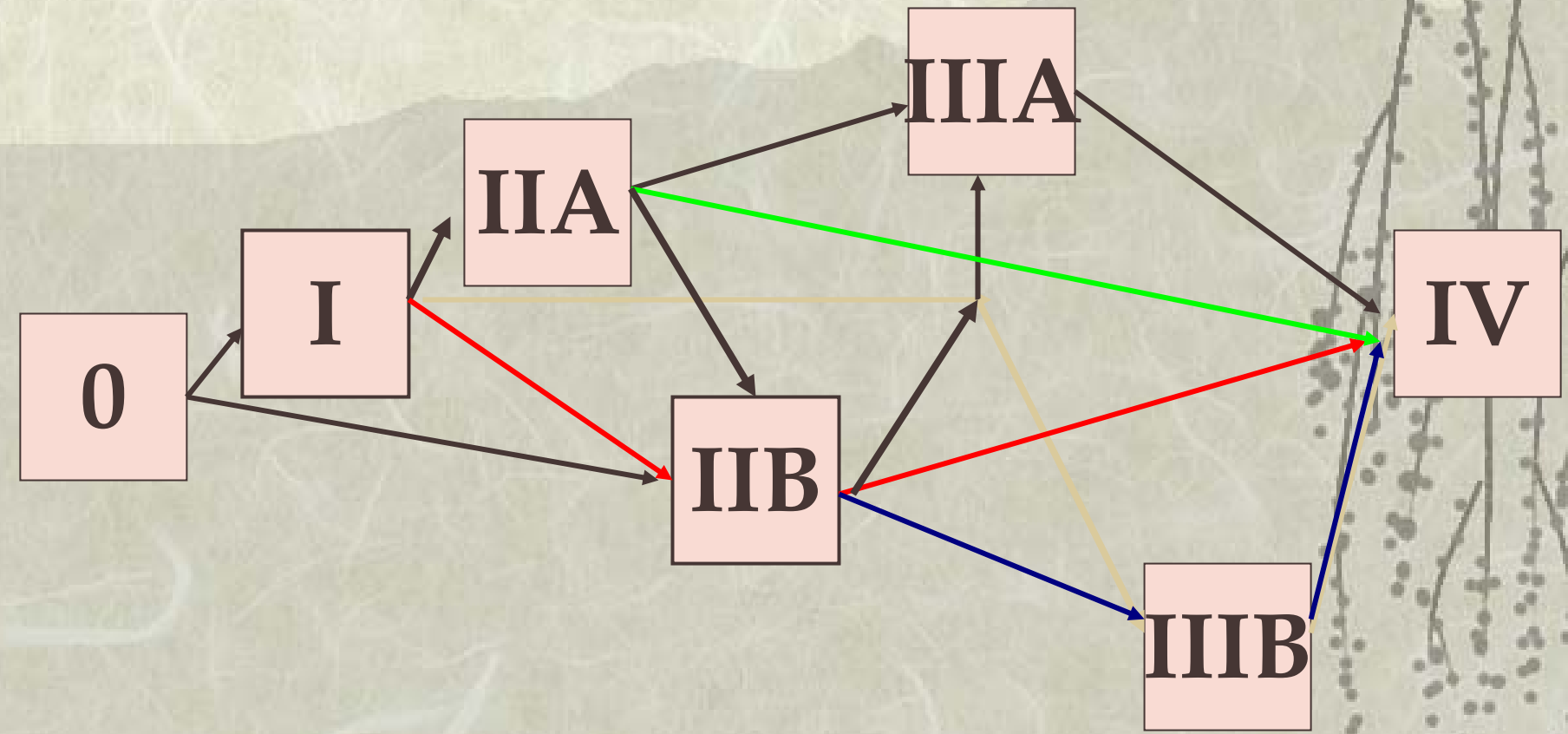
4. Stratifying Disease

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

Cancer Progression



Tumor Progression



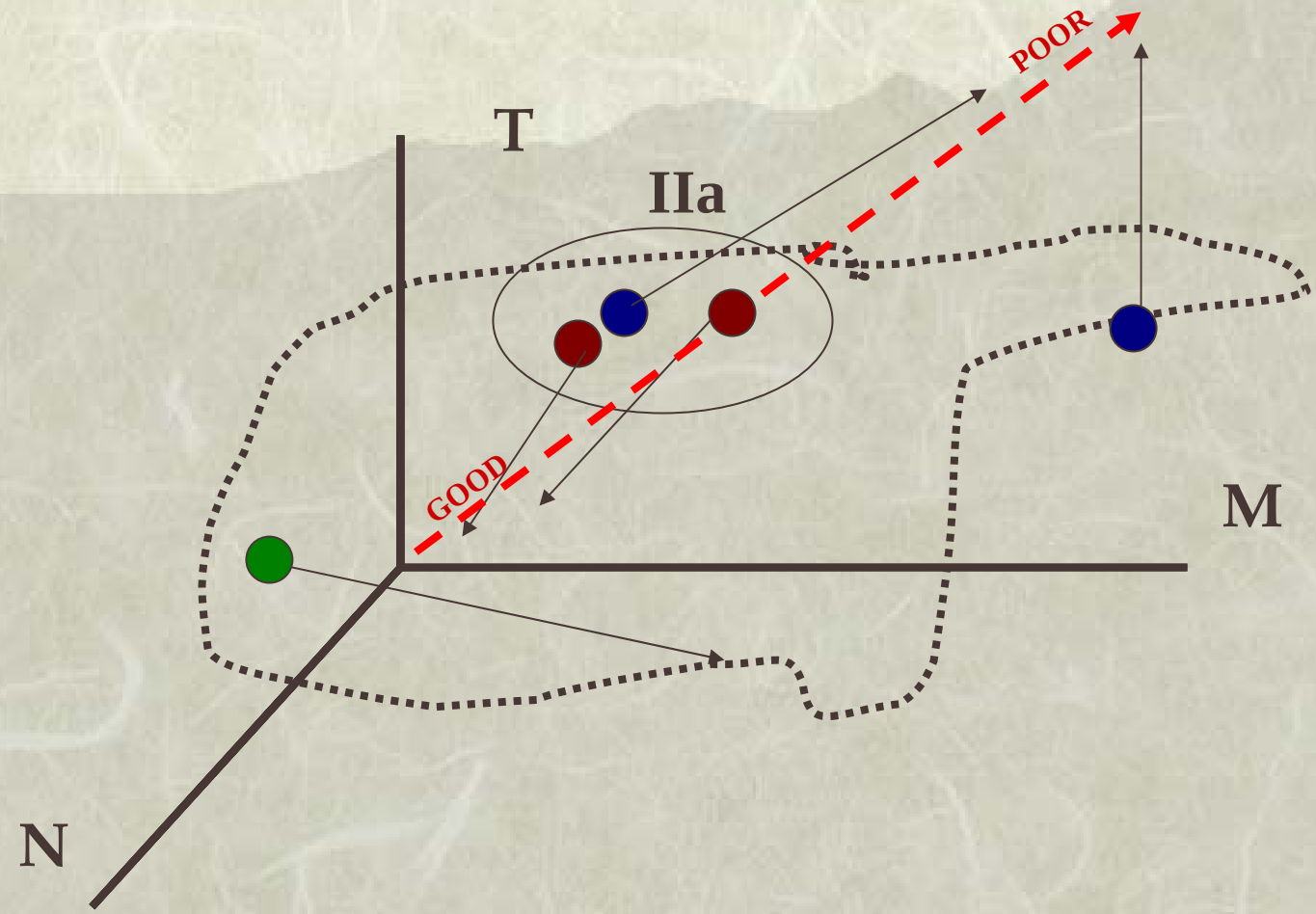
Tumor Staging

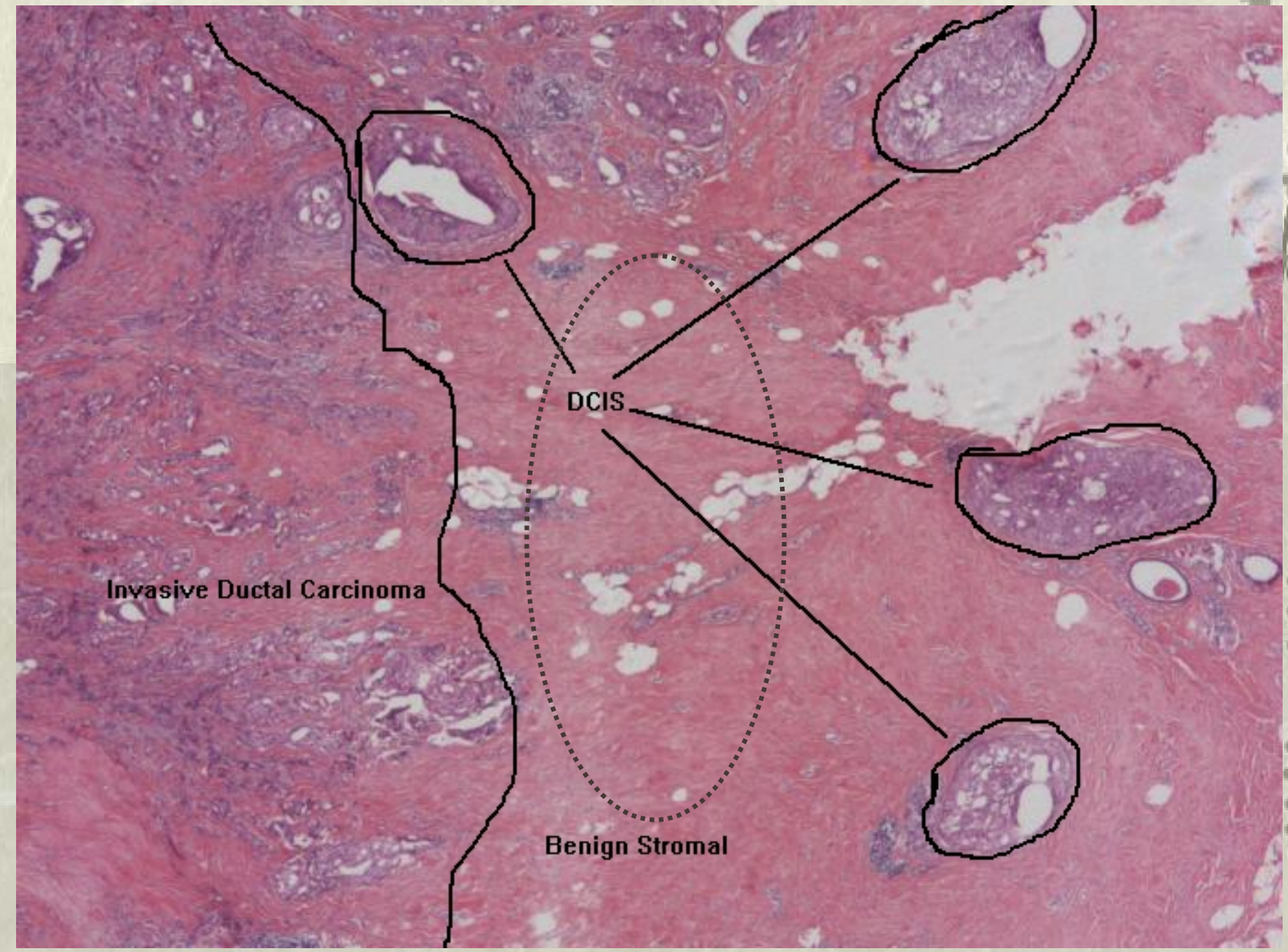
Stage 0
(Tis, N0, M0)
Stage I
(T1, N0, M0) ; [*T1 includes T1mic]*
Stage IIA
(T0, N1, M0); (T1,* N1,** M0); (T2, N0, M0) [*T1 includes T1mic]
[**The prognosis of patients with pN1a disease is similar to that of patients with pN0 disease]
Stage IIB
(T2, N1, M0) ; (T3, N0, M0)
Stage IIIA
(T0, N2, M0); (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




DCIS
Invasive Ductal Carcinoma
Benign Stromal

Data Integration

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

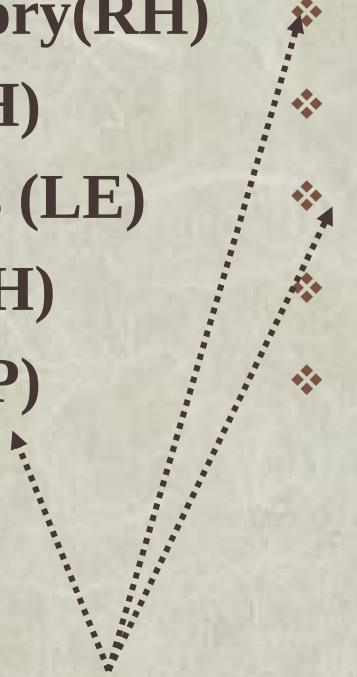
A Patient is:

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 <u>both</u>:**
  - **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
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- Military Cancer Institute

Patients, Personnel and Family!

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