# Integration of In Vivo Imaging Data: What's Missing?

Michael W. Vannier
University of Iowa

# Outline

- Post-genomic biology
- Imaging informatics
- Molecular imaging
- Industrialization of R&D
- Challenges
- Conclusion

UCSF cancer center

# Paradigm shift in biological research

## Biology is shifting from being an observational science to being a quantitative molecular science

### Old biology: measure one/two things in two/three conditions

- High cost per measurement
- Analysis straightforward
- Enormously difficult to work out pathways

### New biology: measure 10,000 things under many conditions

- Low cost per measurement
- Analysis no longer straightforward, but payoff can be bigger
- Biology as a complex system: Can we work out biological pathways this way?

Source: Ajay Jain

WHITE PAPER

# *"Synergy between Medical Informatics and Bioinformatics: Facilitating Genomic Medicine for Future Healthcare"*

April 29th, 2003

EC-IST 2001-35024
BIOINFOMED Study
*"Prospective Analysis of the Relationships and Synergy Between Medical Informatics and Bioinformatics"*

BIOINFOMED Study
April 2003

White Paper

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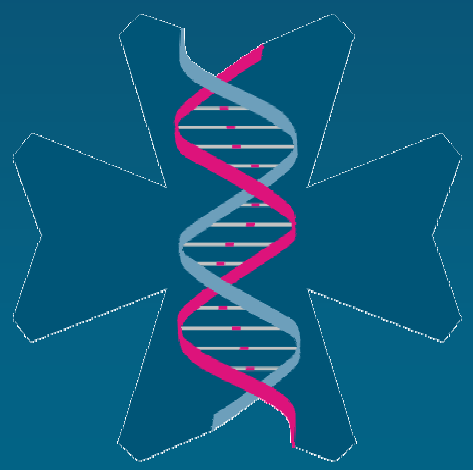
National Institute of Health “Carlos III”
Ministry of Health and Consumer Affairs

Madrid, SPAIN

EC IST BIOINFOMED Study Coordinator

# *Health Information Systems in the age of Post-Genomic Research*



CEN/TC251

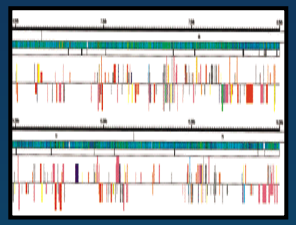
“Joint Working Group Meeting”

Madrid

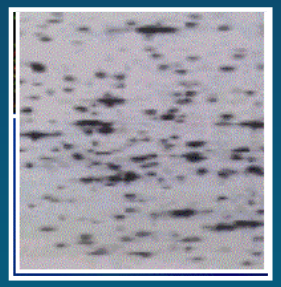
June 3, 2002

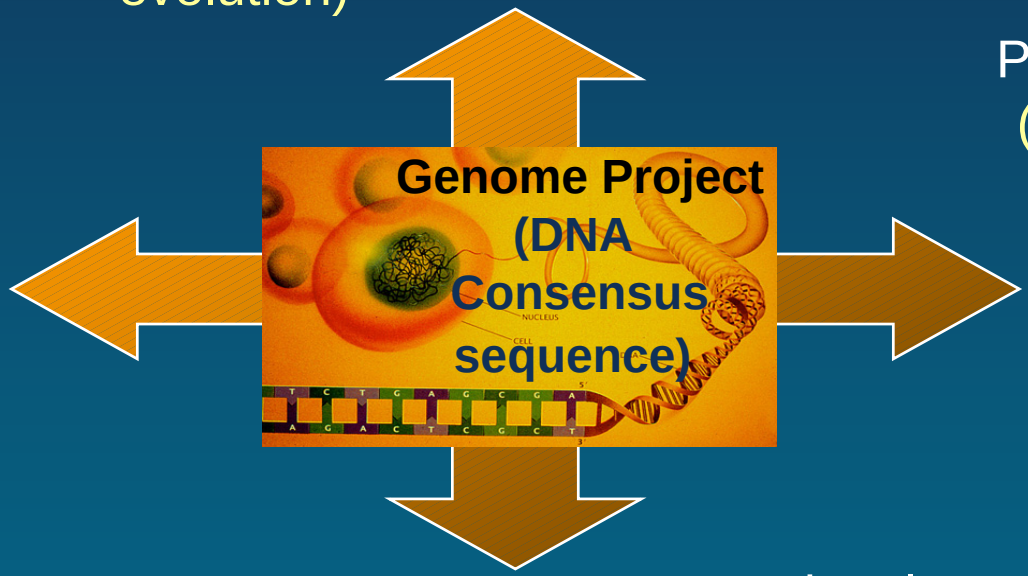
# The Post-Genomics Era

Comparative Genomics (homology, evolution)

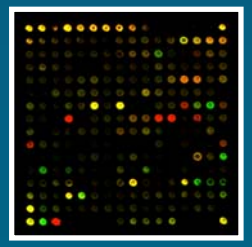


Proteomics (proteins)



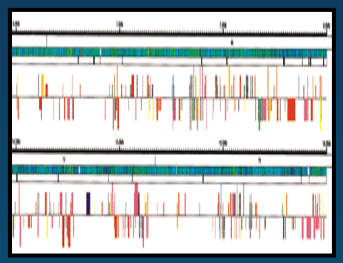


Individual Genomics (mutations, SNPs)

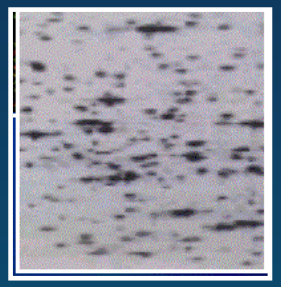


Functional Genomics (mRNAs)

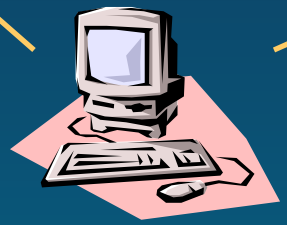
# Bioinformatics in support of Post-Genomic Research

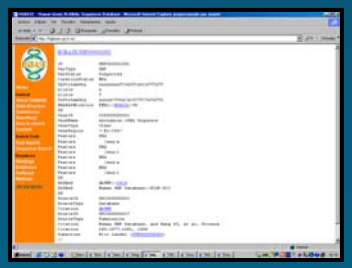


Genomes

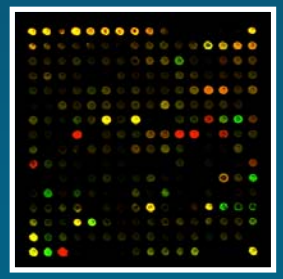


Proteomics



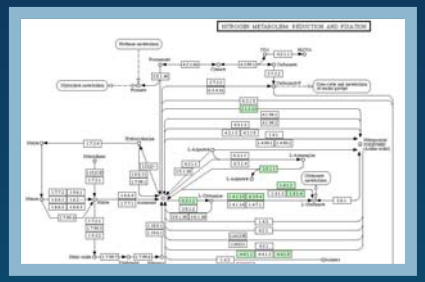


SNPs

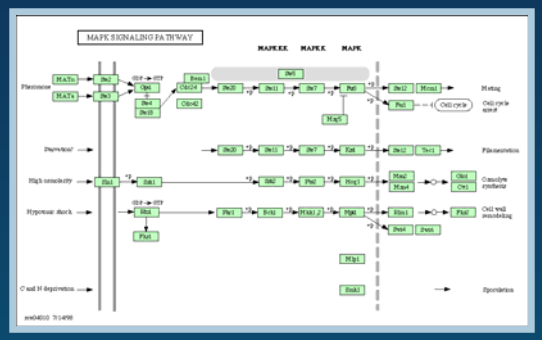


DNA microarrays

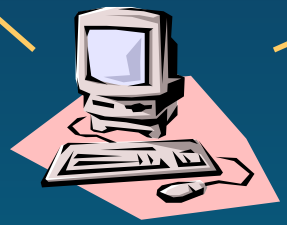
# Bioinformatics in support of Systems Biology

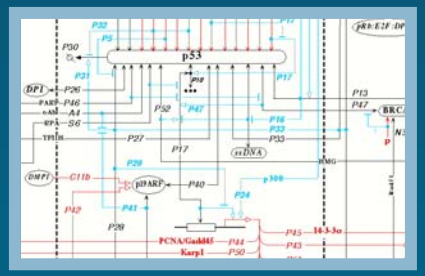


Metabolic Pathways

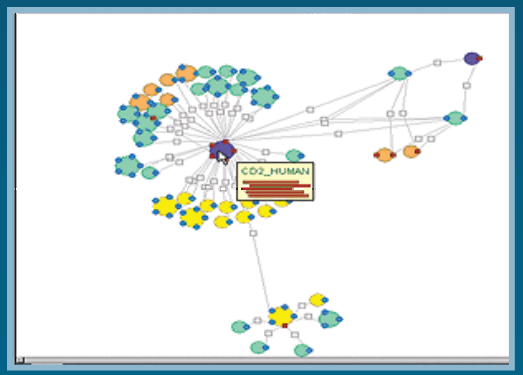


Signaling pathways





Genetic Networks




Interactions

# New opportunities for health informatics

- Genome Project
  - Interest for biologists
  - One gene at a time
  - Monogenic diseases
  - Tedious genotyping
  - DNA level
  - Bioinformatics explosion
- Post-Genomics
  - ***Clinical interest***
  - Hundreds or thousands of genes simultaneously
  - ***Complex diseases***
  - High throughput genotyping
  - DNA, RNA, Proteins
  - ***Integration of clinical and genetic information***

# Overview

Human Genetic Variation

Technologies | Data | Applications

**Genotyping**

**Haplotyping**

**Individual genomics (SNPs and mutations)**

**Diagnosis**

**Pharmaco-genetics**

**Individualised healthcare**

**Genome**

**BIOINFORMATICS & MEDICAL INFORMATICS**

**Information**

**Gene Expression DNA arrays MS, 2D ef**

**Functional genomics**

**proteomics**

**Disease classification Pharmaco-genomics**

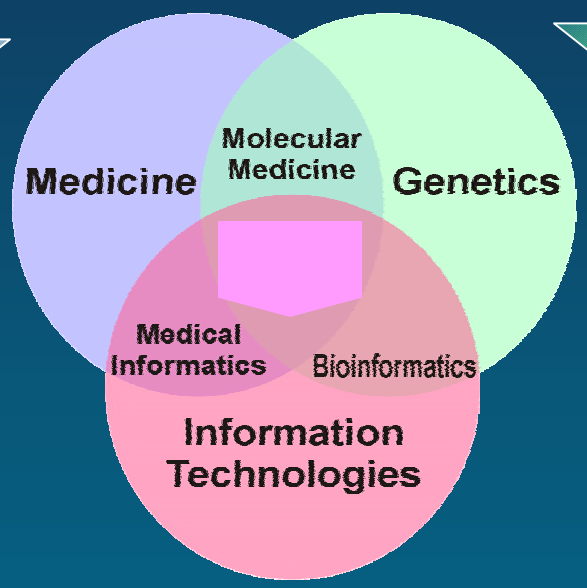
**Molecular medicine**

**Molecular causes of diseases**

# A model for studying interactions

To foster the application of bioinformatics in health

To adapt medical informatics systems to the genetics paradigm




To apply IT to facilitate molecular medicine

# Molecular imaging

- Medical imaging + genomics
- Imaging molecular alterations that are the basis of disease rather than their effects

- *R. Weissleder. Radiology 2001; 219:316-333*

# Levels and technologies

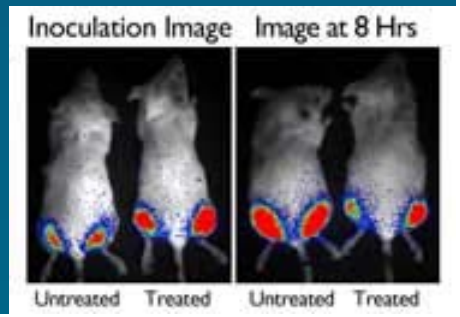
Today

CT
US

Anatomy
Physiology
Metabolism
Molecular

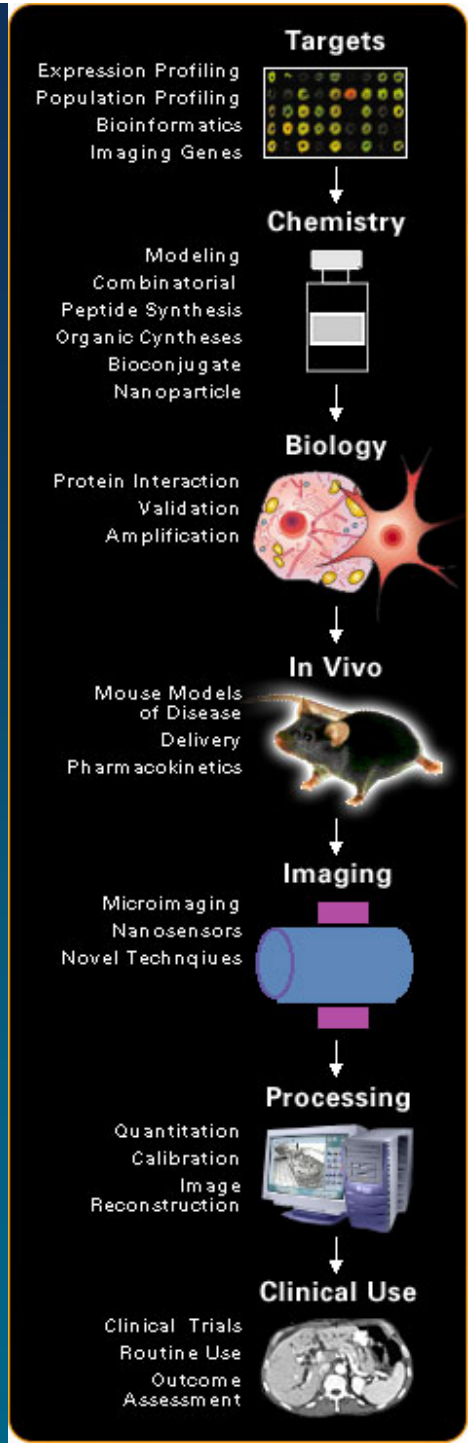
Tomorrow

MRI
Nuclear
Optical
Nano



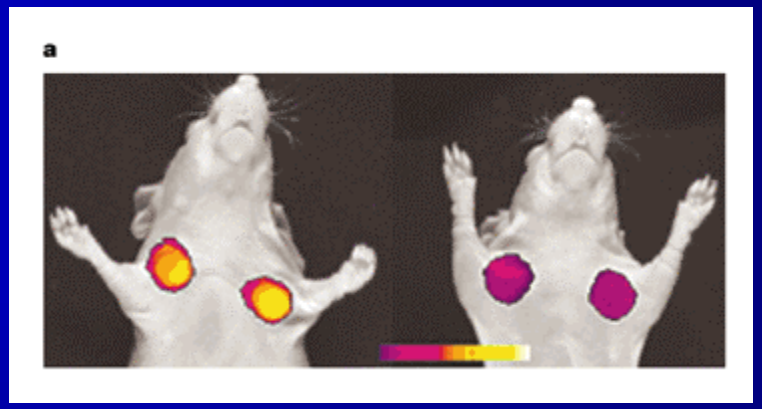
# Molecular Imaging

- New markers for early disease detection
- Specific markers for therapy assesment
- Drug screening
- Imaging of gene expression



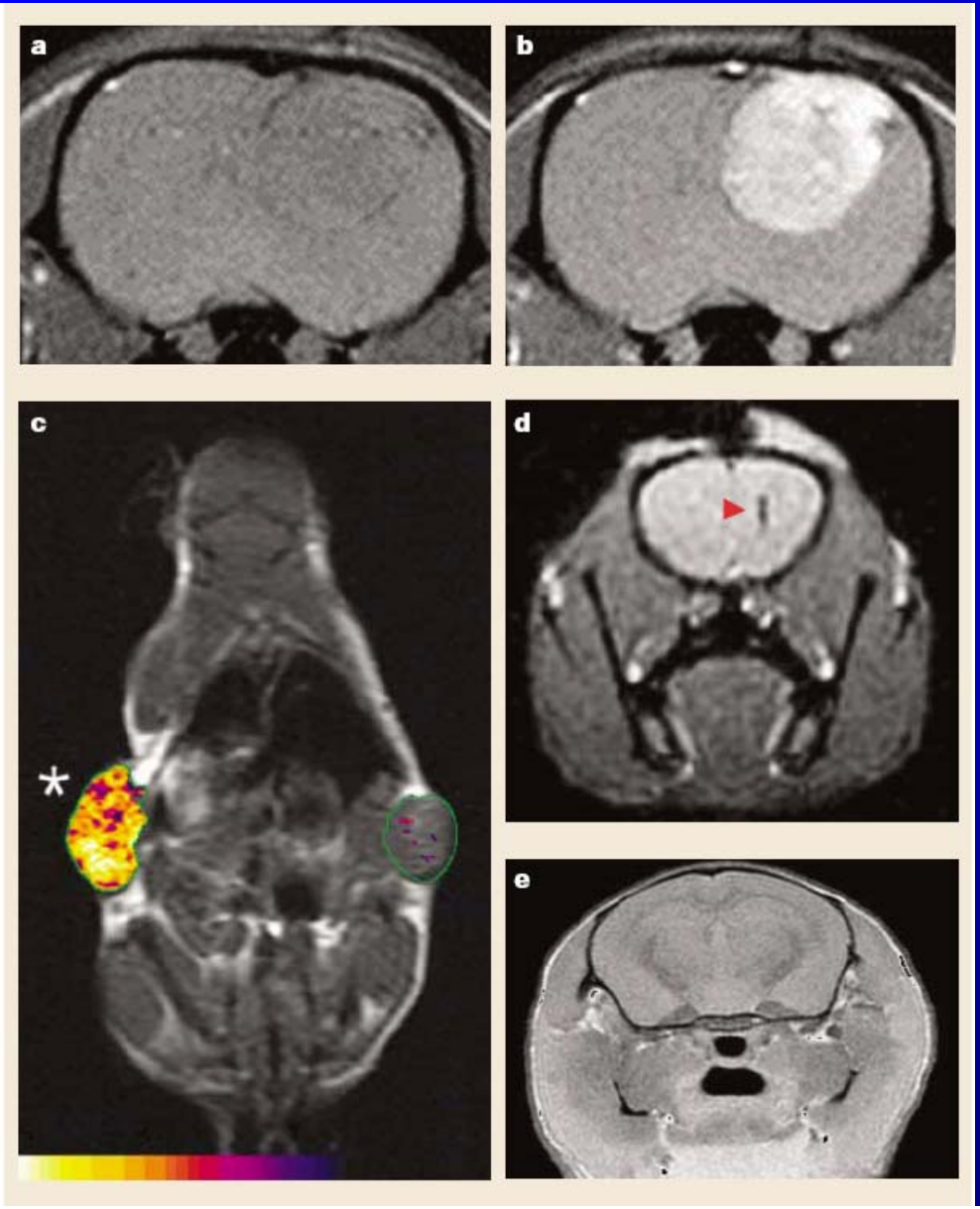
# Molecular Imaging Examples

- NIR Fluorescence imaging of gene expression (in genetically modified mouse)
  - Requires insertion of luciferase or GFP gene in conjunction with gene of interest




- Administration of exogenous agents (radiopharmaceutical) that is receptor-specific or metabolically active
  - PET scans of 18F-DesoxyGlucose (FDG) show preferential uptake by many tumors
  - Bombesin (short peptide) receptor-targeted pharmaceuticals

# Rat brain MRI scans




- MRI scans allow repeat evaluation of tumors
  - Reduces number of animals needed
  - Individuals serve as their own controls
- MRI scans depict anatomy with sub-mm detail
- Administration of exogenous agents allows receptor mapping (Bombesin analog)
- Specific agents are designed to reach targets and produce MR signal that can be superimposed on anatomic map

Scans from B. Ross, Univ. of Michigan

# Keeping Medical Technology Affordable: Diagnostic Imaging

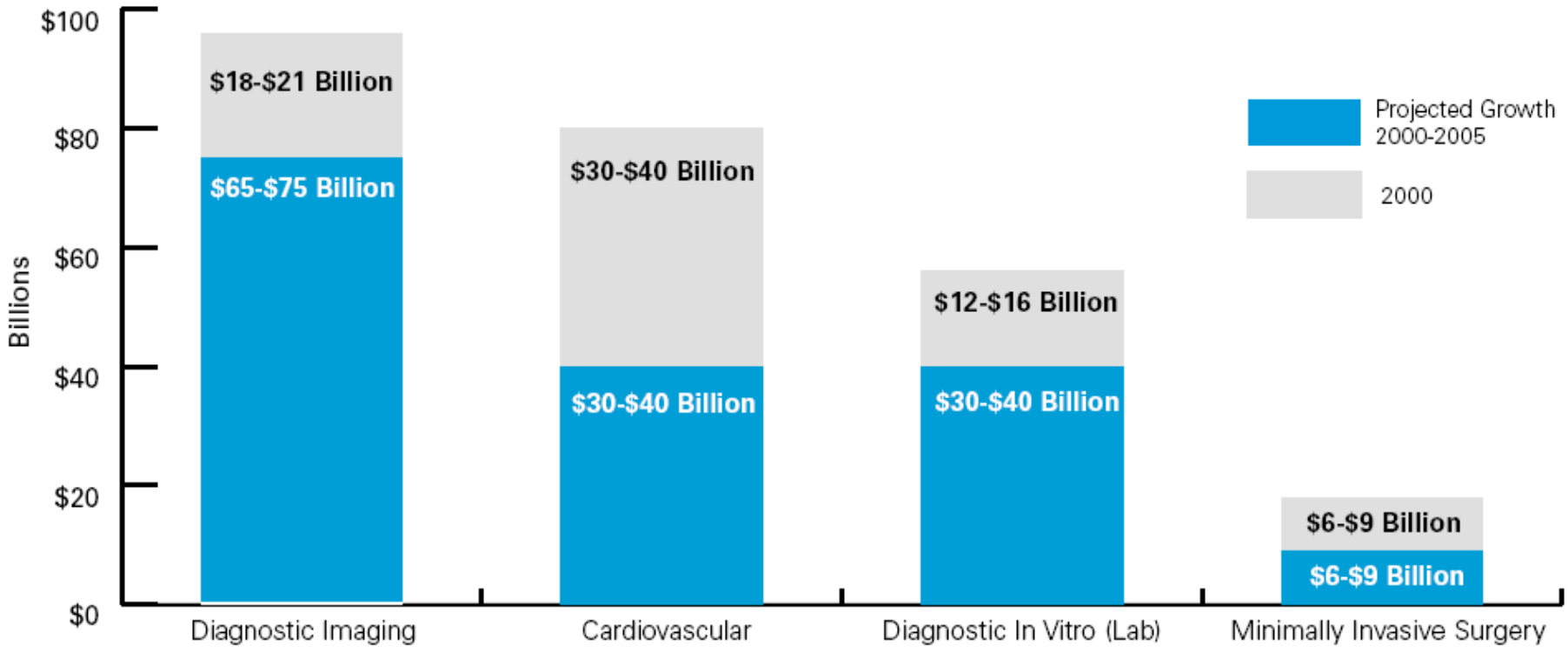
2003

**Table 1.** Size of Diagnostic Imaging Industry

| | Ultrasound | CT scanners | MRI Scanners | PET |
|---|---|---|---|---|
| Number of hospitals that have these machines (2001) | (Probably close to 100%) | 3,779 (79.9%) | 2,412 (51.0%) | 242-300** (Probably less than 10%) |
| Examples of uses | Monitor fetal development | Show whether stroke is caused by blood clot or hemorrhage | Detect brain tumors | Show stage of cancer |
| Benefits of use described above | Determines whether intervention is needed | Indicates whether it is safe to give clot-busting drugs | Replaced exploratory surgery | Determines whether surgery is indicated or cancer has spread so that only chemotherapy is indicated |
| Typical cost of machine* | $250,000 | $1.2 million | $1.35 million | $1.2 million |
| Expected annual growth rate in sales, 2000 to 2005 | 5.8% | 8.9% | 4.0% | 14.3% |

# Expenditures for Technology in 2000 and Projected Growth 2000-2005

**Chart 1.** **Expenditures for Technology in 2000 and Projected Growth 2000-2005**




Sources: Booz Allen Hamilton Analysis of Medical and Healthcare Marketplace Guide data[18]

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October 20, 2003
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BUSINESS

## GE INKS DEAL FOR AMERSHAM

Companies say the merger could lead to a new era in diagnostic medicine

ALEX TULLO

PET SOUNDS This GE Discovery ST positron emission tomography/computed tomography (PET/CT) system is capable of making 2-D and 3-D images. GE PHOTO

General Electric has signed a deal to acquire U.K.-based Amersham for $9.5 billion. The companies say combining GE's expertise in medical imaging engineering with Amersham's in diagnostic imaging chemistry and the life sciences will help spur a "new chapter" in medicine, one based on molecular diagnostics and personalized treatment.

GE Medical System's capabilities in medical imaging devices and information technology are well known. Its main target in the purchase is Amersham Health, which was responsible for 59% of Amersham's $2.4 billion in sales last year. Amersham Health makes imaging agents for procedures such as computed tomography, magnetic resonance imaging

# GE - Amersham

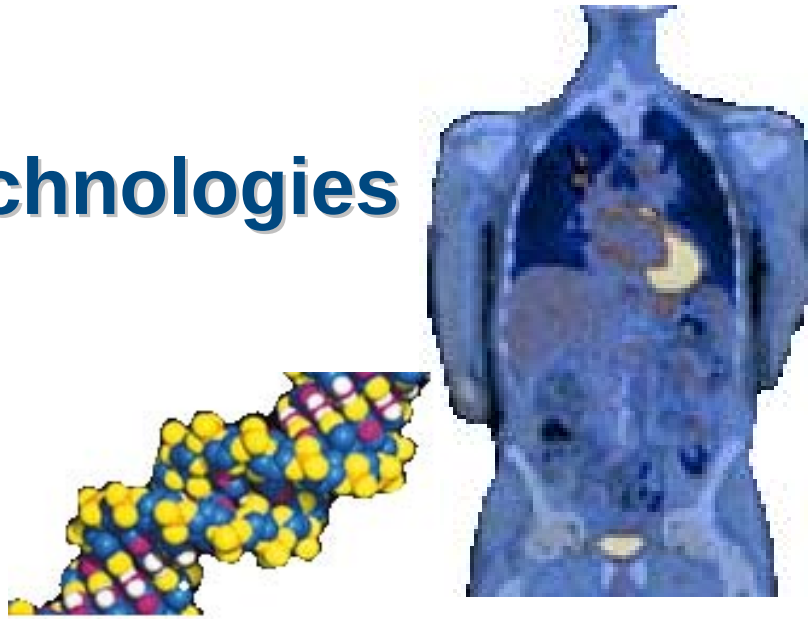
**$9.5B acquisition**

**Serves as the basis for "GE Healthcare Technologies"**

**Intended to commercialize personalized molecular medicine**

*Jun. 2002 - Madrid*

# Creating GE Healthcare Technologies



Amersham

Recommended Acquisition of Amersham

*October 2003*

# GEMS Today - *Growth Engine in Imaging, Services & IT*

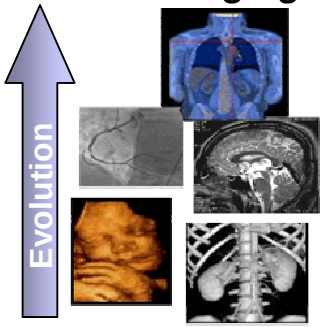
**Key GE Growth Business**
***~$10B '03 Revenue***
***~18% Op Profit Margin***
***(LTM 9/30/03)***

## Diagnostic Imaging

Focus
- *Technology Innovation*
- *Clinical Productivity*
- *Globalization*

***Sales '03E: $5.6B***
***CAGR: ~10%***

***Molecular Imaging***




***Anatomical Imaging***

## Services

Focus
- *Partnership*
- *Whole Hospital*
- *Performance ROI*

***Sales '03E: $2.7B***
***CAGR: ~10%***

***Hospital Productivity***

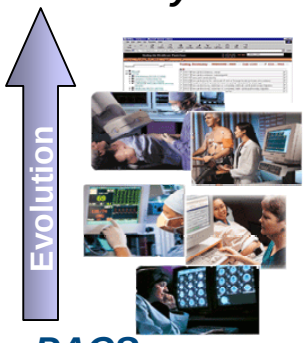
***Maintenance***

## Information Technology

Focus
- *Physician Workflow*
- *Paperless, Filmless, Wireless*

***Sales '03E: $2.0B***
***CAGR: ~30%***

***Clinical IT Systems***




***PACS***

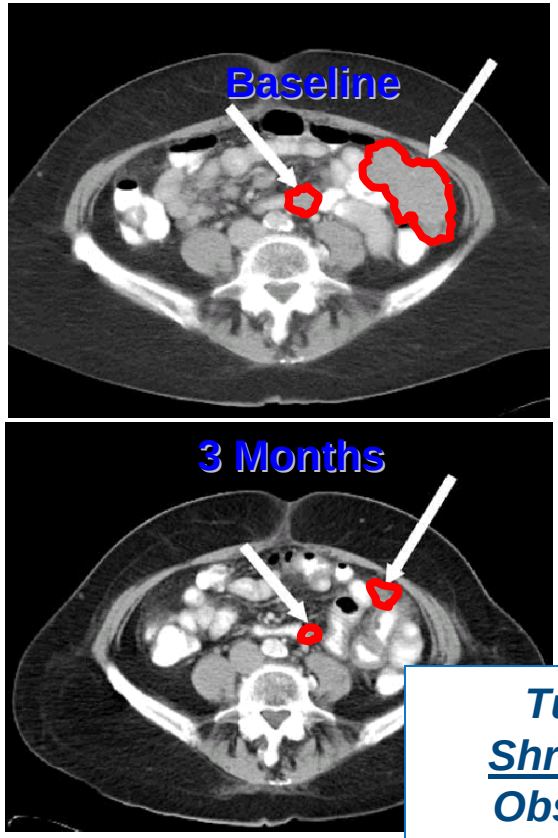
| Trends | GEMS Today |
|---|---|
| Dramatic Increase in Imaging Information | ✓✓✓ |
| Need for Provider Quality & Productivity | ✓✓✓ |
| Emergence of Molecular & Personalized Medicine | ✓ |

**E = This forward looking statement relating to the financial performance of GE has not been prepared or verified to the standards required by the UK City Code on Takeovers and Mergers, including its requirements for reports by auditors and financial advisers.**

CAGR = 2000 to 2003

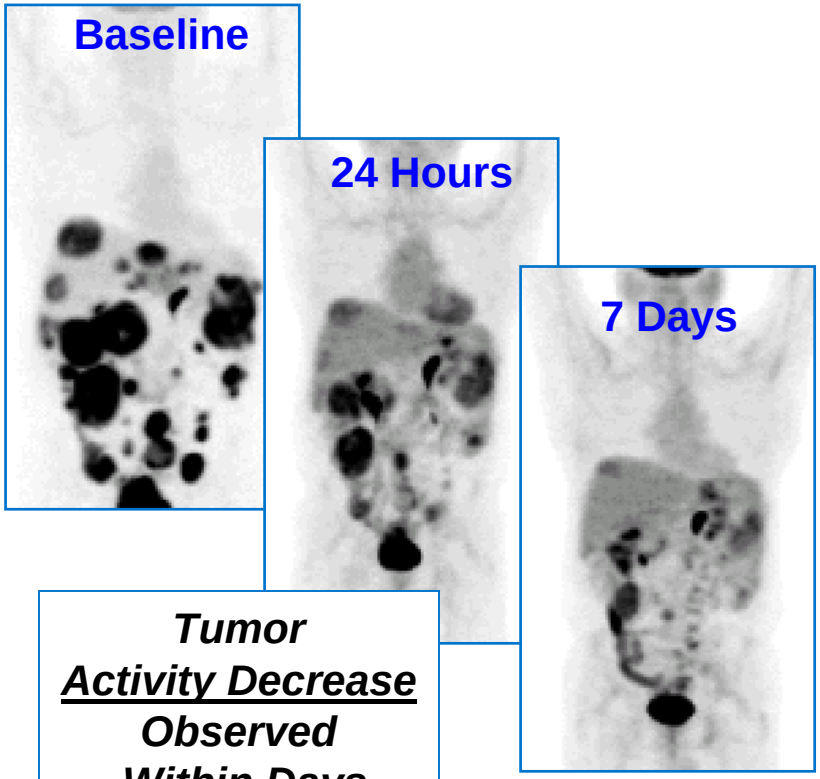
# The Potential of Molecular Imaging – Cancer Therapy

## Standard CT Anatomic Evaluation




***Tumor Shrinkage Observed After Months***

## PET –FDG Metabolic Evaluation




***Tumor Activity Decrease Observed Within Days***

**Provides the Basis for Better Patient Outcomes …**
**And Long-Term Leadership for GE**

# Tomorrow… *GE Healthcare Technologies … Fast Growing*

## Diagnostic Pharma

Focus
- *Diagnostic Productivity*
- *Targeted Imaging Agents*

***Sales '03E:*** ***$1.6B***
***CAGR:*** ***~12%***

***Complementary Platform***
Accelerate Molecular Imaging

***Exciting New Platform***
Tools for Disease Research and Drug Discovery / Development

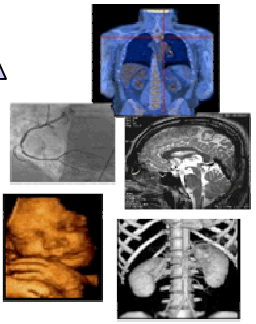
## Diagnostic Imaging

Focus
- *Technology Innovation*
- *Clinical Productivity*
- *Globalization*

***Sales '03E:*** ***$5.6B***
***CAGR:*** ***~10%***

***Molecular Imaging***

Evolution



***Anatomical Imaging***

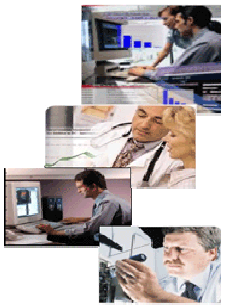
## Services

Focus
- *Partnership*
- *Whole Hospital*
- *Performance ROI*

***Sales '03E:*** ***$2.7B***
***CAGR:*** ***~6%***

***Hospital Productivity***

Evolution



***Maintenance***

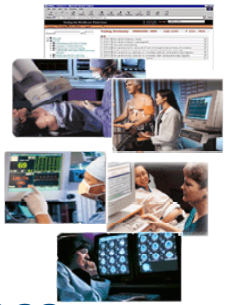
## Information Technology

Focus
- *Physician Workflow*
- *Paperless, Filmless, Wireless*

***Sales '03E:*** ***$2.0B***
***CAGR:*** ***~30%***

***Clinical IT Systems***

Evolution



***PACS***

## Life Sciences

Focus
- *More Effective Drug Dev't*
- *In-vivo Diagnostics*
- *Enabling Molecular Med.*

***Sales '03E:*** ***$1.1B***
***CAGR:*** ***~8%***

***Molecular Medicine***

Evolution

***Proteins***

***Drug Development***

E = This forward looking statement relating to the financial performance of GE has not been prepared or verified to the standards required by the UK City Code on Takeovers and Mergers, including its requirements for reports by auditors and financial advisers.

Source for Diagnostic Pharma & Life Sciences: Average Analyst Estimates

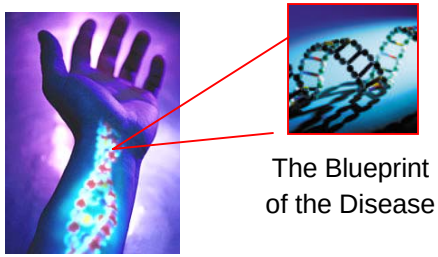
CAGR = 2000 to 2003; $/£= 1.66

# The Approach

**Discover The Basis of Disease** → **Employ High Tech Imaging** → **Diagnose & Treat**

## Biomarkers

Identified from studies of the Human Genome & Proteome

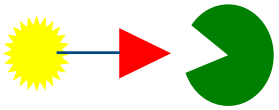


The Blueprint of the Disease

Amersham Biosciences

## Add Targeted Chemistry

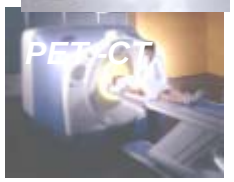
Selectively Binds to Protein / Gene and Amplifies its Signal



Amersham Health

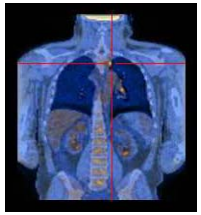
## + Imaging Technology

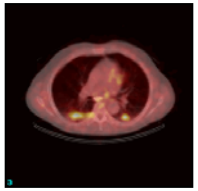
Using high-sensitivity, high-resolution imagers




GE Medical Systems

## Diagnosing In-Vivo & Monitoring Therapy Effectiveness





GE Medical Systems

Amersham

# The Molecular Medicine Opportunity

## Promise For Key Clinical Needs

### Heart Disease…#1 Killer
- > Unique Cardiac Markers
- > Pre-emptive Diagnosis

### Cancer…1 in 3 Afflicted
- > Breast, Prostate, Lung
- > Programmed Cell Death
- > Proliferation Markers

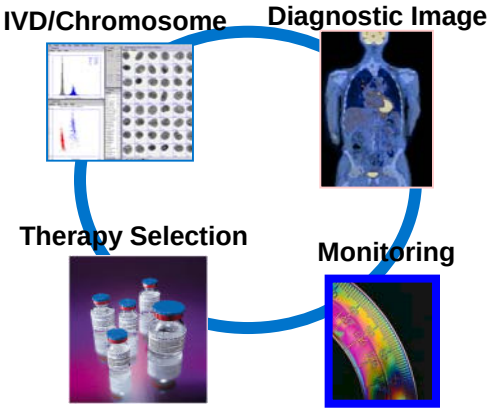
### Alzheimer's
- > Neuronal Loss
- > Cognitive Loss
- > Inflammatory Response

### Respiratory…Global Risk
- > Airway Remodeling
- > Immune Cell Response

***Lung Cancer…***

- ***Most common fatal malignancy***
- ***85% of patients die of their disease***
- ***US direct medical costs >$5 B***

**Detecting & Treating Cancer Earlier ...*More Lives Saved***



**Detection Today**

| Therapy Evaluation | | Indicative 5yr Survival% |
|---|---|---|
| Ia | Small nodule, localized | >70 |
| Ib | Larger, localized | 60 |
| IIa | Small, local lymph node | 50 |
| IIb | Moderate, local lymph node | 30-40 |
| IIIa | Moderate, extensive node | 10-30 |
| IIIb | Large, extensive node | <5-10 |
| IV | Metastasis | <2 |

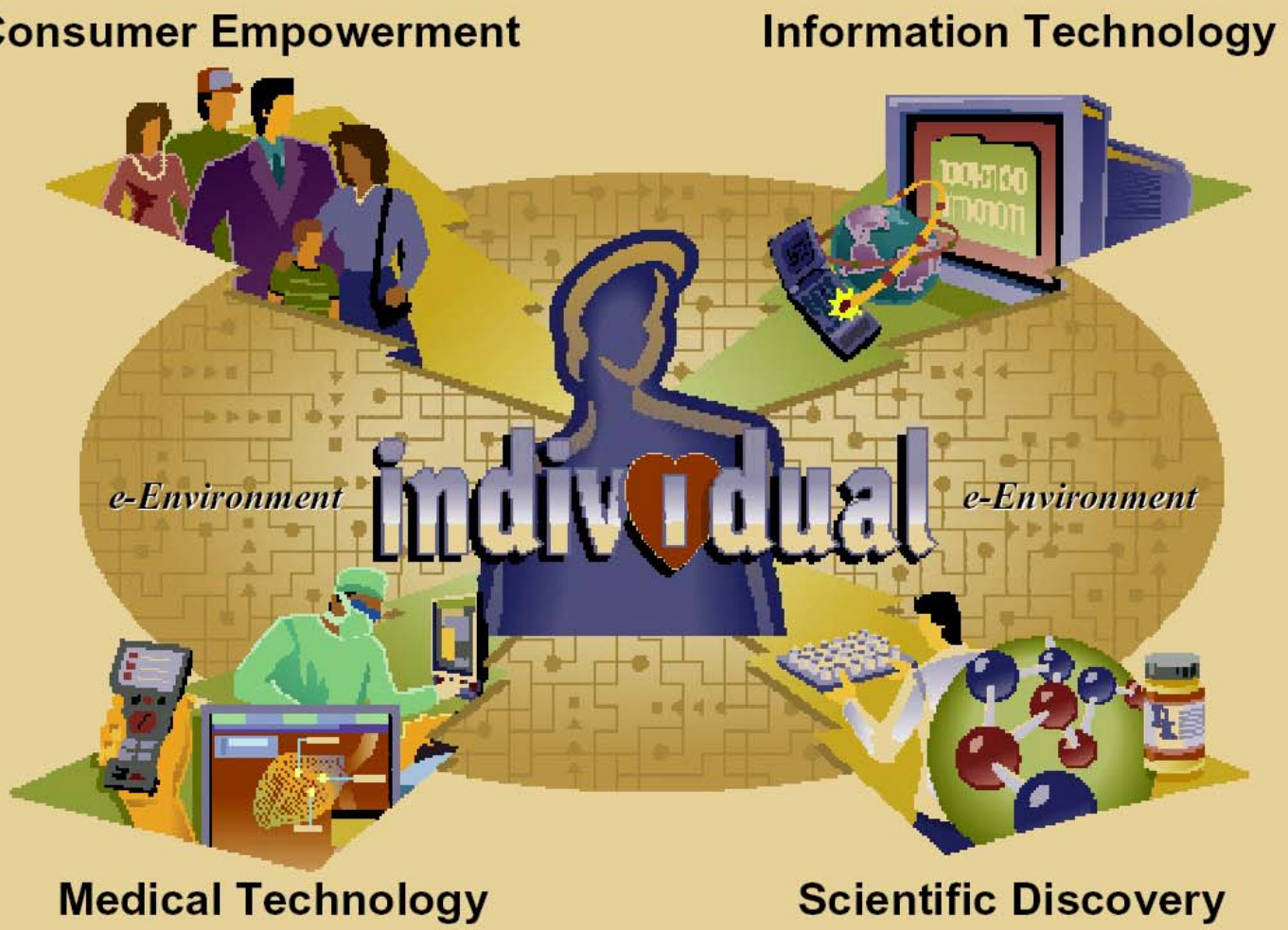
***Survival Rate Based Upon Early Detection***

# The Industrialisation of R&D

## From strategy to tactics

Dr Steve Arlington/Simon Hughes
PriceWaterhouseCoopers

# Forces for change






© PricewaterhouseCoopers 2001

# The Pharmaceutical Industry Today: Blockbusters Rule

- **Role of the blockbuster**
- **Time from lab to medicine chest: 12 years**
- **Only one of 5,000 new compounds is approved**
- **Cost of bringing a drug to market: $880,000,000**

| | Total Sales 2002 (000s) |
|---|---|
| 1. Lipitor | $5,203,982 |
| 2. Prevacid | $3,359,319 |
| 3. Prilosec | $3,103,305 |
| 4. Zocor | $3,099,092 |
| 5. Celebrex | $2,379,539 |
| 6. Zoloft | $2,355,274 |
| 7. Paxil | $2,307,032 |
| 8. Zyprexa | $2,099,951 |
| 9. Norvasc | $1,791,688 |
| 10. Nexium | $1,790,703 |

Source: Medical Economics, 2003
Pharmaceutical Manufacturer's Association, 2000

Wyeth Pharmaceuticals

# Shortcomings of the One-Size-Fits-All Approach

- Blockbusters do not account for subtle variations in genes
- Gene variations ultimately determine drug safety, efficacy, and dose

Source: Newsweek International, 2002
Journal of Gene Medicine, 2003
Cap Gemini Ernst & Young, 2002

Wyeth Pharmaceuticals

# The Era of Personalized Medicine:
## Eventual Impact on Clinicians

- **Reliance on clinical presentation will drop in favor of genetic/biologic markers**
- **Genetic tests will identify:**
  - Disease susceptibility
    - Complications
    - Response
    - Optimal drug therapy
    - Risk of adverse effects
- **Drug development will accelerate with better understanding of molecular basis of disease**

Source: BioPharm, April 2002
R&D Directions, 2002

Wyeth Pharmaceuticals

# The Era of Personalized Medicine:
## Potential Impact on Consumers/Patients

- **Advanced warning of susceptibility to disease**
  - Ability to make appropriate lifestyle changes to avoid/minimize illness
  - Monitoring and treatment can begin sooner
- **Less therapeutic trial and error**
  - Greater likelihood of choosing the best medication first
  - More-accurate dosing, based on the patient's drug metabolism
  - Fewer doctor visits?
- **Fewer adverse effects/events**
  - More targeted drugs with enhanced therapeutic effects
  - Minimal damage to healthy cells

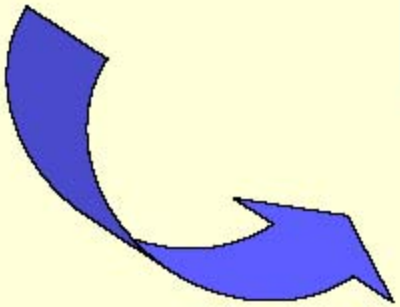
Source: InPharm.com, 2001

Wyeth Pharmaceuticals

# Predictions

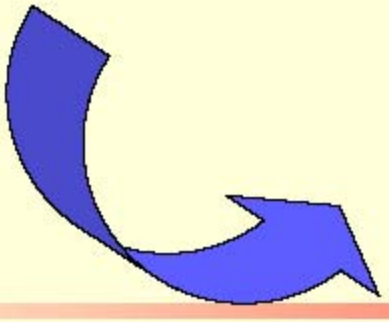
Study of known polymorphisms and metabolic enzyme families of known drug targets

Short term



Role of polymorphisms and candidate genes in drug therapy and toxicity

Medium term

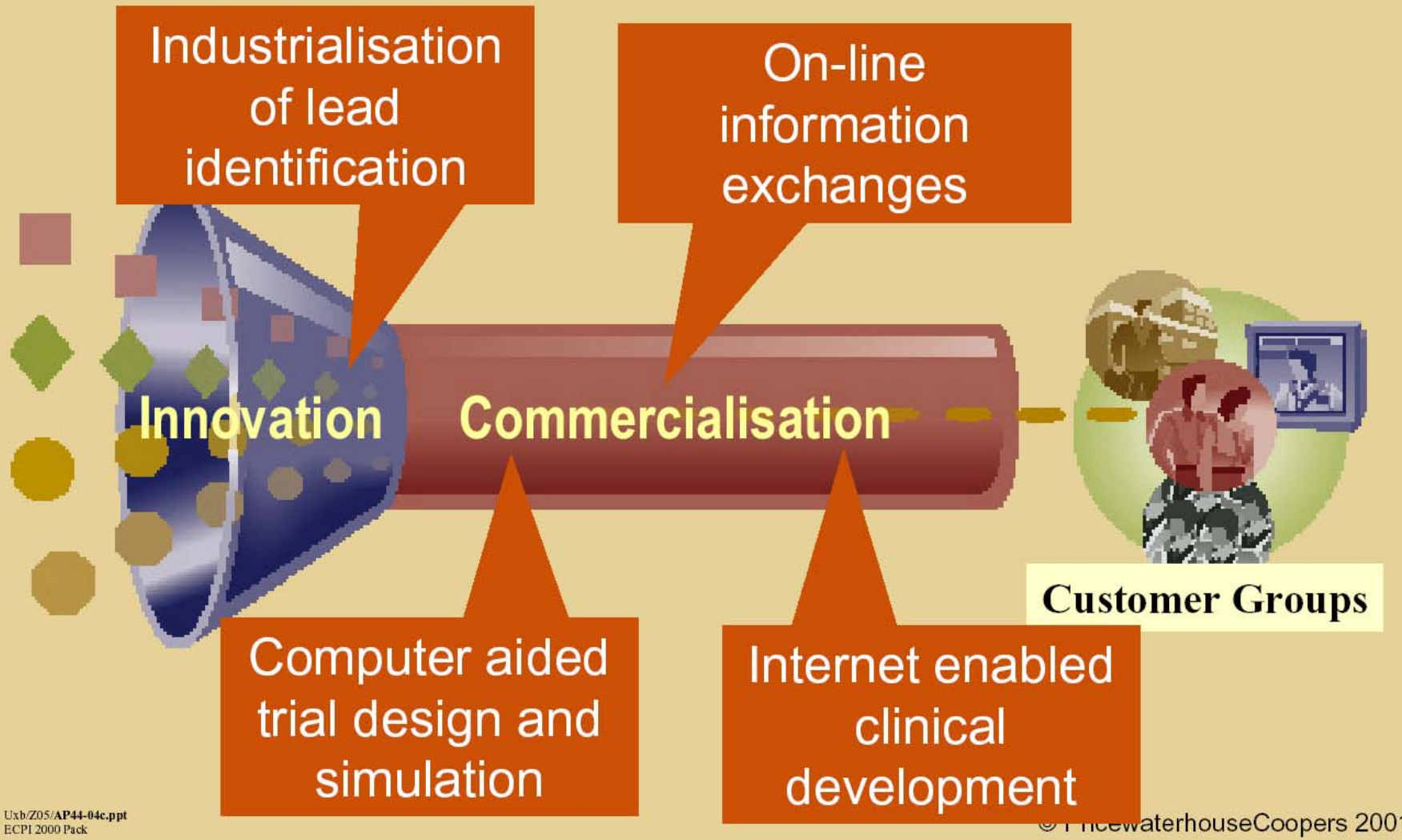


(Genuine personalized medicine) Discovery of new drug-response genes and novel molecules to target these genes

Long term

Wyeth Pharmaceuticals

# 4 key areas for change over next 3 years



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# Simulation - a rapidly emerging technology

| | Discovery | PreClinical | Clinical | Outcomes |
|---|---|---|---|---|
| Molecular Structure Activity | Products Available | Products Available | Products Available | Not appropriate |
| Subcellular | Products Available | Products Available | Products Available | Not appropriate |
| Cellular | Products Available | Products Available | Products Available | Not appropriate |
| Tissues/Organs | Products Available | Products Available | Products Available | Not appropriate |
| Whole Body (animals/humans) | Under Development | Products Available | Products Available | Products Available |
| Clinical Trials | Not appropriate | Under Development | Products Available | Products Available |
| Clinical Programs | Not appropriate | Not currently addressed | Products Available | Not currently addressed |
| Drug Portfolios | Not appropriate | Not appropriate | Under Development | Not appropriate |
| Medical Care Systems | Not appropriate | Not appropriate | Not appropriate | Not currently addressed |

- Not appropriate
- Not currently addressed
- Under Development
- Products Available



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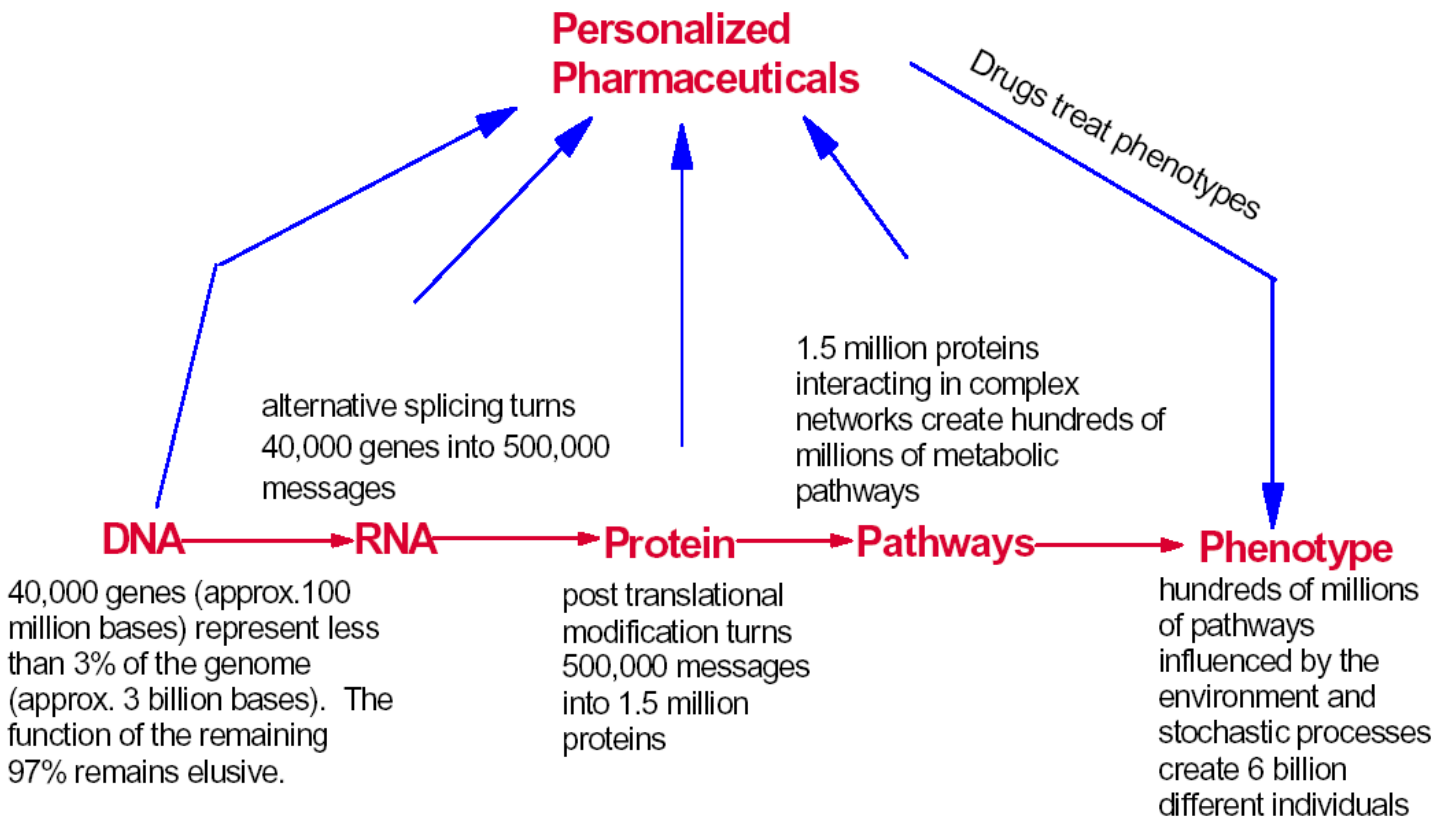
# New Sources of Value Creation

Rational drug development requires managing enormous complexity. Pharmaceutical companies are beginning to differentiate themselves on the power of their information technology platforms. IT Platform intellectual property is likely to be more valuable than content (gene sequences, metabolic pathways, protein structures, etc.)




Historically, 220 targets have generated $3trillion of value. Industrialized genome sequencing has created a target rich, lead poor environment that will slowly reverse over the next several years as in-silico biology drives the discovery of new lead compounds.

IBM Life Sciences

# MOLECULAR IMAGING IN DRUG DISCOVERY AND DEVELOPMENT

*Markus Rudin* and Ralph Weissleder‡*

Imaging sciences have grown exponentially during the past three decades, and many techniques, such as magnetic resonance imaging, nuclear tomographic imaging and X-ray computed tomography, have become indispensable in clinical use. Advances in imaging technologies and imaging probes for humans and for small animals are now extending the applications of imaging further into drug discovery and development, and have the potential to considerably accelerate the process. This review summarizes some of the recent developments in conventional and molecular imaging, and highlights their impact on drug discovery.

Nature Drug Discovery – Feb 2003 – Vol 2; 123-130.

# Imaging in Drug Discovery

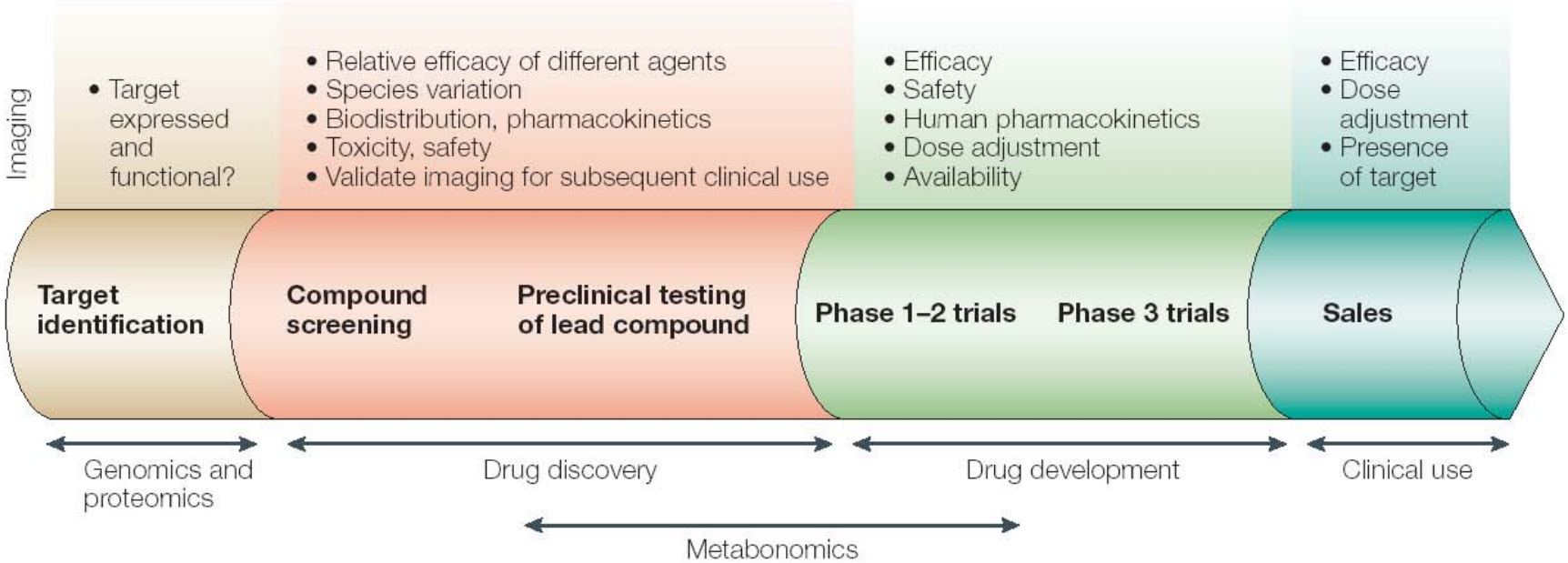



Figure 1 | **Imaging applications in the drug discovery and development process.**



Nature

# Modern biomedical research: an internally self-consistent universe with little contact with medical reality?

*David F. Horrobin*

Congruence between *in vitro* and animal models of disease and the corresponding human condition is a fundamental assumption of much biomedical research, but it is one that is rarely critically assessed. In the absence of such critical assessment, the assumption of congruence may be invalid for most models. Much more open discussion of this issue is required if biomedical research is to be clinically productive.

bear fruit in time given enough further investment. There is, of course, no way to critically evaluate these two alternatives: all we can do is hope.

A fourth possibility does deserve critical evaluation, but attracts surprisingly little open discussion. This is that biomedical science, and hence pharmaceutical science, has taken a wrong turn in its relationship to human disease. This discussion paper raises some issues which have been swept under by the pharmaceutical and medi-

Nature Drug Discovery – Vol 2; Feb 2003; 151-154

# Investigation

Problem / Question

Tools

Results

***Scientific Knowledge***

- Medical & scientific literature
- Sequences
- Taxonomies
- Experimental observations
- Images
- Clinical data
- etc.

The New England Journal of Medicine

# CYCLIN E AND SURVIVAL IN PATIENTS WITH BREAST CANCER

KHANDAN KEYOMARSI, PH.D., SUSAN L. TUCKER, PH.D., THOMAS A. BUCHHOLZ, M.D., MATTHEW CALLISTER, M.D., YE DING, PH.D., GABRIEL N. HORTOBAGYI, M.D., ISABELLE BEDROSIAN, M.D., CHRISTOPHER KNICKERBOCKER, M.S., WENDY TOYOFUKU, B.S., MICHAEL LOWE, B.S., THADDEUS W. HERLICZEK, M.D., AND SARAH S. BACUS, PH.D.

## ABSTRACT

*Background* Cyclin E, a regulator of the cell cycle, affects the behavior of breast-cancer cells. We investigated whether levels of cyclin E in the tumor correlated with survival among patients with breast cancer.

*Methods* Tumor tissue from 395 patients with breast cancer was assayed for cyclin E, cyclin D1, cyclin D3, and the HER-2/*neu* oncogene with the use of Western blot analysis. Full-length, low-molecular-weight, and total cyclin E were measured. Immunohistochemical assessments of cyclin E were also made of 256 tumors. We sought correlations between levels of these molecular markers and disease-specific and overall survival.

*Results* The median follow-up was 6.4 years. A high level of the low-molecular-weight isoforms of cyclin E,

THE prognosis in patients with newly diagnosed breast cancer is determined primarily by the presence or absence of metastases in draining axillary lymph nodes.[1] However, in approximately one third of women with breast cancer who have negative lymph nodes, the disease recurs, and about one third of patients with positive lymph nodes are free of recurrence 10 years after local–regional therapy.[2,3] These data highlight the need for more sensitive and specific prognostic indicators.

A number of biologic factors have been used to refine risk categories in breast cancer. We have focused on the role of cyclin E in determining the virulence and metastatic potential of tumor cells.[4-8] In normal dividing cells, cyclin E regulates the transition from

N Engl J Med, Vol. 347, No. 20, **1566-1575** November 14, 2002

overall survival. Total cyclin E levels and the level of low-molecular-weight forms of cyclin E as measured by Western blotting but not by immunohistochemical analysis proved to be strongly associated with survival among patients with breast cancer.

## METHODS

### Tissue Samples and Study Patients

Tumor tissue was obtained from a centralized reference laboratory (Quantitative Diagnostic Laboratories). A total of 430 samples consisting of a minimum of 100 mg of breast-cancer tissue were available. Each patient had received a diagnosis of breast cancer between 1990 and 1995 at 1 of 12 hospitals in the Chicago area. Specimens were shipped to the Wadsworth Center research laboratories for Western blot analysis. This study was approved by the institutional review board of the Wadsworth Center.

The reference laboratory also provided base-line pathological and demographic data (obtained from the individual hospitals), as well as the steroid-receptor status, the DNA index, and the proliferation index (as described below). Information concerning clinical staging and survival was obtained from the tumor registries of each hospital. Patients whose death was clearly documented to be due to breast cancer were considered to have died of breast cancer; other deaths were considered not to have been caused by breast cancer. The data presented here are from 395 patients for whom data on outcome were available.

### Hormone-Receptor, DNA, and Proliferation Assays

The procedures for the hormone-receptor and proliferation assays

values obtained from normal tissues. Fo
pression was scored as high if the value w
than the highest value for normal breast
normal tissue samples were examined.
weight and total cyclin E, specimens wi
were classified as high. All normal-cell
cyclin D3 and HER-2/*neu*. On Western
ues for these proteins clustered into thre
as negative, low level, or high level. Den
were used to standardize for equal protei
ples assayed. The Western blot analysis an
tioned biologic markers were performed
unaware of the patients' outcomes.

### Immunohistochemical Studies

A subgroup of 256 samples of tumo
immunohistochemical analysis with the
polyclonal antibody to cyclin E.[5] We us
corresponding to amino acids 381 to 4
tigen in the affinity purification. This po
the same epitope as monoclonal HE12 a
Western blots to detect both the full-le
weight isoforms of cyclin E.[5,7,8] Snap-froz
in Optimal Cutting Temperature compo
tervals, placed on coated slides, fixed, and
viously described.[22-24] At least two represe
each patient with breast cancer were ex
from 0 to 10 on the basis of the intensi
centage of tumor cells stained. In 15 case
were tested along with tumor tissue. Sc
controls ranged from 0 to 2. The tum
ignated as having eithe

RAND

www.rand.org/publications/MR/MR954

# Handbook of Human Tissue Sources: A National Resource of Human Tissue Samples

**Elisa Eiseman**
**Susanne B. Haga**

Reviewer's comments

## Contents

Preface
Figures
Tables
Summary
Acknowledgments
Abbreviations

Chapter One: Introduction

Historical Perspective
Types of Tissue/Organ Banks
Uses of Tissue/Organ Banks for Biom
An Inventory of Tissue Sources in the

Chapter Two: Methods

Definitions

Appendix A

## QUANTITY OF STORED TISSUE SAMPLES IN THE UNITED STATES

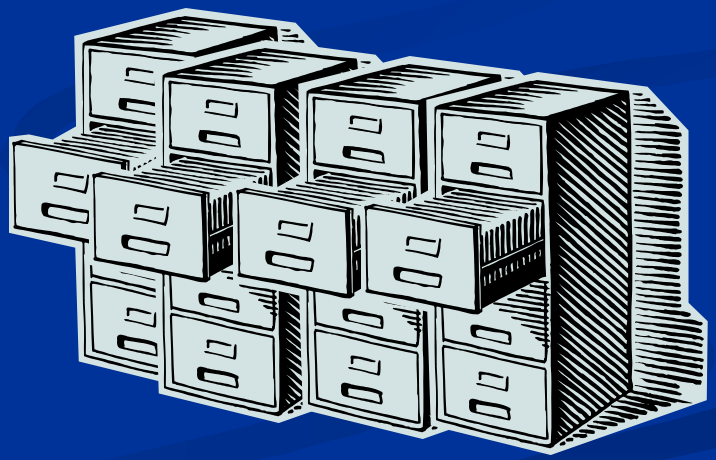
| Type of Repository/Institution | Number of Cases | Number of Specimens | Cases/Year |
|---|---|---|---|
| **Large Tissue Banks, Repositories, and Core Facilities** | | | |
| AFIP DNA Specimen Repository | | >2.8 million | 10,000 |
| AFIP National Pathology Repository | >2.5 million | >92 million | 50,000 |
| Brain and Tissue Banks for Developmental Disorders | 2,507 | 34,943 | |
| Cancer Tissue Bank—VAMC Minneapolis | | >2,000 | |
| **Newborn Screening Laboratories** | | | |
| 50 states, District of Columbia, Puerto Rico, and Virgin Islands | >13.5 million | >13.5 million | <10,000 to >500,000 |
| **Forensic DNA Banks** | | | |
| 48 states with Forensic DNA Banks | 1.4 million | 1.4 million | |

# Image Repositories

- Open access to image archives is rare
- Image archives are not organized for research queries
- Image archives are not linked to other forms of biological data
- In general, there is no equivalent of a "specimen repository" for images
- This is a major problem for imaging research

# Silo of Data

=



# The Problem

- Most biological knowledge is stored in databases
- Creation, expansion, and integration of these databases has become central to the advancement of biology and medicine
- Many image databases are isolated "silos"
- Medical imaging is unique in that there are few publicly accessible databases, links to mainstream biological knowledge collections are absent, and there are few (software) tools available that allow you to use them

# (protein/nucleic acid) Sequence Data and Molecular Biology Journals

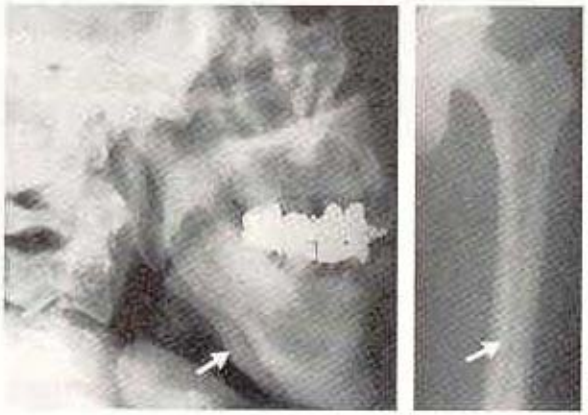
- Prior to publication, peer-reviewed molecular biology journals require that the authors deposit their data sets in a publicly-accessible archive and obtain an Accession Number.
- The Accession Number is included with the publication (both printed and electronic form)
- In many cases, the software tools used to analyze the sequence data are in the public domain

# Why are imaging databases important?

- Images contain the phenotype
- In other fields (e.g., astronomy, geoscience, neuroscience, …), the integration of image (and other) databases has had a revolutionary effect
  - Coalescence of the scientific community
  - Open the field to rapid technological advancement
  - Possible to address questions that could not otherwise be answered (e.g., trans-species, multiscale, ad hoc group collaboration)

# This Week in the Journal

May 16, 2002



## High Bone Density Due to an *LRP5* Mutation

Osteoporosis can be caused by a loss-of-function mutation in the gene for low-density lipoprotein receptor–related protein 5 (*LRP5*). In this study, the authors, reasoning that a gain-of-function mutation in the same gene might be associated with high bone density, performed biochemical and genetic analyses of a kindred with high bone density, a prominent mandible, and torus palatinus. Genetic analysis revealed an *LRP5* mutation, the substitution of valine for glycine at codon 171, that segregated with the clinical findings. In vitro studies demonstrated that the defect in LRP5 resulted in changes in signaling events with other molecules that normally interact with this receptor-related protein, resulting in increased bone density.

*The findings suggest that molecules that interact with* LRP5 *may provide targets for the treatment of osteoporosis.*

The New England
Journal of Medicine

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VOLUME 346 MAY 16, 2002 NUMBER 20

# HIGH BONE DENSITY DUE TO A MUTATION IN LDL-RECEPTOR–RELATED PROTEIN 5

LYNN M. BOYDEN, PH.D., JUNHAO MAO, PH.D., JOSEPH BELSKY, M.D., LYLE MITZNER, M.D., ANITA FARHI, R.N., MARY A. MITNICK, PH.D., DIANQING WU, PH.D., KARL INSOGNA, M.D., AND RICHARD P. LIFTON, M.D., PH.D.

## ABSTRACT

*Background* Osteoporosis is a major public health problem of largely unknown cause. Loss-of-function mutations in the gene for low-density lipoprotein receptor–related protein 5 (*LRP5*), which acts in the Wnt signaling pathway, have been shown to cause osteoporosis–pseudoglioma.

*Methods* We performed genetic and biochemical analyses of a kindred with an autosomal dominant syndrome characterized by high bone density, a wide and deep mandible, and torus palatinus.

OSTEOPOROSIS is a major public health problem, and its prevalence is increasing.[1-3] In the United States, nearly 1 million fractures occur annually in people over the age of 65 years, the majority of which are due to osteoporosis.[1,4] Osteoporotic fractures are associated with substantial morbidity, and the estimated rate of death in the first year after a hip fracture is 25 to 30 percent.[5,6]

Bone mass, a major determinant of the risk of os-

gle propeller of the low-density lipoprotein (LDL) receptor in humans, mice, rats, pigs, hamsters, and rabbits. Moreover, glycine is also found at this position in the first propeller of the *Drosophila melanogaster* LDL-receptor–related protein homologue, *arrow*. In addition, glycine is present at this position in a wide range of other YWTD propellers, including those in other LDL-receptor–related proteins, as well as those in the epidermal growth factor precursor, the very-low-density lipoprotein receptor, and the vitellogenin receptor in fruit flies and mosquitos (protein sequences are available at http://www.ncbi.nlm.nih.gov/entrez). The evolutionary conservation of this glycine residue is strong evidence of the functional importance of its mutation in our kindred.

**Protein sequences are available at**

**ENTREZ**

### Molecular Studies

If this mutation indeed causes gain of LRP5 function and increased Wnt signaling, downstream target genes in the Wnt signaling pathway should show increased expression in vivo. A direct transcriptional target of Wnt signaling is the extracellular matrix protein fibronectin.[31] Fibronectin levels were markedly elevated in the affected members of our kindred, with

es an autosomal dominant disorder characterized by high bone density, torus palatinus, and a wide, deep mandible.

Our in vitro and in vivo studies show that the $LRP5_{V171}$ mutation increases Wnt signaling. The mutation impairs antagonism of Wnt signaling by Dkk-1 in vitro, and the levels of fibronectin, a downstream target of Wnt signaling, are increased in vivo in patients with this mutation. These findings indicate that unopposed Wnt signaling due to loss of action of a

It is striking that the same mutation is associated with nonsyndromic high bone mass in one family and syndromic high bone mass in the other. These findings suggest that alleles of other genes or environmental factors influence phenotypic manifestations of the mutation and that other phenotypes in kindreds with autosomal dominant high bone mass may also arise from

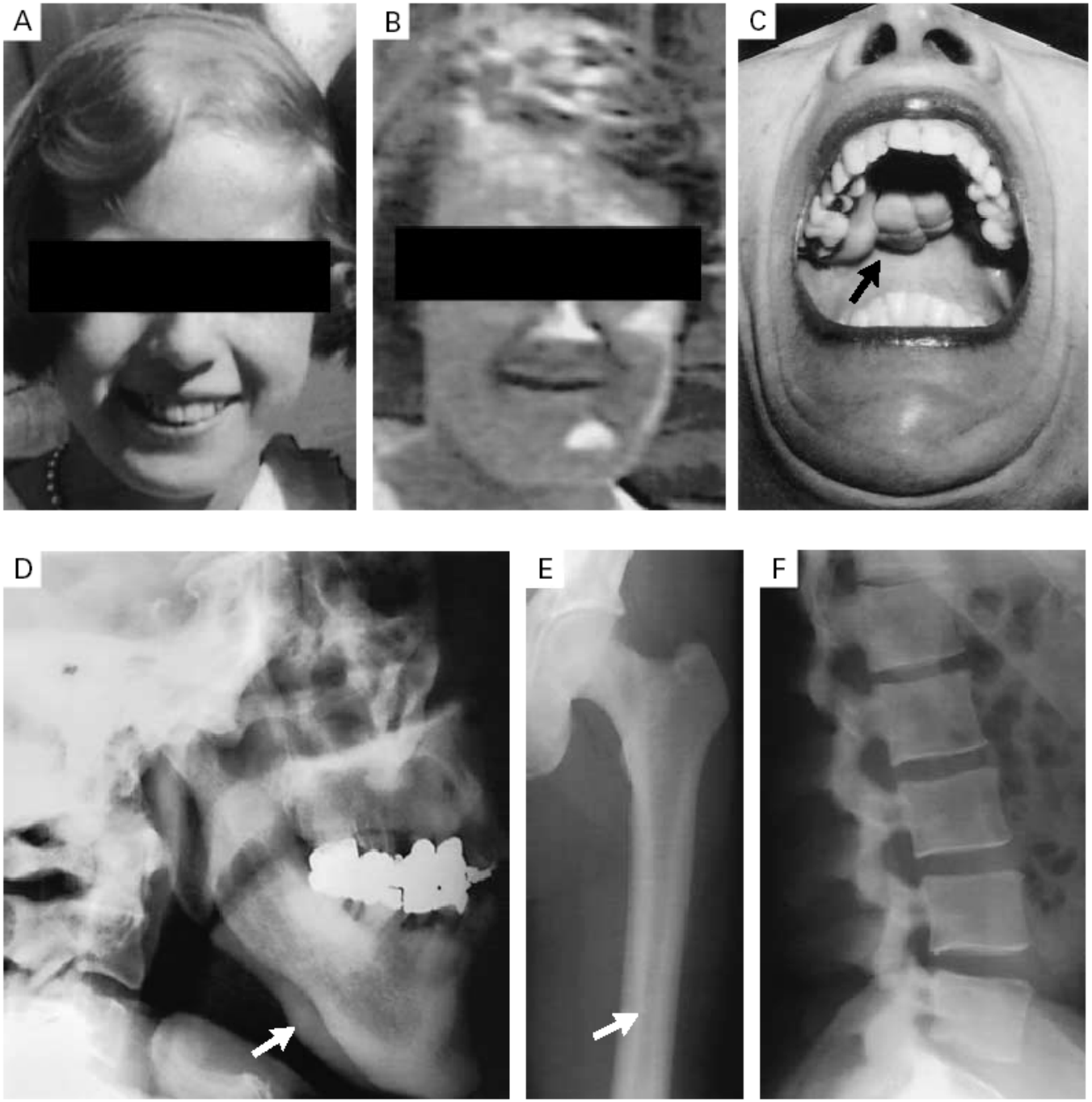


**Figure 1.** Clinical and Radiographic Features of Affected Members of the Kindred.

Figure 1

Page 1515

Entrez-PubMed - Microsoft Internet Explorer

File Edit View Favorites Tools Help

Back Search Favorites Media

Address http://www.ncbi.nlm.nih.gov/entrez/query.fcgi Go Links

NCBI

PubMed

National Library of Medicine NLM

PubMed Nucleotide Protein Genome Structure PopSet Taxonomy OMIM Books

Search PubMed for Go Clear

Limits Preview/Index History Clipboard Details

About Entrez

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Tutorial
New/Noteworthy
E-Utilities

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PubMed, a service of the National Library of Medicine, provides access to over 12 million MEDLINE citations back to the mid-1960's and additional life science journals. PubMed includes links to many sites providing full text articles and other related resources.

**Bookshelf Additions**

**Developmental Biology, 6th ed.** by SF Gilbert

**Surgical Treatments - Evidence Based and Problem-Oriented** edited by RA Holzheimer & JA Mannick

and NCBI's **Genes and Disease.**

These three resources are now available for interactive searches on Bookshelf.

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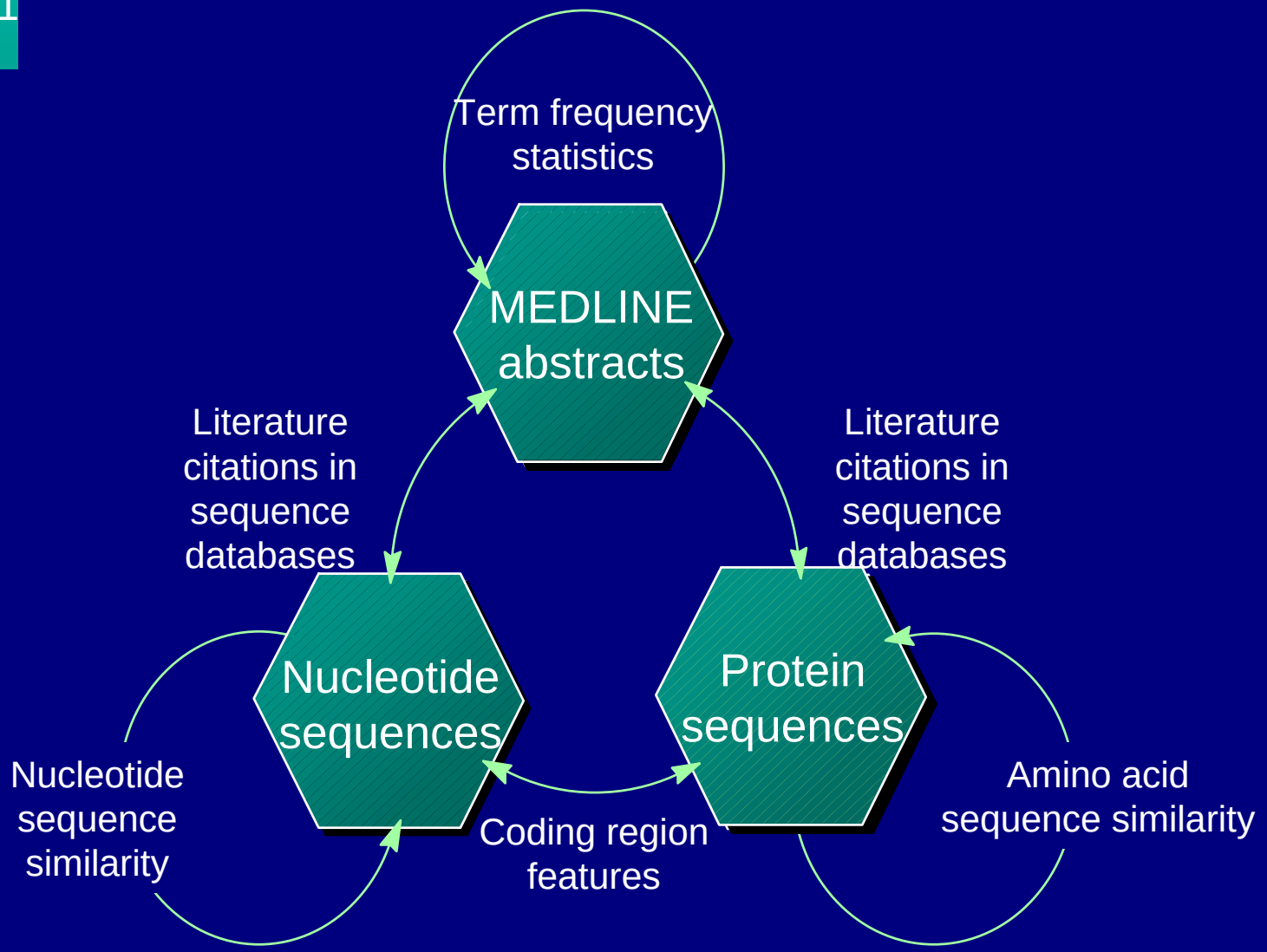
LinkOut is a jumping-off point from PubMed citations to relevant resources on the web, such as, full-text articles, library holdings, commentaries, author biographies, practice guidelines, consumer health information, and research tools. Example LinkOut resources are available.

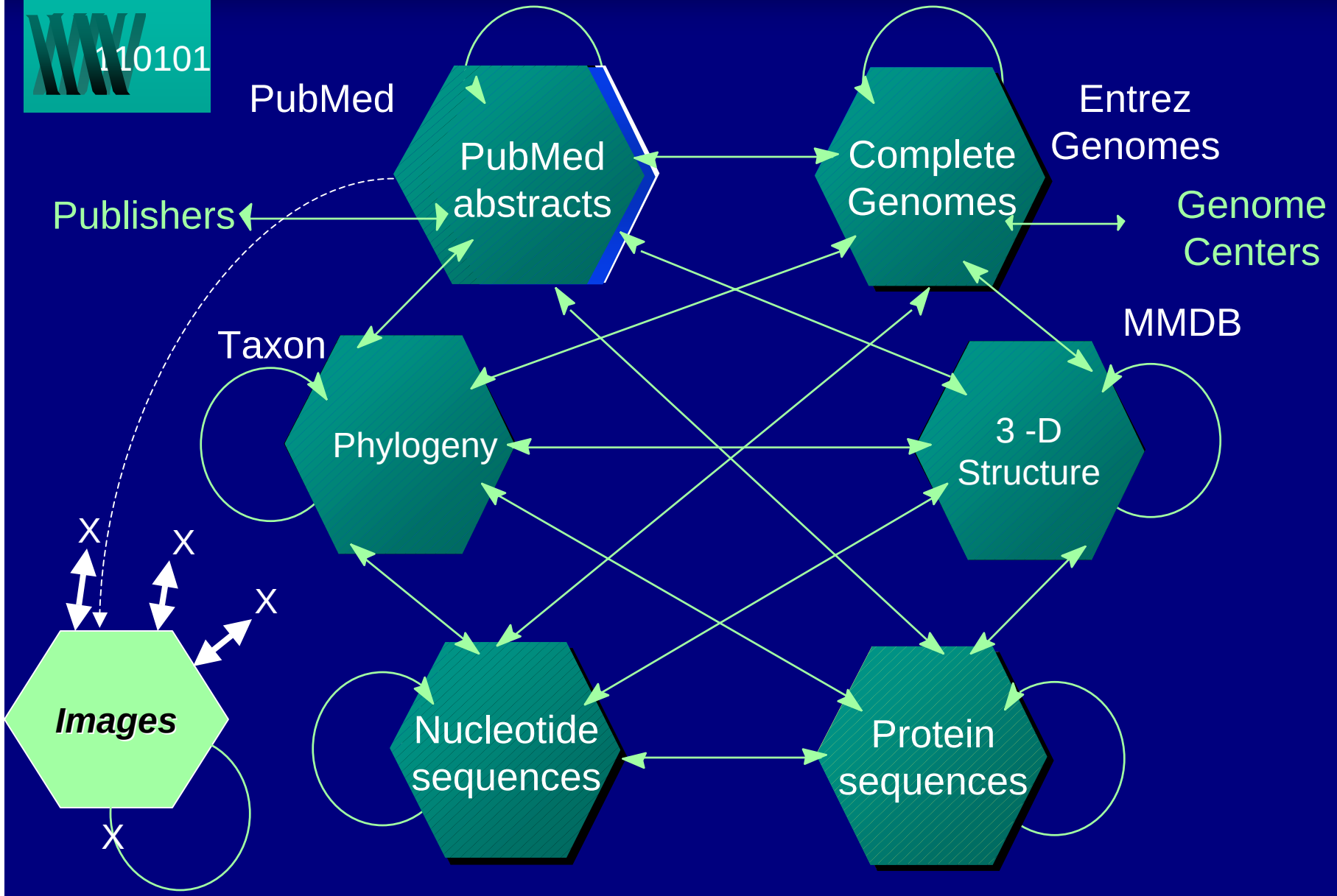
Done Internet

Entrez PubMed

# *Entrez*: Pathway to Discovery

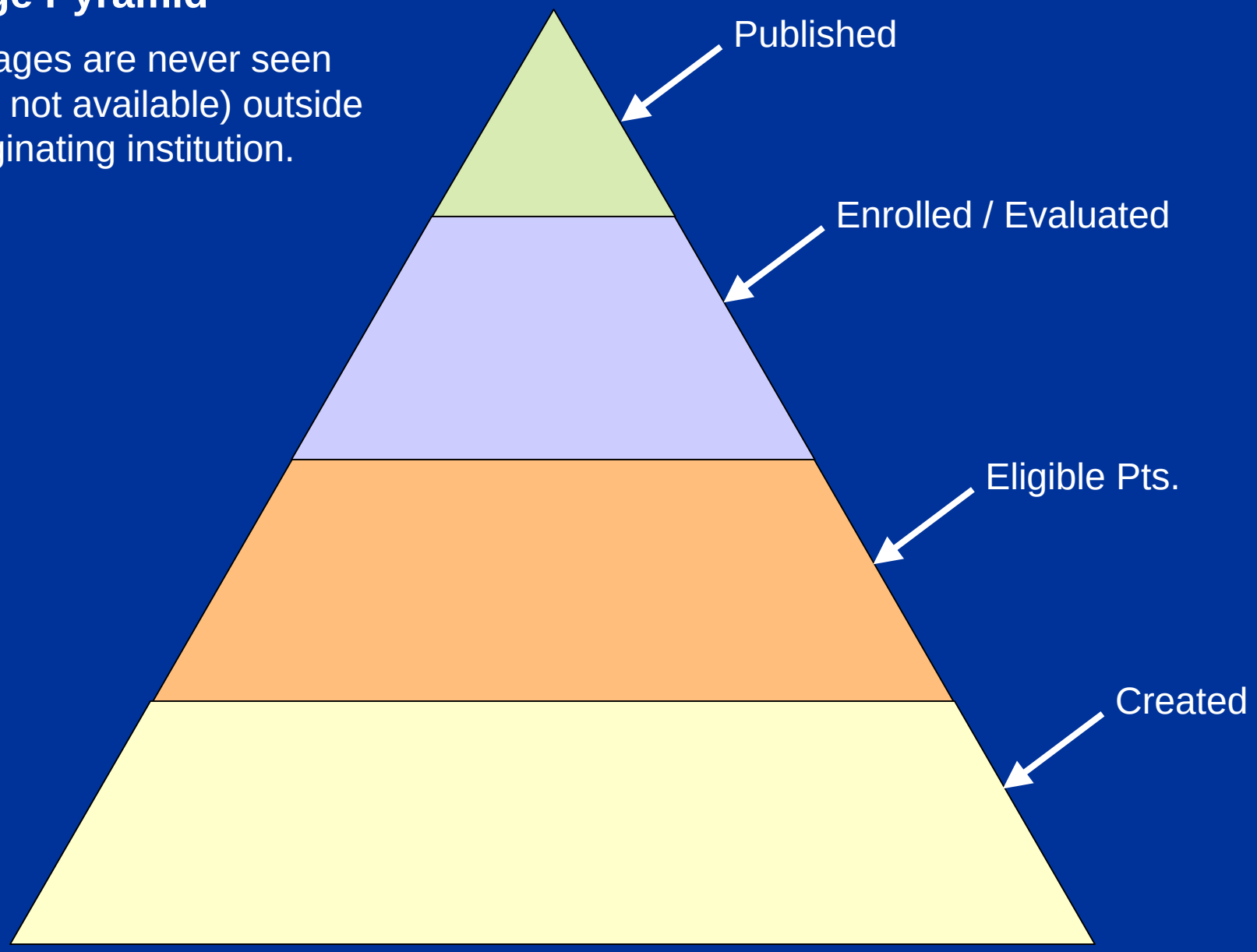


# Entrez Increases Discovery Space



## Image Pyramid

Most images are never seen (and are not available) outside their originating institution.



# Current Informatics Status

- Genomics / Proteomics
  - Public repositories are common
  - Links to primary data are integrated into publications
  - Indexing and retrieval are "free", open and available to anyone
  - There are open source tools to use biological knowledge resources and apply them in investigations
- Imaging
  - Few public repositories
  - Few links to primary data in publications
  - Primary data is rarely available, even temporarily
  - Few open source tools that operate on images in conjunction with other forms of biological knowledge/databases

E-BioSci / ORIEL
Open Meeting 28/4/03

National e-Science
Centre, Edinburgh

# The BioImage Database

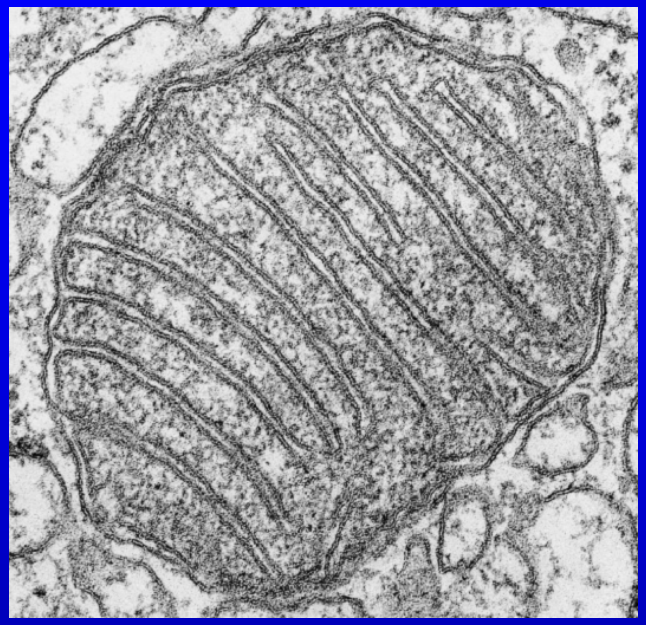
David M. Shotton

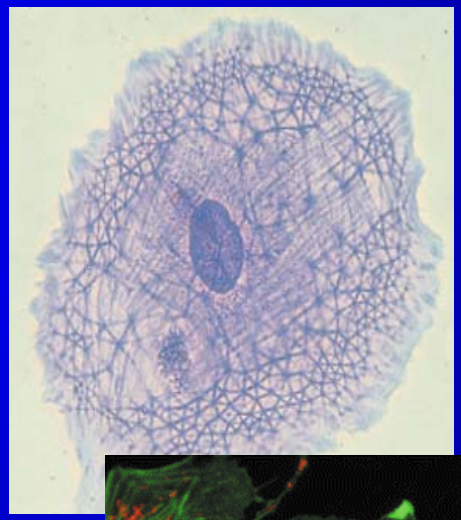
Image BioInformatics Laboratory
Department of Zoology
University of Oxford, UK

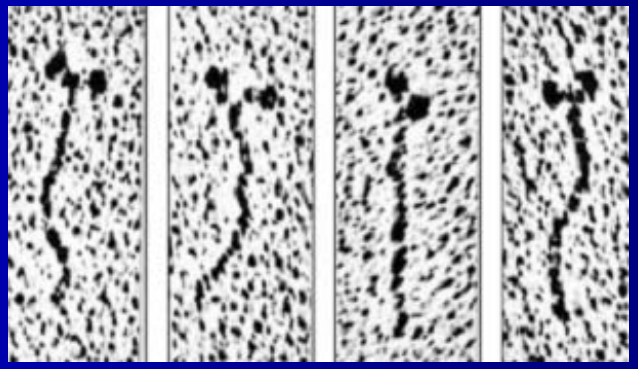
e-mail: david.shotton@zoo.ox.ac.uk

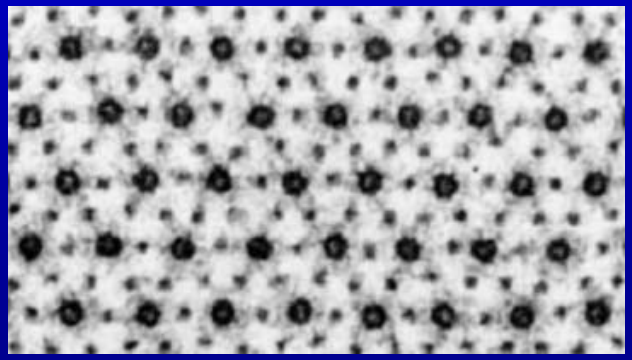
© David Shotton 2003

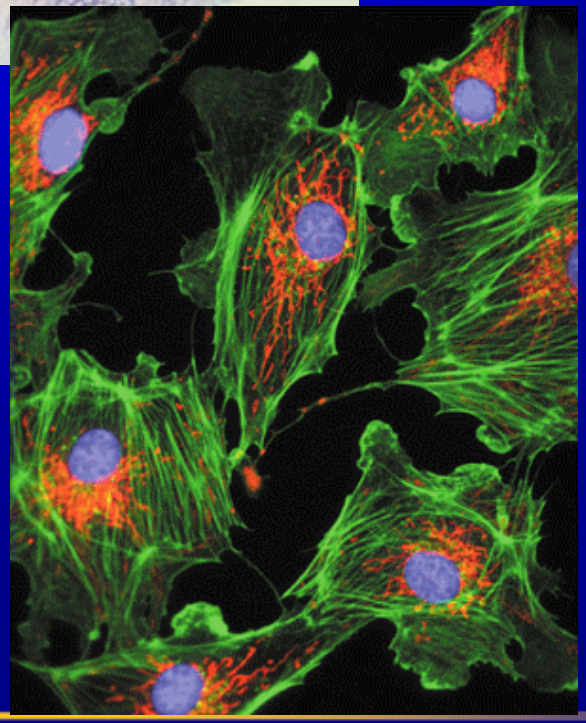
# Images in Biology: static and dynamic

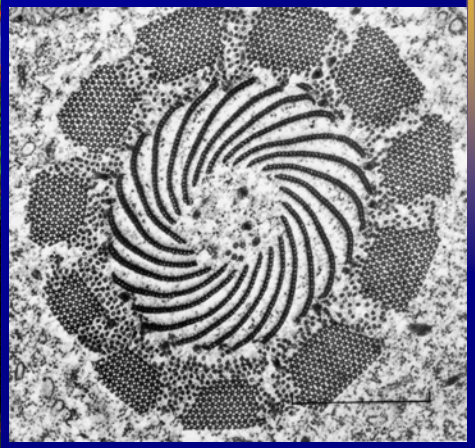












bioimage

# BioImage development within ORIEL

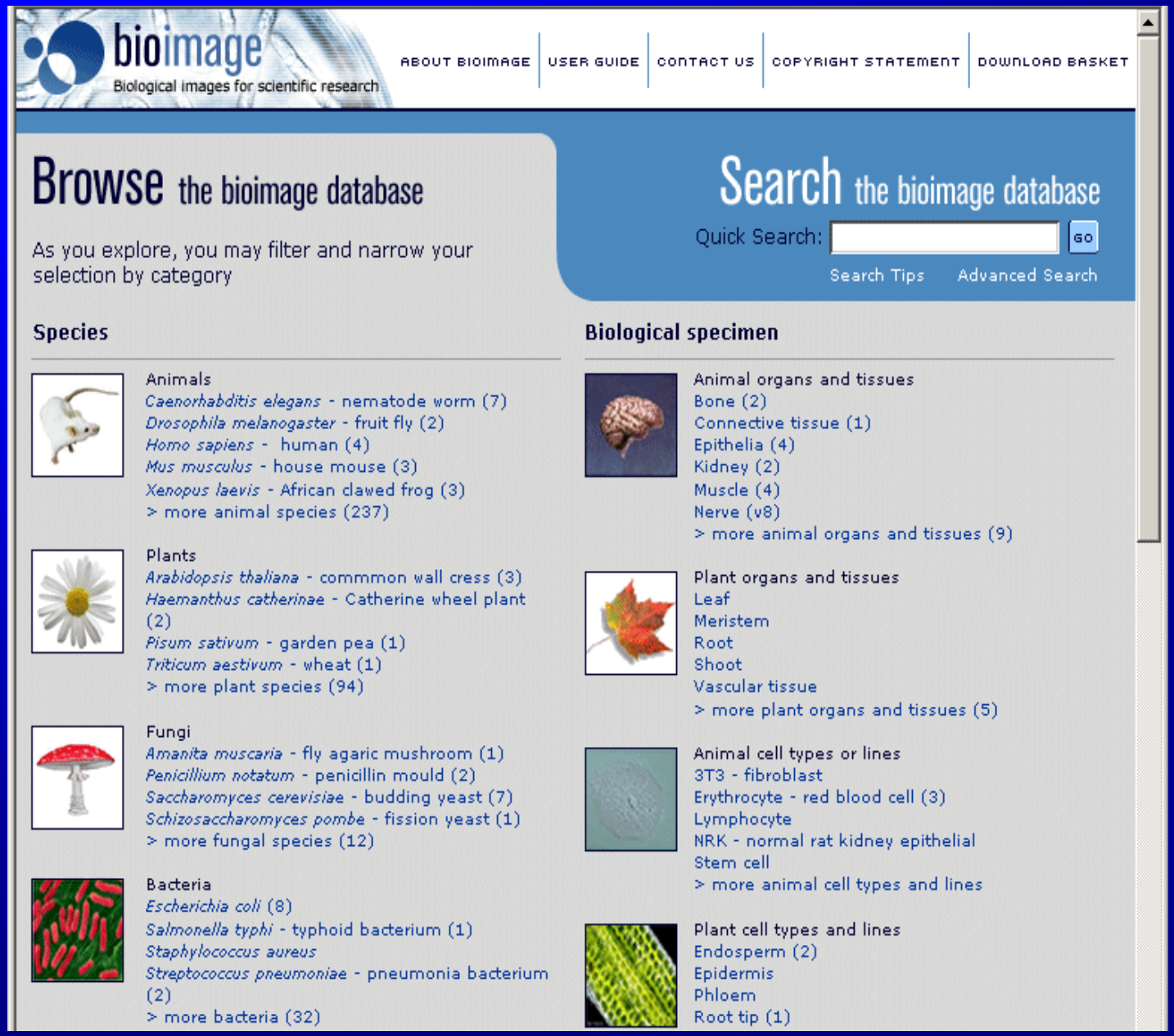
The aims of the BioImage Database Project within ORIEL are:

- To provide a searchable database of high-quality scientific images of biological specimens, with detailed supporting metadata on
  - the biological specimen
  - the experimental procedure
  - details of image formation and subsequent digital processing
  - the people involved
  - the metadata curation and provenance
- To integrate such multi-dimensional digital image data with other life science resources in the ‘factual’ and literature databases, accessible from the E-BioSci platform

# The BioImage home page

bioimage.org

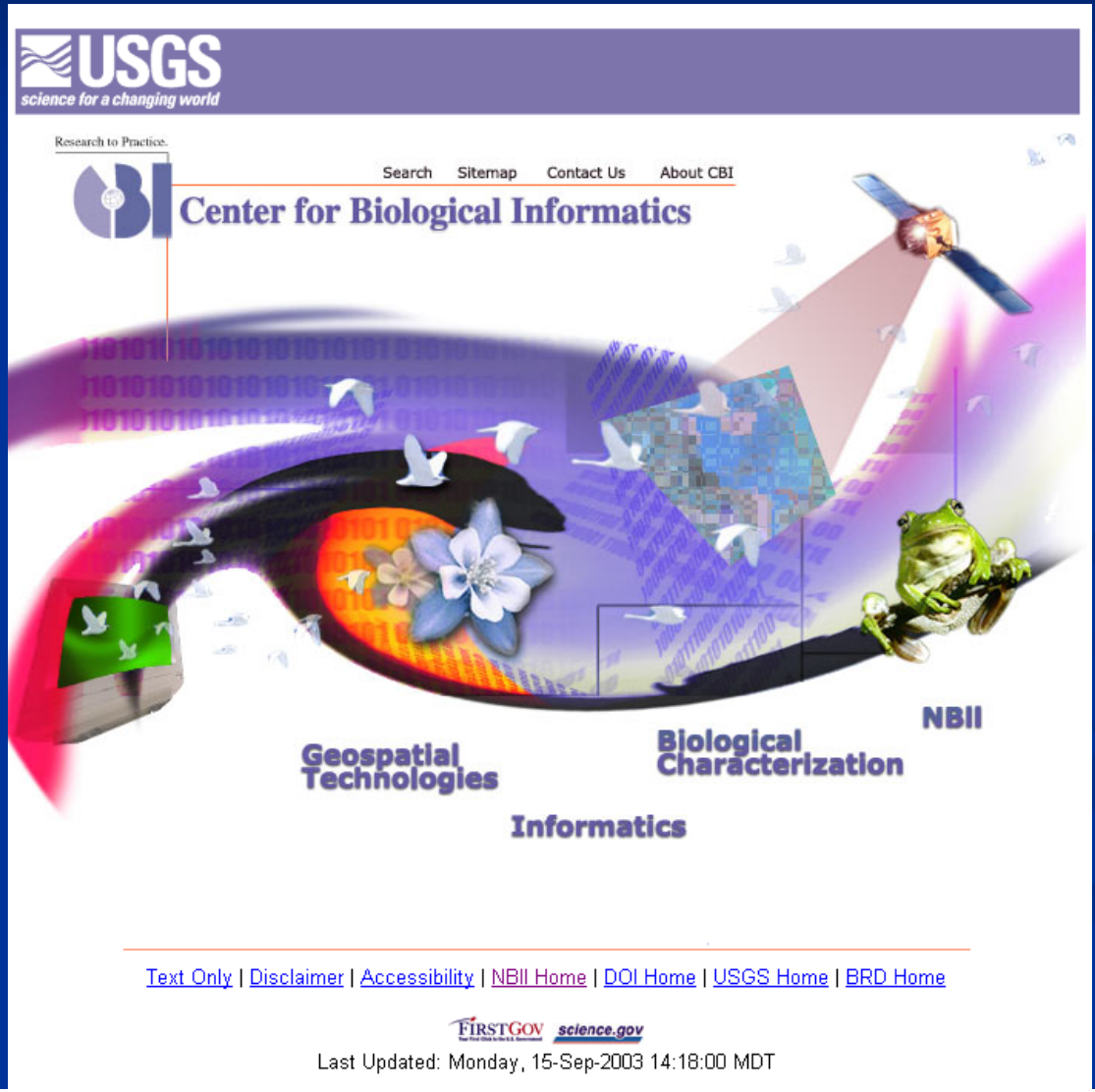
Note the alternative browse - search arrangement




bioimage

# National Biological Information Infrastructure (www.nbii.gov)

# USGS Center for Biological Informatics (biology.usgs.gov/cbi/)



what's new?
search
NSDI
metadata
clearinghouse
standards
framework
stakeholders
fgdc organization
CAP/funding
publications
data
calendar
Geospatial One-Stop
International
I-Teams

# Federal Geographic Data Committee

The Federal Geographic Data Committee is a 19 member interagency committee composed of representatives from the Executive Office of the President, Cabinet-level and independent agencies. The FGDC is developing the National Spatial Data Infrastructure (NSDI) in cooperation with organizations from State, local and tribal governments, the academic community, and the private sector. The NSDI encompasses policies, standards, and procedures for organizations to cooperatively produce and share geographic data.

## latest news

- Staff Director for FGDC Announced
- Register for Geography Week & GIS Day 2003
- FGDC announces 2003 CAP funding for 51 projects in 29 states
- ISO announces approval of ISO 19115: Geographic Information
- GIS Monitor: Metadata Crosswalk
- FGDC-GAI Geospatial Interoperability Reference Model, v1.0
- OMB Launches New Geospatial One-Stop Portal
- The Geographic Foundation of America's Information-Based Society
- Public Health GIS and the Internet
- GAO Report: GIS - Challenges to Effective Data Sharing
- FGDC Geographic Information Resources
- Geospatial Standards (Article 1 of 4) - Now Online
- 2002 Reports on NSDI Implementation
- New revision of A-16 by OMB
- Homeland Security and Geographic Information Systems
- NSDI Communications Toolkit Available

Public Documents Directory

FGDC, USGS, 590 National Center, Reston, VA 20192
URL: http://www.fgdc.gov /index.html
Last content review/update: Wednesday, 22-Oct-2003 08:29:09 EDT
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FIRSTGOV

**FGDC**

**Federal Geographic Data Committee**

**www.fgdc.gov**

# Federal Geographic Data Committee (FGDC)

- The Federal Geographic Data Committee is a 19 member interagency committee composed of representatives from the Executive Office of the President, Cabinet-level and independent agencies.
- The FGDC is developing the National Spatial Data Infrastructure (NSDI) in cooperation with organizations from State, local and tribal governments, the academic community, and the private sector.
- The NSDI encompasses policies, standards, and procedures for organizations to cooperatively produce and share geographic data.

# National Spatial Data Infrastructure (NSDI)

- Consistent means to share geographic data among all users could produce significant savings for data collection and use and enhance decision making.
- Executive Order 12906 calls for the establishment of the National Spatial Data Infrastructure
- The goal of this Infrastructure is to
  - reduce duplication of effort among agencies,
  - improve quality and reduce costs related to geographic information,
  - make geographic data more accessible to the public,
  - increase the benefits of using available data
  - establish key partnerships with states, counties, cities, tribal nations, academia and the private sector to increase data availability.

# The National Digital Information Infrastructure and Preservation Program (NDIIPP)

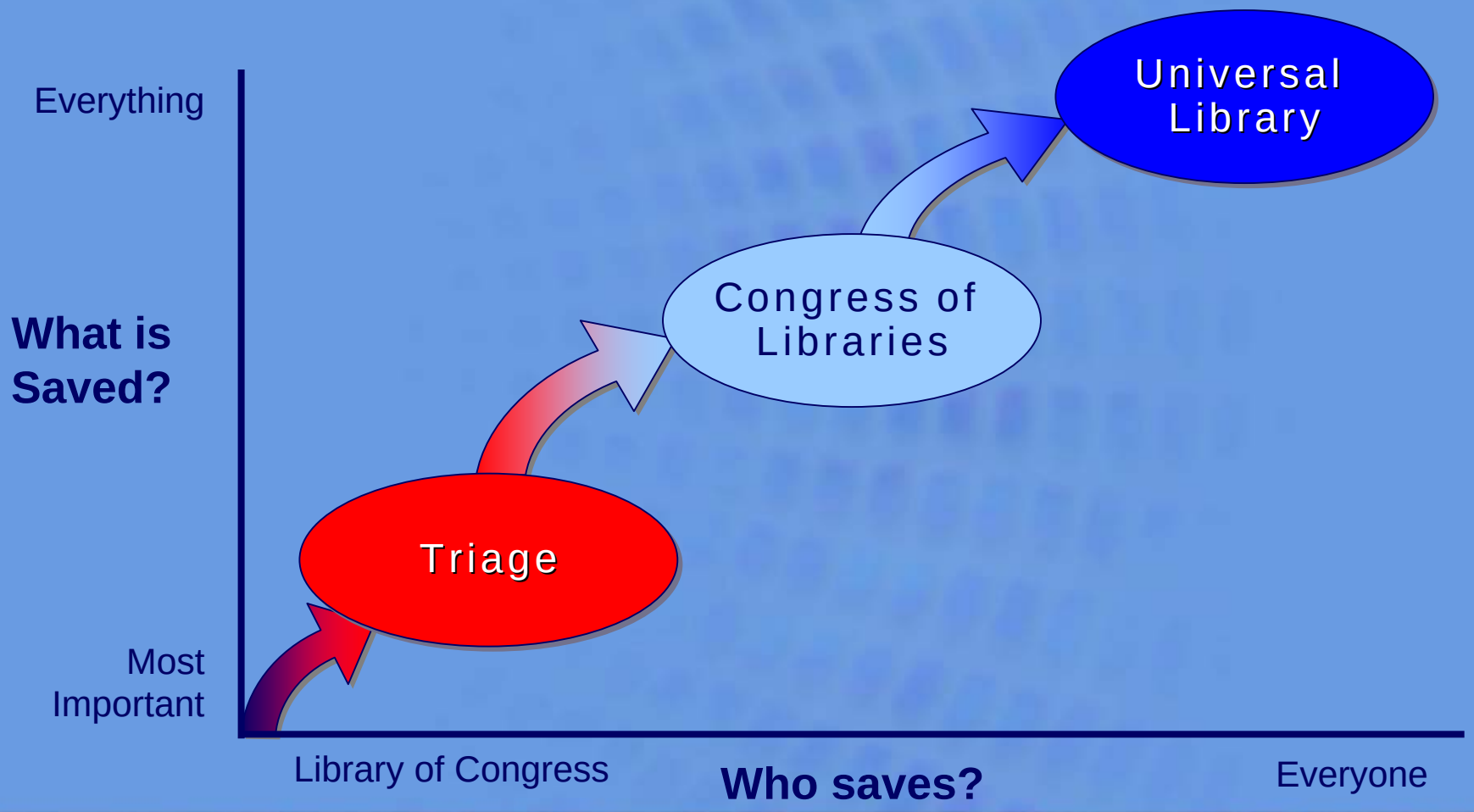
## Challenges and Solutions

Laura E. Campbell
Associate Librarian for Strategic Initiatives
Library of Congress

# NDIIPP Goal

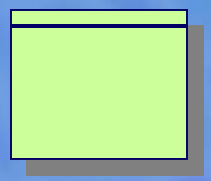
- To develop a nationwide collection and preservation strategy for digital materials in cooperation with the information and technology industry, concerned federal agencies, libraries, research institutions and not-for-profit entities.

# Scenario Planning: What's Plausible?

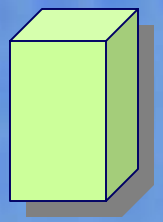


# Preservation Architecture

- 4 Layers Between People and Bits

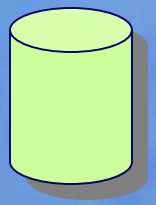


Collections



Interfaces

Gateways



Repositories

# NDIPP http://www.digitalpreservation.gov

# Challenges

- Preservation of digital collections (long term)
- Need ability to reproduce published results from archived data
- Transparency; ease of use; quality of service; validity; reproducibility
- Information infrastructure that includes images and integrates them with everything else

# Conclusion

- Imaging is important today and will continue to grow.
- Images define phenotypes (normal and abnormal)
- Need informatics support for imaging to achieve personalized pharmaceuticals
- Must eliminate sequestration of imaging data
- Major opportunities – molecular imaging, tool and infrastructure development, increased specificity, open databases – to improve the value of imaging in research and clinical practice

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