Personalized Health Care: Opportunities and Challenges in Dentistry

NIDCR: Powering up for Personalized Health Care

AADR
March 22, 2012

Martha J. Somerman, DDS, PhD

Topics

- NIH/NIDCR Overview
- NIH: Building the "Personalized Revolution"
- NIDCR:

  Research informing oral health

  Opportunities & Challenges

NIH: Largest Federal Biomedical Research Agency

NIH is an institution
(Intramural Research)

~Approx. 6,000 scientists
~Approx. 10% of NIH budget

NIH supports institutions & people
(Extramural Research)

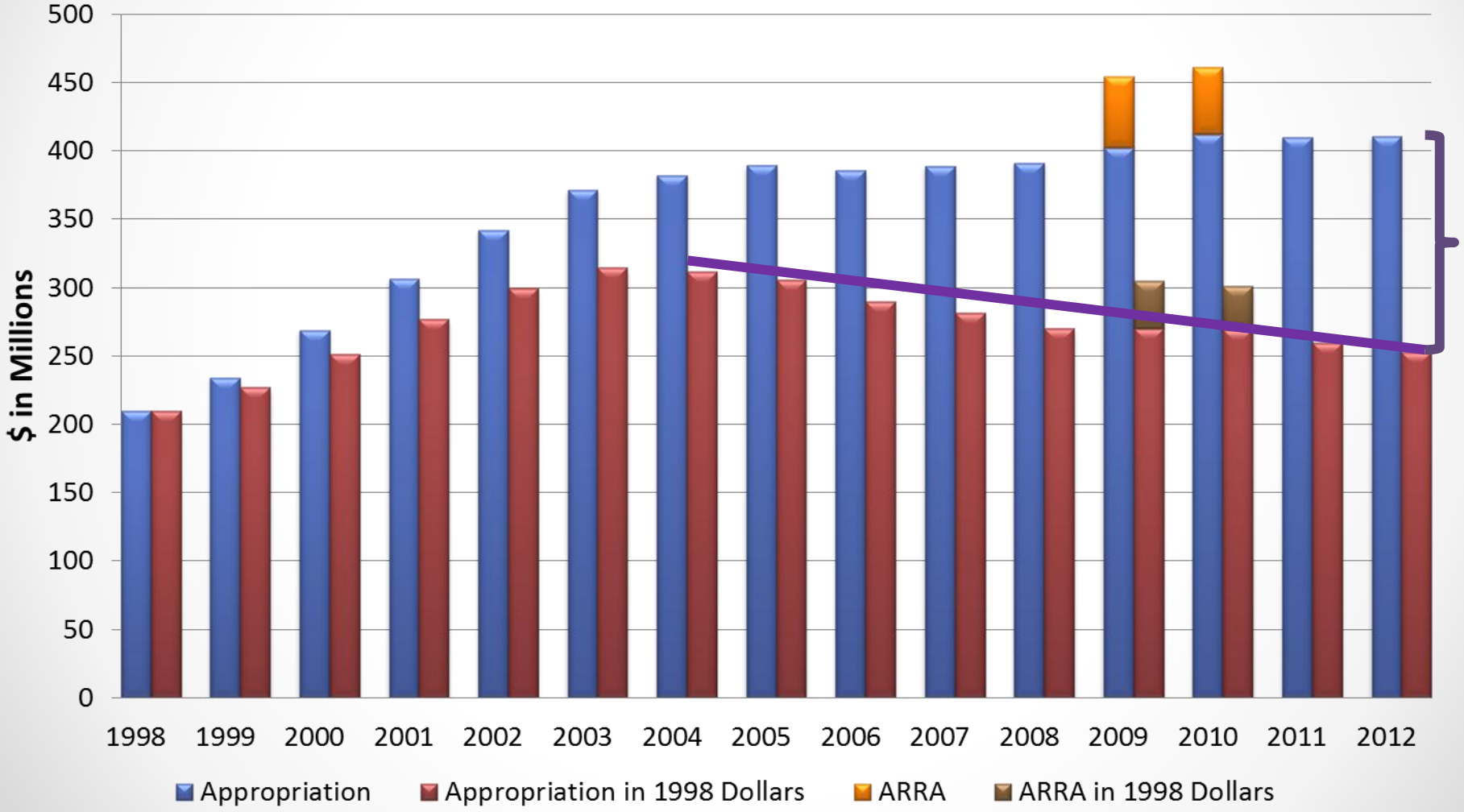
>4,000 institutions
>300,000 scientists & research personnel
~Approx. 80% of the NIH budget

National Institute of Dental and Craniofacial Research

- To improve oral, dental and craniofacial health through
  - research
  - research training
  - dissemination of health information
- Annual FY '12 budget of ~$411 million
- NIDCR is the third oldest Institute at NIH
- Founded in 1948 -- dental readiness crisis among WWII recruits
- Supports the majority of dental research funding and nearly all dental research training at NIH

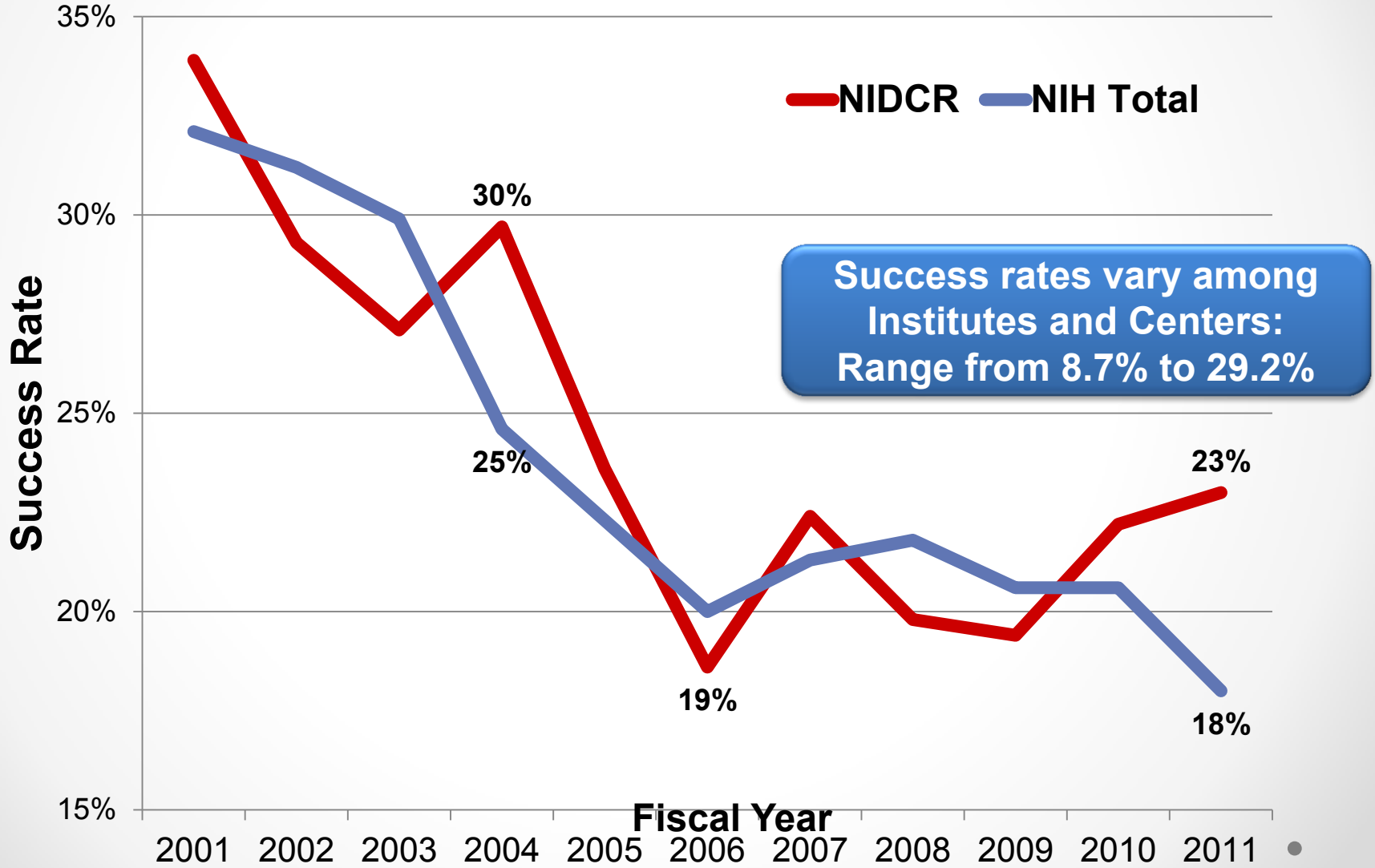
NIDCR Appropriations

FY 1998 – 2012: Appropriations vs. Purchasing Power



Success Rates

RPGs from FY '01- FY '11



Topics

- NIH/NIDCR Overview
- NIH: Building the "Personalized Revolution"
- NIDCR:

  Research informing oral health

  Opportunities & Challenges

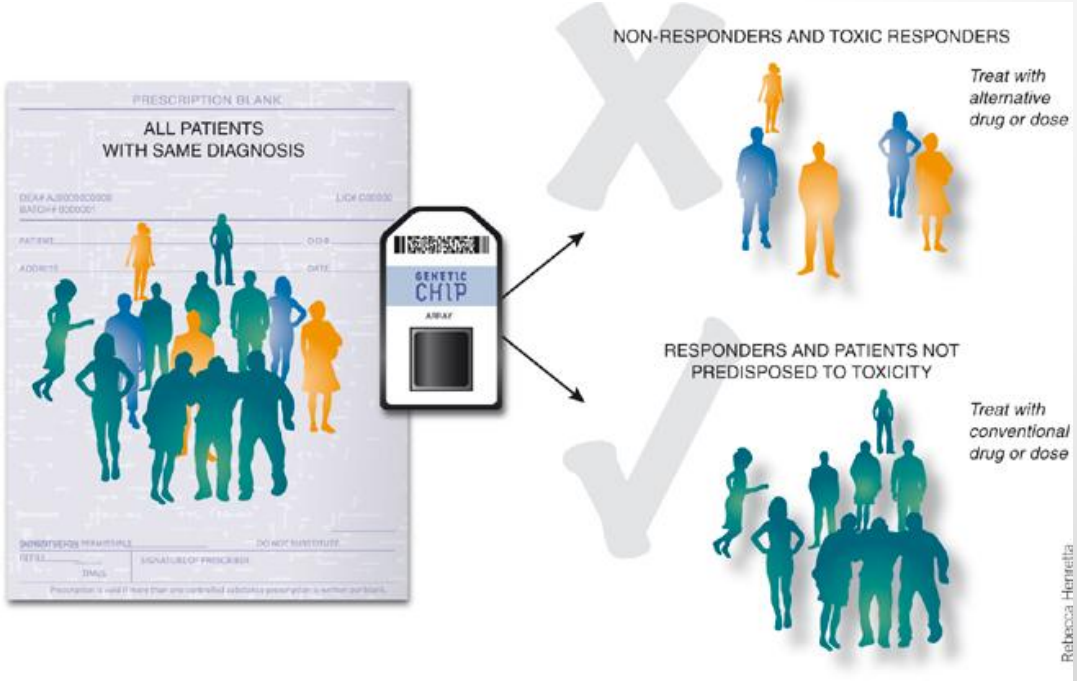
PERSONALIZED MEDICINE

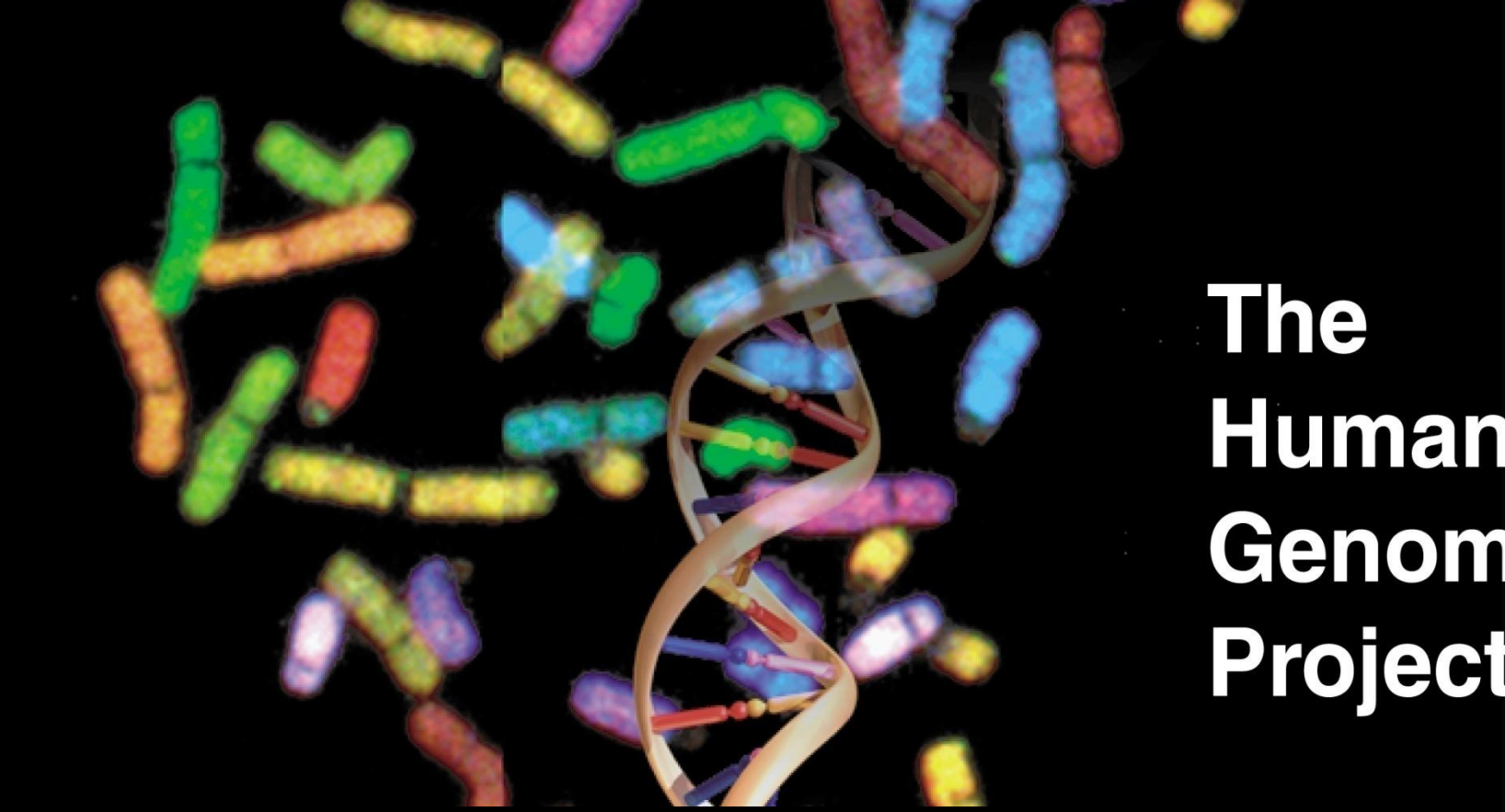
- *So what's new?* Personalized medicine in the sense of the 'right treatment for the right patient at the right time"-has been practiced for millennia.

  Personalized Medicine: something old, something new. Steele, F. Pers. Med. 2009.6,1-5.

- *New advances:* Personalized medicine is "a form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease"

  NCI 2011





The Human Genome Project

With the mapping of the Human Genome & Technologies we now have a set of research tools to find the genetic contributions to common diseases.

A Complex, Cross-discipline Process

Disease	Target ID	Assay Dev.	HTS	Probe to Lead	Pre-Clinical	FDA IND	Ph. I	Ph. II	Ph. III	FDA Re-view	Clinic

- Therapeutics move through this system slowly, and often get stuck
- NIH is collaborating with FDA & others to streamline process

Evolution of BMPs as Therapeutics

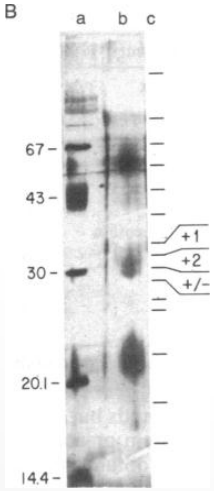
Subfamilies	Involved in
BMP-2,4	Cartilage, bone, teeth formation
BMP-5,6,7,8	Cartilage, joint, liver, kidney
BMP-9,10	CNS, liver, angiogenesis, heart

1965 First report of ectopic bone formation induced by demineralized bone matrix, and subsequently coined "Bone Morphogenetic Proteins"

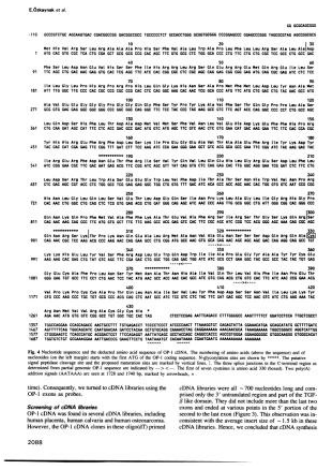
Science AAAS

Bone: Formation by Autoinduction
Marshall R. Urist
12 November 1965

1988 - Discovery and purification of BMP-2



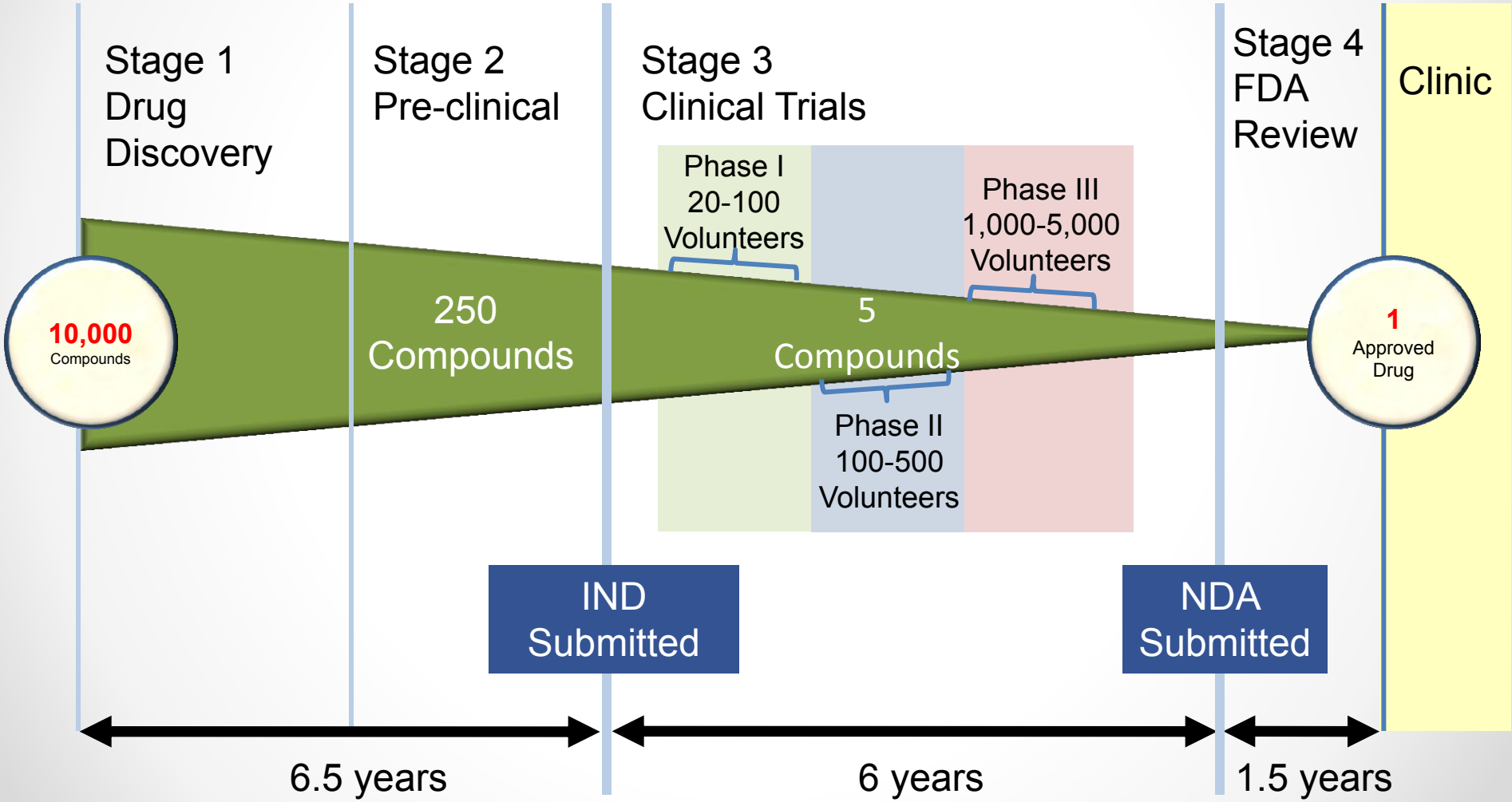
1990 - Discovery and sequencing of osteogenic protein-1 (OP-1 or BMP-7)



2004 - FDA approved OP-1 Putty (rhBMP-7) for treatment of fractures and nonunions

2007 - FDA approved InFUSE (rhBMP-2) as bone filling material for dental use

Development of New Therapeutics



Genomics is Guiding Health Care Decisions

- Early on there was Herceptin – target breast cancers that overexpress Her2/neu receptor
- Then came others:
  - Coumadin - CYP2C9/VKORCC1 gene test
  - AmpliChip CYP450 – metabolic profiling
- Next steps from NIDCR:
  - Risk Assessment/Diagnostic tests to Inform therapies

Topics

- NIH/NIDCR Overview
- NIH: Building the "Personalized Revolution"
- NIDCR:

  Research informing oral health

  Opportunities & Challenges

Mouth: The Gateway to the Body

Genomics

Diagnostics

Oral Cancer

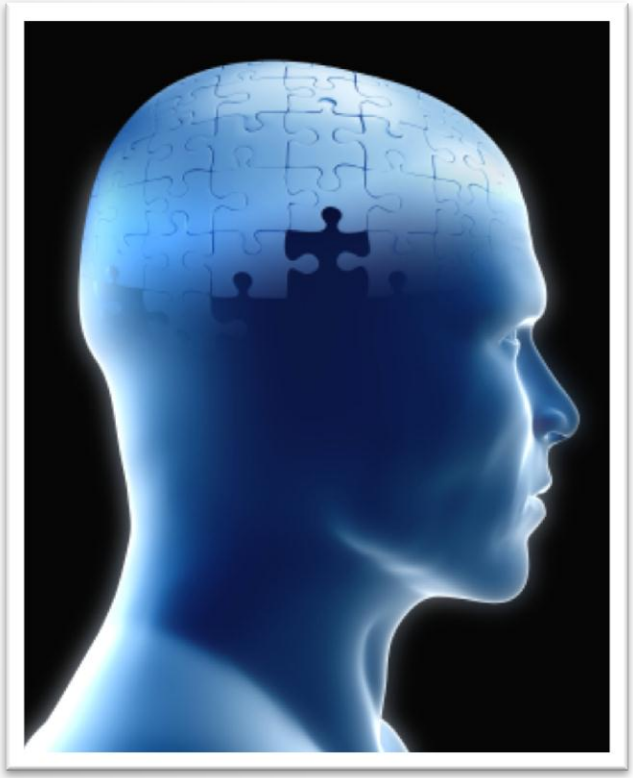
Pain

Microbiome, Caries, Taste

Behavioral & Social

Informing therapies

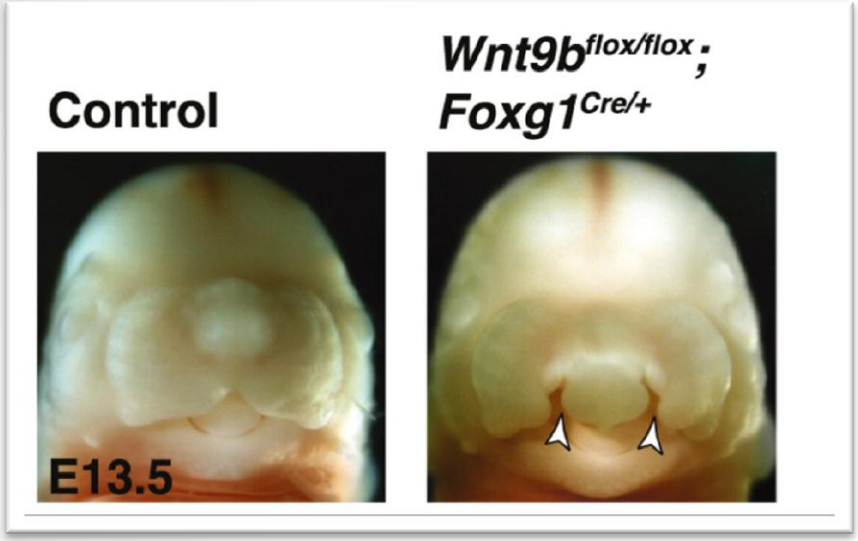
NIDCR Current and Planned Genomic Studies

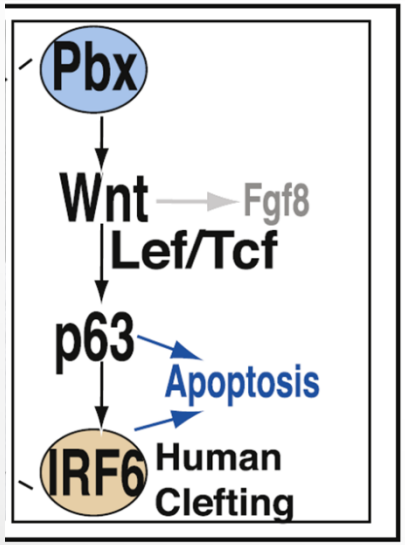


Oral Cleft Lip/Palate
Facial Shape
Sjogrens Syndrome
Dental Caries
Dental Fluorosis
Periodontal Disease

FY2011 Initiative: Building a Genetic and Genomic Knowledge Base in Dental and Craniofacial Conditions and Diseases

Cleft Lip Corrected Genetically in Mouse Model



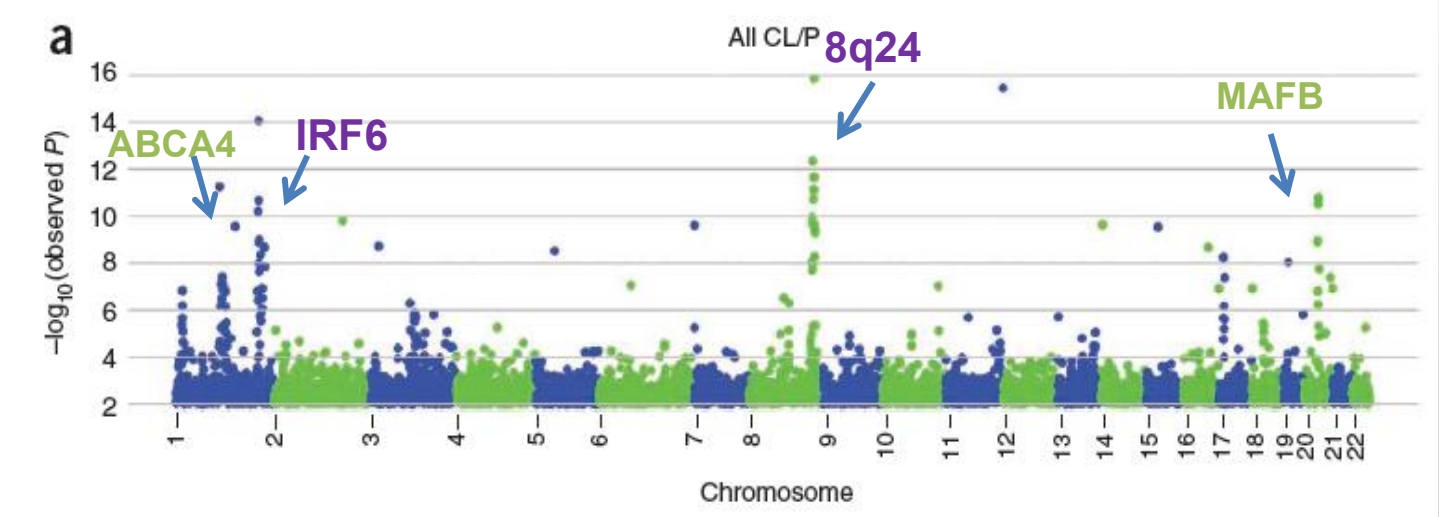


- One of the most common birth defects, strong evidence for genetic control; we need pre-clinical methods to study CL/P
- Researchers developed a multigenic mouse model of CL/P, affecting multiple genes in the wnt pathway
- Genetically restoring Wnt activity to developing mouse embryos with these mutations completely repaired the CL/P

Ferretti et al.,. *Developmental Cell*, 2011; 21 (4): 627

Setting the stage for Translation: GWAS of Cleft Lip and/or Palate

- Consortium tested ~1,900 affected families from eight countries and validated in 1,965 more affected families from 12 countries, for a total of 8,115 people.
- Detected variations close to genes, MAFB and ABCA4.
- Confirmed MAFB expressed during development of the palate
- Confirmed role for previously identified gene IRF6 and a suspected segment of chromosome 8



Beaty et al. *Nature Genetics*: 2010; 42:525

Diagnostics

HIV Rapid Test: Survey for Use in Dental Care Settings

- FDA approved
- Blood (finger stick) or oral fluid (swab), results in 20 minutes
- Potential to expand testing
- Supported by 1/5 states for dental care settings
- Positive feedback with concerns

Lisa Metsch, Ph.D., Stephen Abel, DDS

Feasibility of Diabetes Diagnostic Testing in Dental Settings

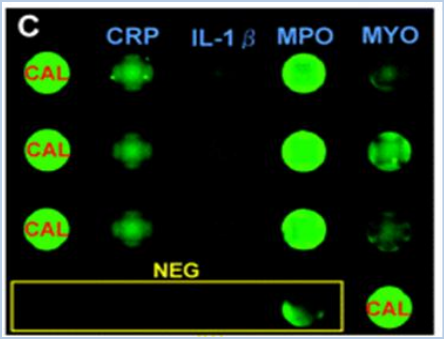
- CTSA: blood sampled from the oral cavity could be used to test for hemoglobin A1c

- PBRN: feasibility of blood glucose testing

High level of acceptance by both providers and patients

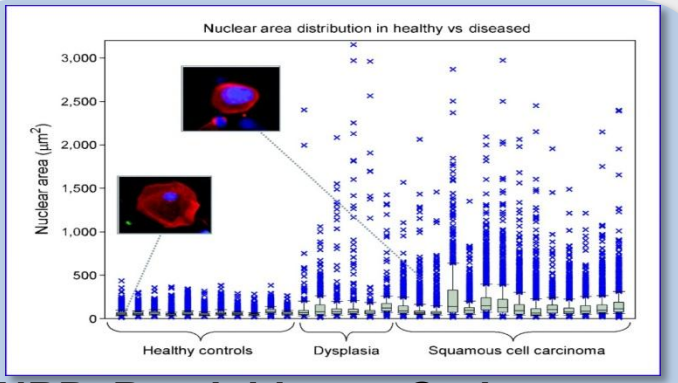
Sheila Strauss et al., *Journal of Periodontology,* 2011, doi:10.1902/jop.2011.110386
Andrei Barasch, et al.,*JADA* 2012;143;262-269

Advances in Diagnostic Testing

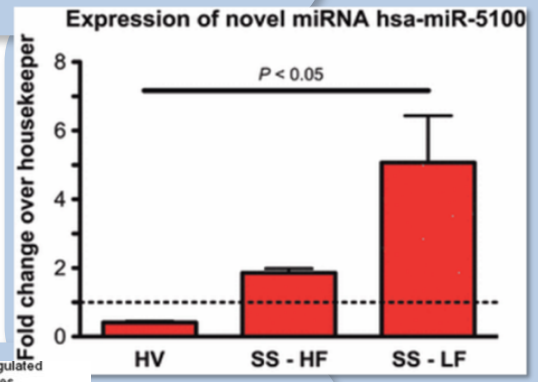


non-ST-elevation myocardial infarction

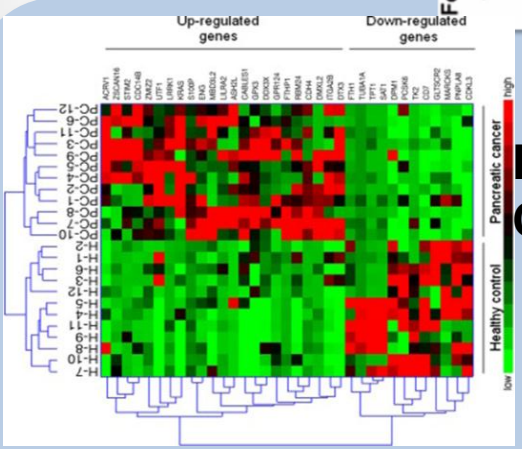
Nano-Bio-Chip: Salivary proteins



NBP: Brush biopsy, Oral cancer

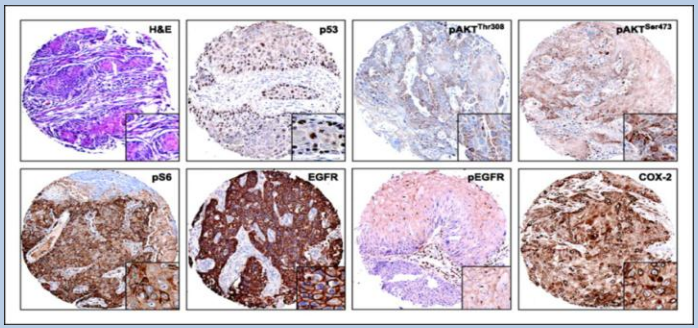


Micro RNA: Salivary glands, Sjogren's syndrome



Pancreatic Cancer

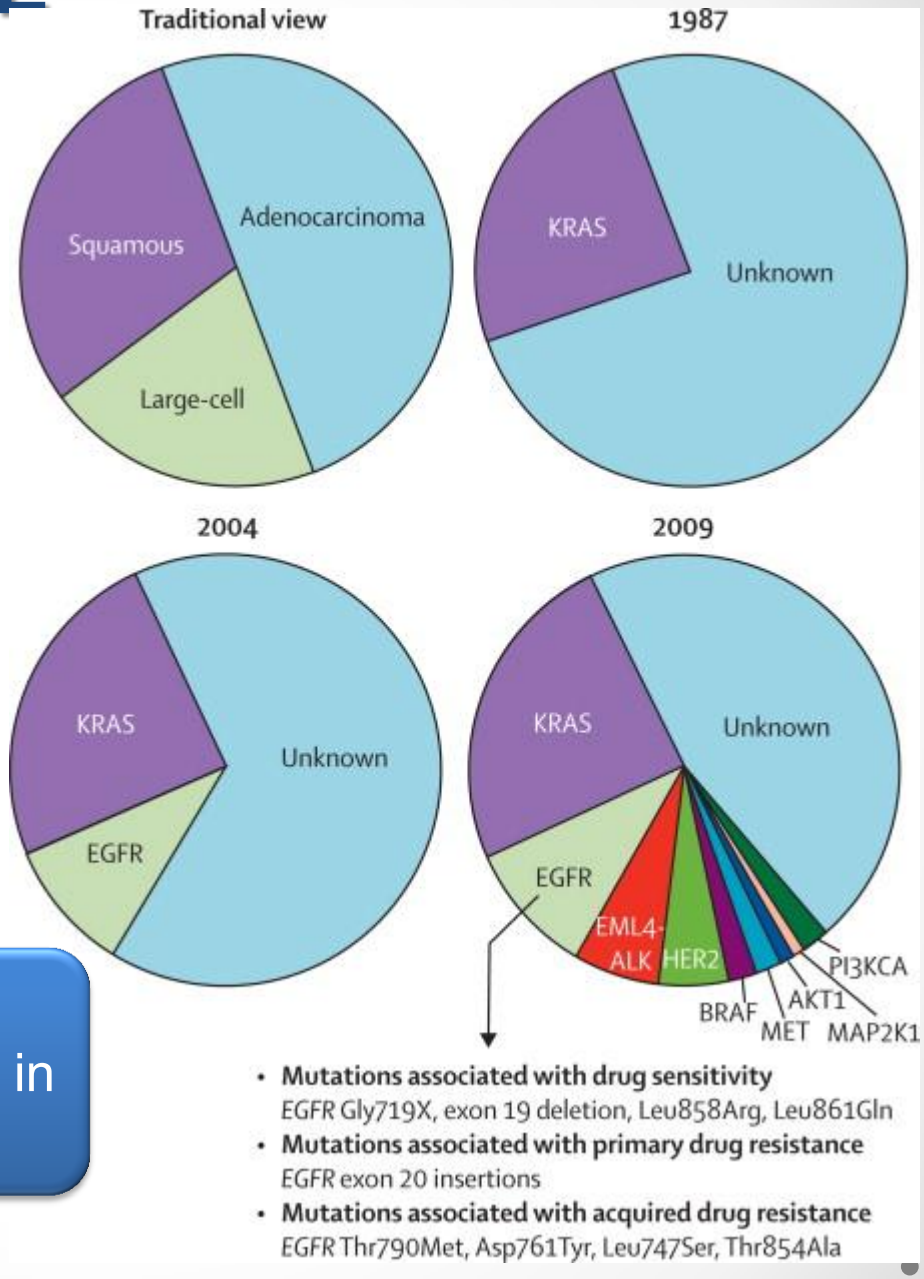
Microarray: Salivary mRNA markers



Tissue arrays: Head & Neck Cancer

Non-small Cell Lung Cancer:

Evolution from Histology-Based to Genetic-Based Classification



FDA approved two targeted therapies built on diagnostic tests in 2011 - one was for lung cancer

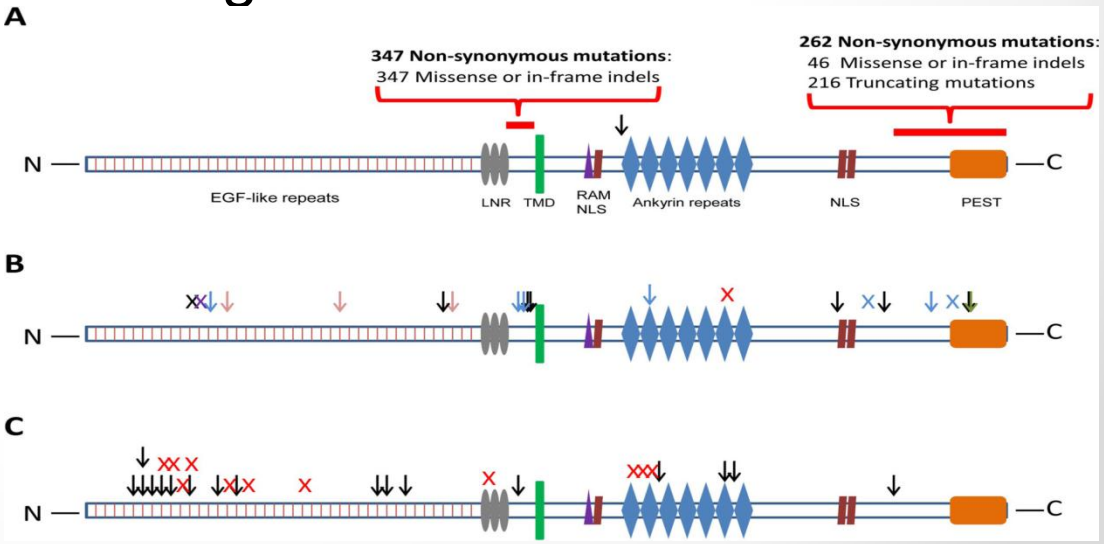
Pao W, Girard N. 2011 *Lancet Oncol.* Feb;12(2):175-80.

Oral Cancer Genome Project

- Designed to develop a comprehensive catalog of genomic alterations associated with oral cancer
- Using high-throughput exome sequencing identified *Notch1* as a potential tumor suppressor gene mutated in ~15% of tumors
- A majority of genetic alterations involved tumor suppressor genes requiring alternative strategies
- Future: validation, improved diagnosis and treatment

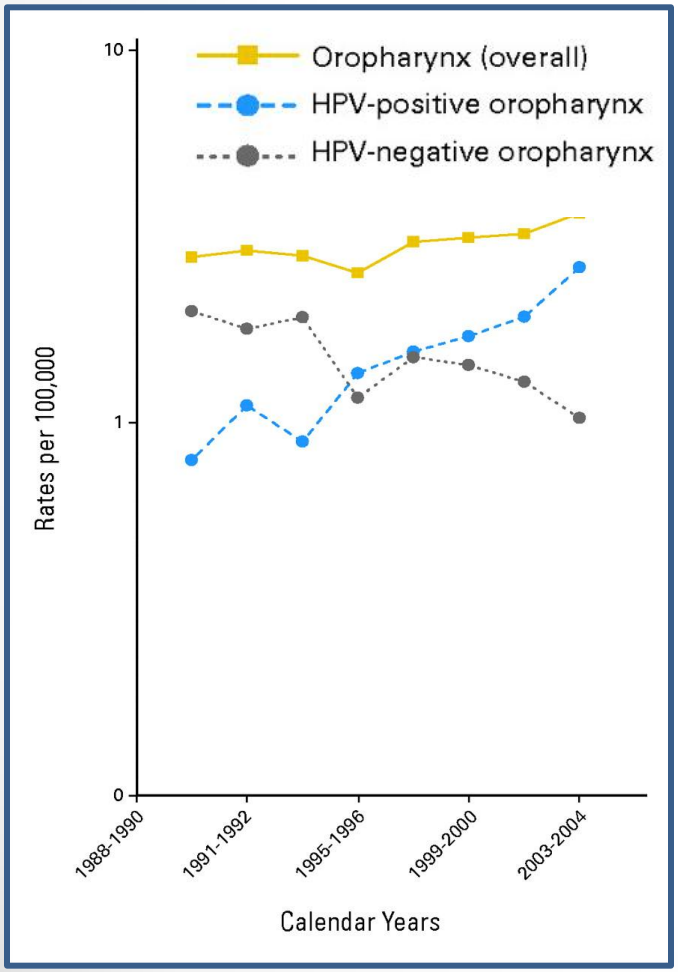
Schematic depiction of mutations in *NOTCH1*.

Agrawal et al. & Stransky et al.
Science 2011; 26.



Addressing Rising Public Health Challenges:

HPV-Related Oropharyngeal Cancer



- Estimates suggest HPV-related oropharyngeal cancer (OPC) incidence more than tripled from 1988 to 2004
- HPV-OPCs have distinct genetic profile, prognoses, response to treatments
- Knowledge gaps:
  - incidence,
  - risk factors
  - natural history and biology
  - efficacy of the HPV vaccine in preventing OPC

Chaturvedi A K et al. JCO 2011;29:4294-4301; Gillison ML et al. JAMA 2012;307,693-703

Mouth: The Gateway to the Body

Genomics

Diagnostics

Oral Cancer

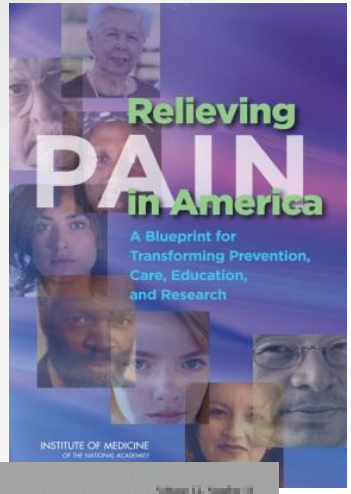
Pain

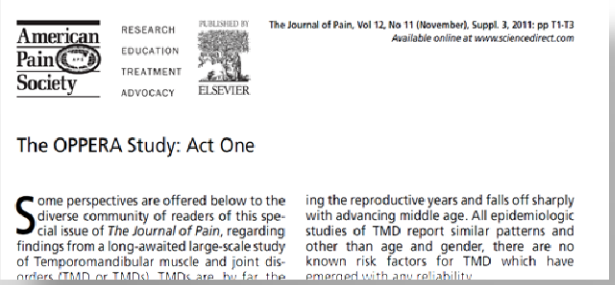
Microbiome, Caries, Taste

Behavioral & Social

Informing therapies

Pain is a National Challenge



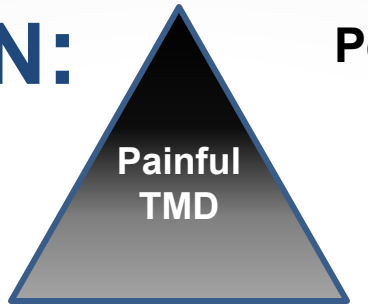


- **IOM Report (2011)**
  - Affects at least 116 million American adults
  - Costs society $560–$635 billion annually
  - Interdisciplinary approaches are required

- **OPPERA** (Orofacial Pain: Prospective Evaluation & Risk Assessment)
  - Follows 3,200 initially pain-free for 3 - 5 years
- **To Date**
  - Risk increases with age, not socio-economic status
  - Changes in NS parts that control pain perception
  - Genetic risk factors identified
- **Next Steps:**
  - Define molecular mechanisms of chronic pain, and transition from acute to chronic pain
  - Determine phenotypic and genotypic profile of large cohorts of subjects with orofacial pain and other co-occurring chronic pain disorders

Orofacial Pain:

Prospective Evaluation & Risk Assessment, OPPERA



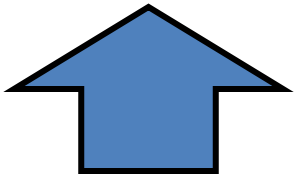
Persistent TMD

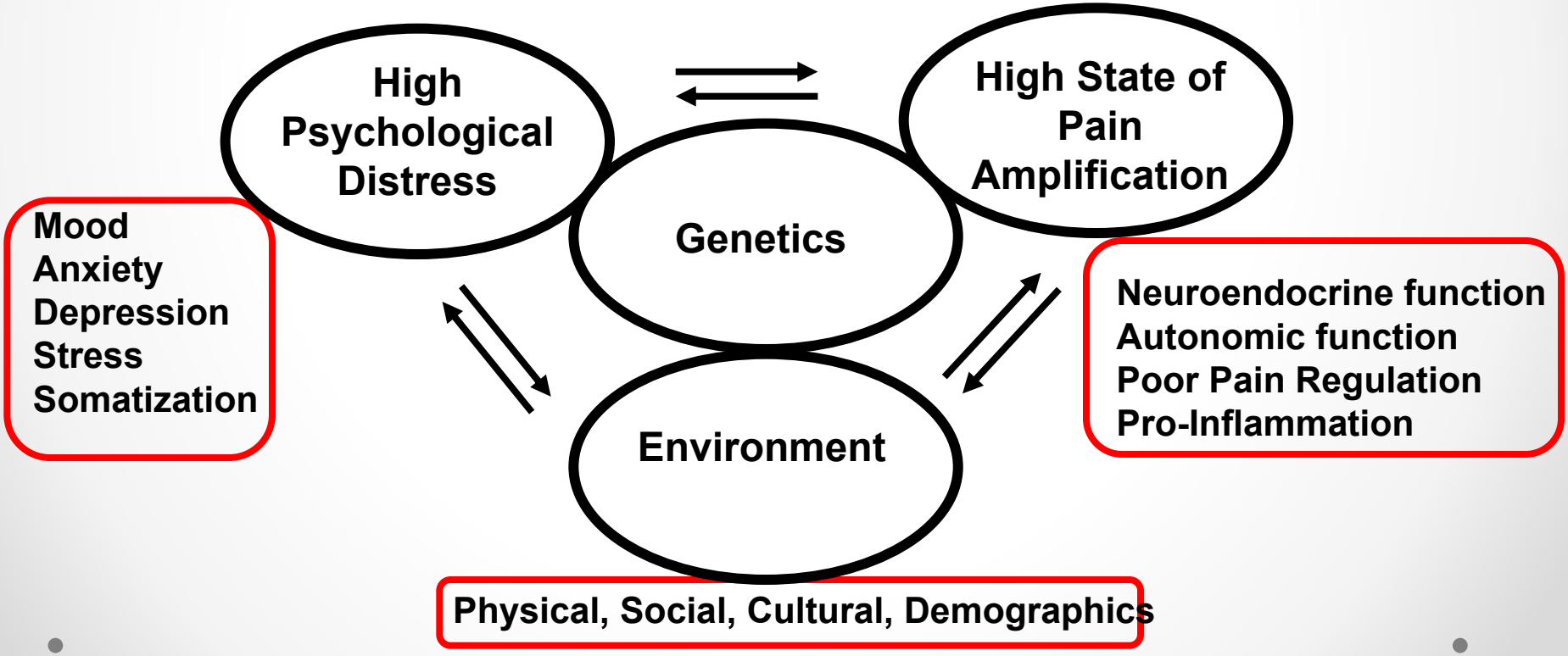
Transient TMD

Subclinical signs & symptoms

Severity

Scientific Model of TMJD Onset and Persistence



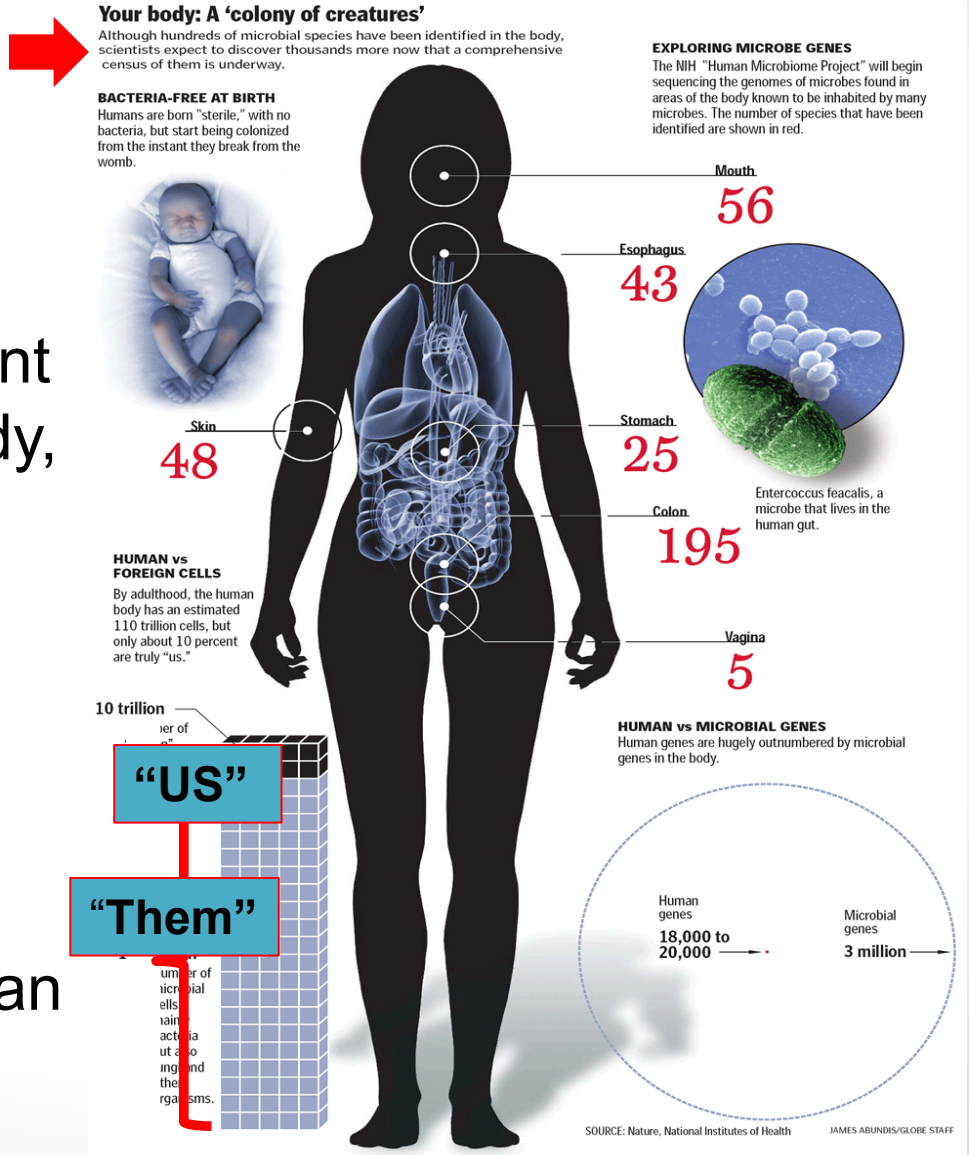


W. Maixner et al. J Pain, 2011

Tackling Complex Systems: Human Microbiome Project

Goal:

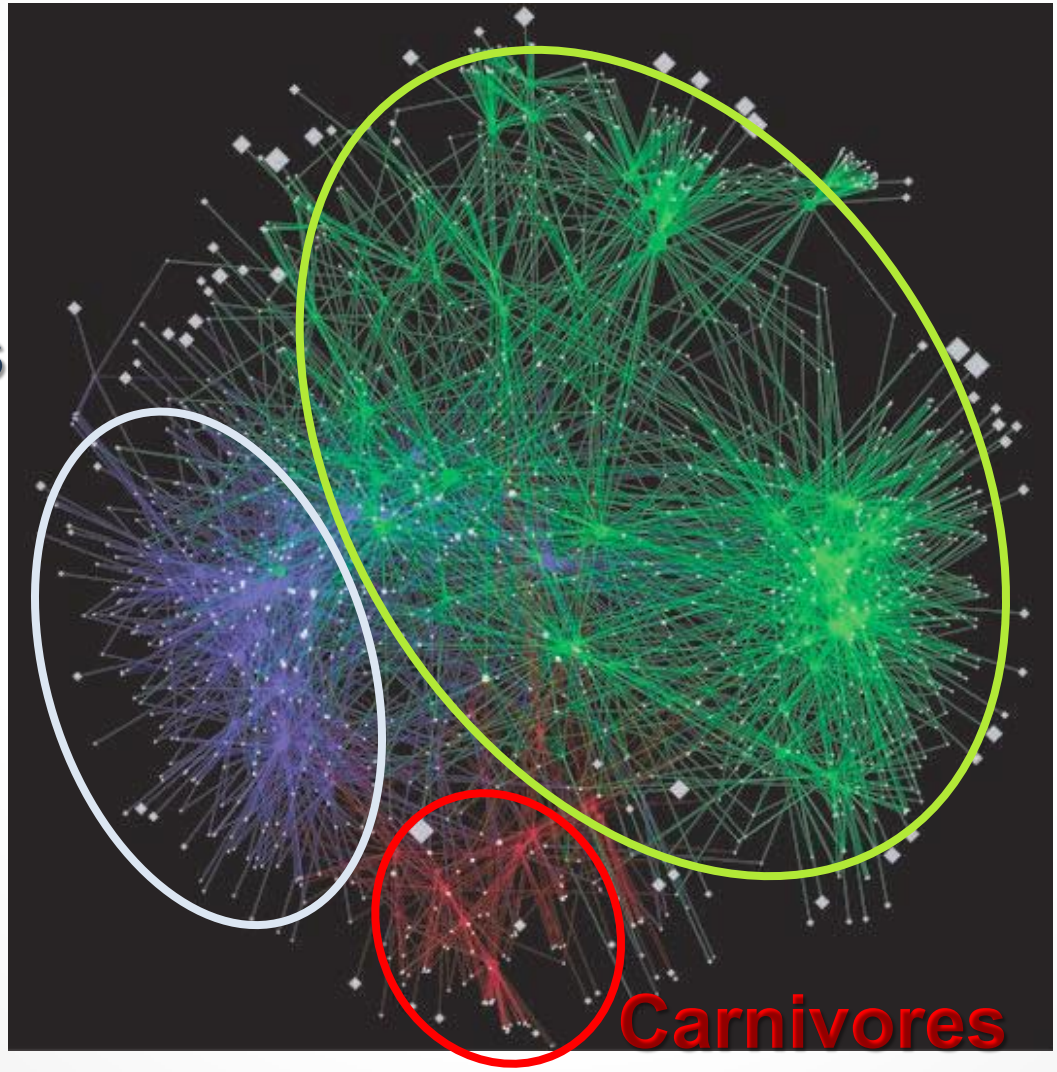
- to characterize the microbial communities found at several different sites on the human body, including:
  - nasal passages
  - oral cavity
  - skin
  - gastrointestinal tract
  - urogenital tract
- to analyze the role of these microbes in human health and disease.



We Are What We Eat:

Gut Microbes in Mammals Cluster by Diet

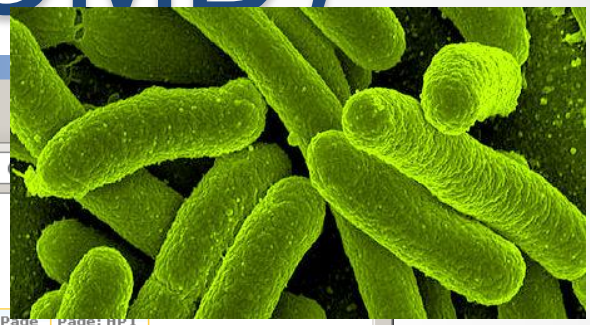
Omnivores



Herbivores

Ley, RE et al., *Science, 2008, 320:1647*

Human Oral Microbiome Database (HOMD)



HOMD :: Human Oral Microbiome Database - Mozilla Firefox

File Edit View History Bookmarks Tools Help

HOMD :: Human Oral Microbiome Database | bacteria - Google Search

www.homd.org/index.php

HOMD at The Forsyth Institute

Human Oral Microbiome Database

Home | Taxon Description | Identify 16S rRNA Sequence | Genomes | Tools & Download | HOMD Information | How to Use This Page | Page: HP1

Taxon Description
- Taxon Table
- Taxonomic Hierarchy
- Taxonomic Level

Identify 16S rRNA Sequence
- BLAST Sequence(s)
- 16S rDNA RefSeq Download

Genomes
- Taxa with Annotated Genomes
- Taxa with Genomes In Progress
- View All Genomes

Tools & Download
- HOMD Genome Viewer
- View Dynamic Annotation
- BLAST Against Genome
- Downloa HOMD Data

HOMD Information
- How to cite HOMD
- Project Description
- Strains and DNA Availability
- Team

http://www.homd.org/index.php

Welcome to HOMD

The goal of creating the Human Oral Microbiome Database (HOMD) is to provide the scientific community with comprehensive information on the approximately 600 prokaryote species that are present in the human oral cavity. The majority of these species are uncultivated and unnamed, recognized primarily by their 16S rRNA sequences. The HOMD presents a provisional naming scheme for the currently unnamed species so that strain, clone, and probe data from any laboratory can be directly linked to a stably named reference entity. The HOMD links sequence data with phenotypic, phylogenetic, clinical, and bibliographic information. Full and partial oral bacterial genome sequences determined as part of this project and the Human Microbiome Project, are being added to the HOMD as they become available. HOMD offers easy to used tools for viewing all publically available oral bacterial genomes. Welcome!

Investigators contributing to this project: Tsute Chen, Floyd E. Dewhirst, Derrick E. Fouts, Jacques Izard, Bruce J. Paster, Anne Tanner, and William G. Wade

Contributors: Oxana Baranova, Jessica Blanton, Wen-Han Yu, Abby Lakshmanan, and Akila Ganesan

Meta-Database Search

Advance | Search

Announcement

2010-08-02 10:14:44
HOMD publication available for download. [more]

2010-06-10 09:45:25
Forsyth Scientists Support The Human Microbiome Project [more]

2008-04-04 09:33:24
Press Coverage for HOMD [more]

2008-03-25 09:32:45

Database Update

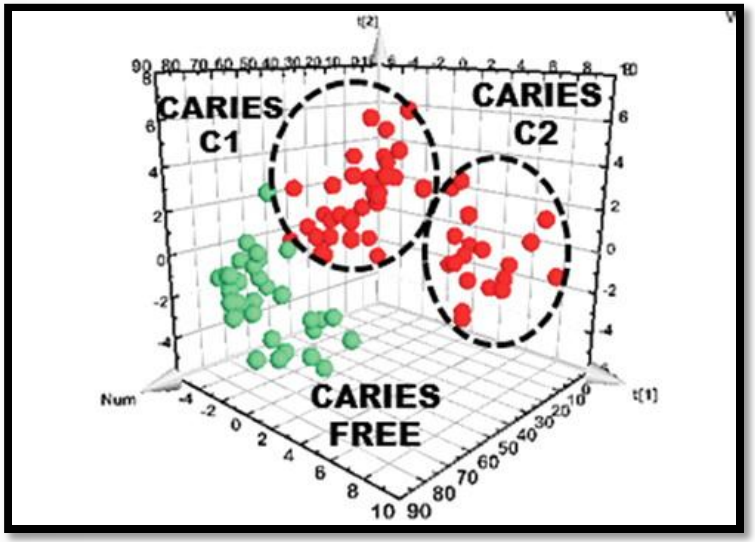
2011-12-02 09:12
Genome Annotation Update - Listeria monocytogenes Clip81459 [more]

2011-12-02 06:12
Genome Annotation Update - Lactococcus lactis subsp. lactis IL1403 [more]

2011-12-02 04:12
Genome Annotation Update - Lactobacillus salivarius UCC118 [more]

2011-12-02 02:12

Microbiota of Severe Early Childhood Caries



Slackia exigua,
S. parasanguinis I & II,
Prevotella species,
Neisseria flavescens,
Bifidobacteriaceae,
S. wiggsiae,
S. mutans

- Bacteria
- Diet
- Host

] Environment
Socio-economic status

Tanner A *et al. J DENT RES* 2011;90:1298-1305

JDR JOURNAL OF DENTAL RESEARCH

Certain Genes May Predict and Protect From Caries

- Researchers identified two genes important in taste-sensing that are associated with dental caries risk and/or protection
- GWAS for childhood dental caries to address the role of genes and gene-by-fluoride interactions in disease
  - No single SNP exhibited statistical significance
  - Several genomic regions showed suggestive evidence for association.

S. Wendell, et al., *Journal of Dental Research*, 2010
J.R. Shaffer, et al., *Journal of Dental Research*, , 2011

Leveraging Data in Risk Assessments

- Microbiotic and genetic data promising as part of a valid, reliable, and practical caries risk assessment instrument for clinical use
- In addition to clinical exam this may include:
  - Sociodemographic factors
  - Dietary habits
  - Exposomes (eg. Fluoride)
  - Host-response

Behavioral Interventions Targeted for Specific Individuals/Communities

Test motivational approach delivered in the dental setting to improve ECC & parental OH behaviors

- Caretakers of East Asian infants in Vancouver

Test home-based motivational approach to improve ECC

- Native American mothers and children

Test multi-media education based on stages-of-change to improve ECC

- Caretakers of children in the poorest areas of Detroit

Test motivational approach delivered by peer advocates to improve OH behaviors and care-seeking

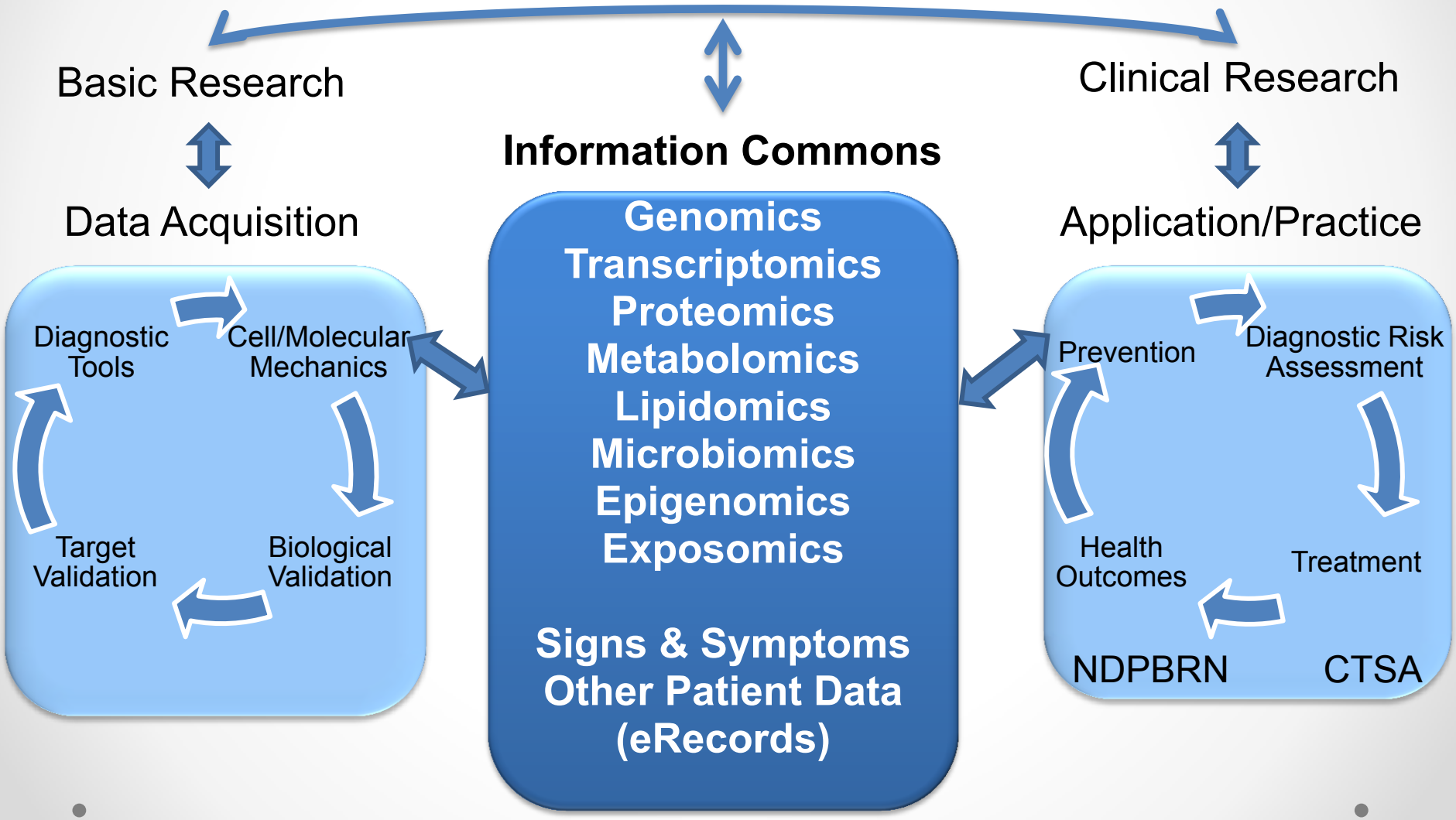
- Mothers and children in Boston public housing

A Few Grapples…….

- Communication across disciplines, basic to clinical
- Diagnostic tools
- Biomarkers
- Clinical trial design
- Collaborative networks (CTSAs, HMOs, eRecords, etc.)
- Educational advances
- Social, ethical & legal issues

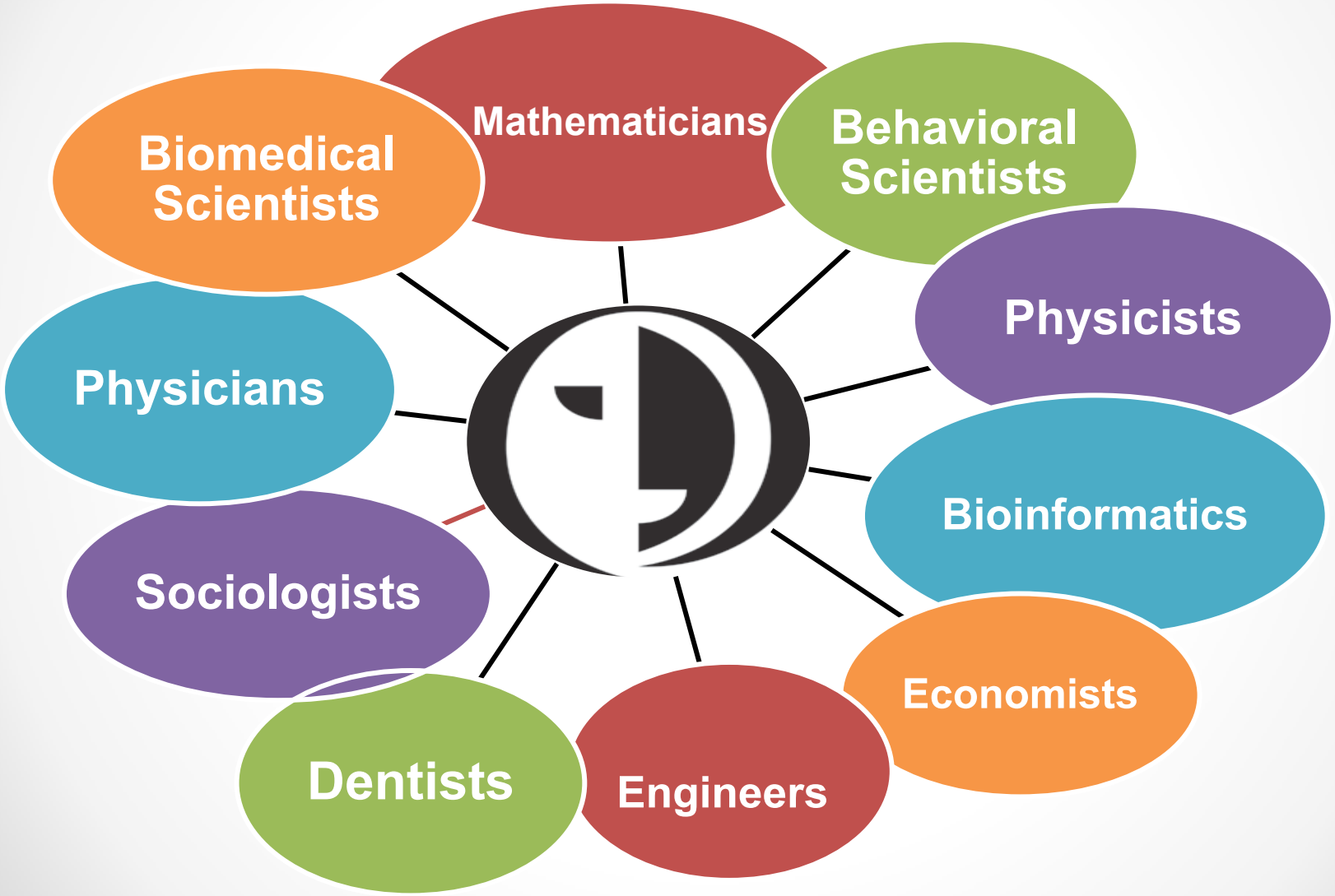
GTACT
CAAGT
CTA
TCC
TAC
CCGA
TAGG
ATCC
TGG
ATCC

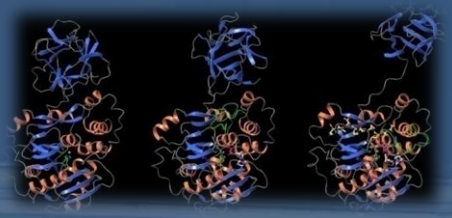
Toward Accelerating Precision Health Care

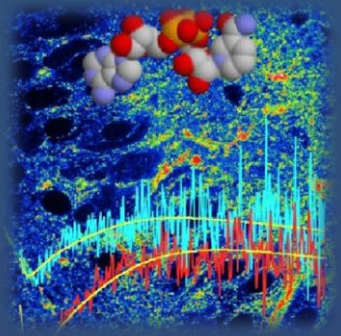
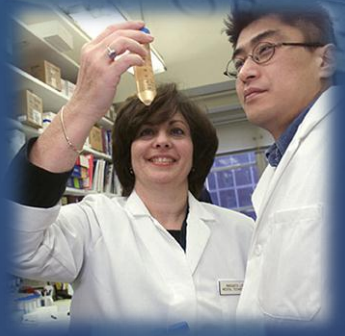
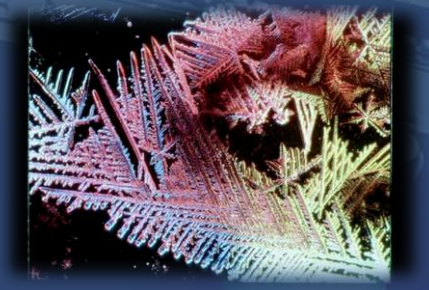


Adapted from: *Toward Precision Medicine* (2011 IOM Report)

Future Advances Will Come at the Interface of Disciplines





NIDCR

Advancing Personalized Oral Health Through Research and Innovation