The Birth, Development and Future Prospects for Craniofacial Biology

Hal Slavkin, Professor & Dean Emeritus
Center for Craniofacial Molecular Biology, Herman Ostrow School of Dentistry, University of Southern California, Los Angeles, California (slavkin@usc.edu)

Opening General Session: Keynote Address

72nd Annual Meeting & Symposia of the American Cleft Palate-Craniofacial Association
Westin Mission Hills Golf Resort & Spa Hotel, Rancho Mirage, April 22nd, 2015
Dedicated to the Memory of Professor Samuel Pruzansky (One of the Midwives for Birth of a Discipline: Craniofacial Biology)

- Organized the First International Symposium on Craniofacial Malformations in 1959
- Coined the term “Craniofacial Biology”
- Served as Chair for the First “Dental Study Section” at NIDR, NIH
- Founded the First Center for Craniofacial Anomalies at the University of Illinois College of Medicine in 1967
- First President of Craniofacial Biology Group at IADR in 1968
- Received the “Honors of the Association” in 1976 From American Cleft Palate-Craniofacial Association
- Published 190 Scientific Publications
- Authored the Forward for my book “Developmental Craniofacial Biology” (1979)
- His Death in 1984

Role Model
Mentor & Coach
Advocate
Leader
Listener
Inspirational Friend for 16 years
Three Examples of Innovative Craniofacial Clinical Scholars

Paul Tessier
French Surgeon who created major transformations of craniofacial surgery; consulted for NIDR in 1960s-1980s; provided training for craniofacial surgeons such as Dr. Henry Kawamoto; close friends with Drs. Sam Pruzansky and John Converse

Carl Witkop, Jr.
Lab Chief, 1st Genetics Branch, NIDR, NIH (1950s); Pioneer of enamel and dentin genetic diseases and disorders (amelogenesis & dentinogenesis imperfecta; AI & DI)

Robert Gorlin
Father of craniofacial genetics of dysmorphology
SELECTED EVENTS

- Social Security Act included funds for the care of children with congenital birth defects-1935
- 1st Cleft Palate Clinic- (Dr Herbert Cooper); 1st Craniofacial Team-1938 (creation of Inter Professional Teams for Health Care)
- *NIDR* created-1948 (*with Cancer & Heart Institutes*)
- *NIDR* formed the very first genetics branch at NIH (1950)
- Thalidomide Epidemic (10,000 babies) – October 1957
- NIDR supports Gatlinburg Conference-December 1959
- 1st March of Dimes Conference on Birth Defects-1960
- Dr Sam Pruzansky coins term “craniofacial biology” – 1968 (*synthesis of embryology, biochemistry, clinical specialties*)
- Japanese, USA, UK, France, Australia, Canada, Scandinavia Cleft lip and Cleft Palate Centers for Clinical Services as well as Research Institutes created
- Eurocleft led to WHO (2000) led to Americleft (2006) led to CLEFT-Q
- Regenerative medicine & dentistry, clinical trials for ED, Gordon Conferences, NIDCR FaceBase, Precision Health Care, 3-D Imaging, Nanotechnology, $1,000 for patient’s complete genome, and era of the microbiome in 21st Century
Dr Herb Cooper’s Interprofessional Team at Lancaster, PA (1938)

Dr. Cooper with patient

Cooper Protocol for CL/CP

Team Timeline
Cleft Palate Only

Team Visits

- Palate Repair
- Ear Tubes
- Speech Therapy
- Speech Surgery
- Initial Orthodontics
- Operative Orthodontics
- Audiology
- Early Childhood Intervention
- Special Education
- Genetics Evaluation
- Developmental Psychology
- Genetic Counseling
- Feeding Problems
- Pediatric Dentistry
- Psychiatry

*If necessary/desired
Composition of Craniofacial Interprofessional Health Teams
(~200 CF Teams in USA, Canada, Japan, Australia, Europe & Beyond)

Core Competencies for Interprofessional Education & Clinic Care (May 2011)

American Association of Colleges of Nursing
American Association of Colleges of Pharmacy
American Association of Colleges of Osteopathic Medicine
American Dental Education Association
American Association of Medical Colleges
American Association of Public Health Colleges

**Competency Domain 1. Values/Ethics of Interprofessional Practice**

**Competency Domain 2. Roles/Responsibilities**

**Competency Domain 3. Interprofessional Communication**

**Competency Domain 4. Teams and Teamwork**
After high school, pursued dental technician training at Fort Sam Houston, Texas, and then dental and craniofacial technology at Walter Reed Hospital, DC, and Forest Glen, Maryland (severe facial burns unit - - -acquired craniofacial anomalies)

Worked as dental tech (“crown & bridge”) through undergrad & dent school (1958-1965)

After 1yr (Richard Greulich, Anatomy, UCLA) & 2yrs (Lucien Bavetta, Biochemistry, USC) postdoctoral fellowships, joined USC in 1968 & served for 46 years on faculty (minus 5yrs as director NIDCR and 4yrs various sabbatical leaves)
...my discovery of doing science as a dental student (1963-1965)...

“Craniofacial biology, as a life science, is a single fabric of interconnected facts and concepts in which, as in all dynamic works, the structure and strength of each portion depends significantly on the condition of the others.” S. Pruzansky 1968
The Burden of Congenital and Acquired Craniofacial Anomalies

- 1 out of every 10 people in industrial countries present craniofacial-oral-dental disease or disfigurements.
- 1 million people in USA have severe congenital craniofacial-oral-dental disfigurements (e.g. non-syndromic and syndromic clefts, birth marks, hemangiomas, oligodontia, severe malocclusions).
- Acquired craniofacial-oral-dental diseases and disorders include severe craniofacial facial burns, head and neck trauma, head & neck cancers, hypertrophic scars, and severe acne with facial scars impacting many millions of people.
- Total direct & indirect global health care costs are ~ $500 billion per year.
The burden of craniofacial conditions cause $95.9 billion per year in medical and wage/household work costs (1999 dollars). A baby is born every hour with CL/CP in USA, every minute world-wide, and often requires surgery, speech, hearing, learning, orthodontics, dental, feeding needs, social services & psychosocial health care needs.
PHENOTYPE + GENOTYPE = PHENOMICS
from single nucleotide polymorphisms to patient, family & population craniofacial phenotypes

Phenotype (Examples)

- Cleft lip and/or Cleft palate (CLP)
- Unilateral vs Bilateral, Ethnicity
- Male vs. Female
- Chromosomal, Mendelian, Complex, and Teratogenic; Syndromic & Non-syndromic
- CLP affects 1/700 live births with wide variability across geography, racial & ethnic groups, SES & environmental exposures


Genomics (Examples)

TGFalpha, RARA, IRF6, MSX1, FGFR1, FGFR2, TP63, PAX7,NOG and Other Gene Networks (e.g., BMPs, TGF-beta (1-3), Wnts, Shh)

See Leslie and colleagues (2015) Identification of functional variants for cleft lip with or without cleft palate in or near PAX7, FGFR2 and NOG by targeted sequencing of GWAS loci. Amer J Human Genetics 2/20/2015.
Vertebrate fossils show craniofacial birth defects
Aristotle and biological observations
Charles Darwin “On The Origin of Species” (1859) & “The Expression of the Emotions of Man” (1872) first used term “craniofacial”; first PubMed citation
Thomas Huxley (1876) with evolutionary biology
Creation of National Association of Teachers of Speech in 1925
Synthesis of genetics, biochemistry, embryology to become “Evo-Devo”
Hans Spemann receives Nobel Prize in 1935 (studies in craniofacial biology)
Herbert Cooper creates first craniofacial team (1938)
World War II and ultrasound, antibiotics, anesthesiology and surgery
Vannevar Bush and creation of the NIH (cancer, dental, and heart) in 1948
NIDR creates “1st” Genetics Branch at entire NIH (1950)
NIDR first grants for craniofacial in 1957 to Lancaster
Landmark Conference December 6-9, 1959 called “Gatlinburg Conference” or “Congenital Anomalies of the Face and Associated Structures” (Pruzansky, editor)
Paul Tessier, John Converse, Peter Randal, Poul Fogh-Andersen (surgeons), Bob Gorlin, Carl Witkop, F. Clark Fraser, Michael Cohen, Jr., Marilyn Jones (genetics), Sam Pruzansky, R. Bruce Ross, Ross Long (orthodontist), Duane Spriestersbach, Betty Jane McWilliams, & Don Warren all Exemplars of Clinical Scholars (late 1960s – 1980s, and beyond)
Creation of American Speech-Language-Hearing Association (ASHA) in 1978
Basic, translational & clinical research in craniofacial diseases and disorders
Joseph Murray Plastic/Craniofacial Surgeon receives Nobel Prize in 1990
NIDR to NIDCR in 1998 (budget doubles) “50 Year Anniversary”
NIDCR sponsors “Face Base Initiative” 2004-present
Gordon Conferences “Craniofacial Morphogenesis and Tissue Engineering”
Precision craniofacial medicine and dentistry
An American Perspective

- Head & Neck Trauma
  Wars Advance Clinical Care

- 1938-Present
  Birth, Development, and Differentiation of Craniofacial Teams

- 1950-Present
  Thalidomide (teratology), March of Dimes, NIH (NIDR & NIDCR, NICHD) & Birth Defects
Disruptive Technology = displaces established technology or provides a product or service that creates a completely new industry

- Head & Neck Trauma from Wars and Head & Neck Cancers
- Craniofacial Teams
- Inter-professional Education & Health Care (GME in 1960s)
- Basic, Translational & Clinical Research (e.g. Pharmaceuticals, Medical Devices, Speech-Language-Hearing, Clinical Psychology and Preventive & Social Services)
- Gene-based diagnostics (saliva & blood)
- Digital 3-D imaging & CAD-CAM
- Haptics: Computer-assisted sensory perceptions
- “FaceBase” a NIDCR Resource
- Voice-activated computer technology
NIH Plans Million-Person MegaStudy 2015

- 2004: Cost of sequencing one human genome = $4 million dollars and 2 years of time
- 2004: 1 million smart phones in USA
- 2004: 25% health providers use electronic records
- 2015: Cost of sequencing one human genome = $1,000 and less than a day of time
- 2015: 160 million smart phones in USA
- 2015: >90% health providers use electronic records

Accelerate the development of treatments and therapeutics tailored to individual patients; Integrate phenotype and genotype datasets for each patient (phenomics); Increase precision or personalized health care; Increase preventive services; Reduce costs.
Strategic Plan of NIDCR 2014-2019

“Enable Precise and Personalized Craniofacial-Oral-Dental Health Care”

Martha Somerman DDS, PhD.
Director, NIDCR,
Expanding the foundation for personalized medicine: implications and challenges for dentistry (Garcia, Kuska & Somerman, 2013 in JDR “Clinical Reviews in Oral Biology & Medicine 92(suppl 1):3-10s)

- Personalized health care aims to individualize care based on a person’s unique genetic (genotype), environmental, and clinical profile (phenotype)
- The completion of the Human Genome Project (2004), cost-effective whole genome-wide sequencing methods and bioinformatics (2013), enable clinicians to formulate decisions based upon the patient’s genotype and phenotype (e.g. risk assessment, diagnosis, treatment, prognosis)
- Now is the time for craniofacial-oral-dental health professionals to prepare for the arrival of personalized or precision health care
Changing Knowledge & Therapy

Understanding at cellular level

Genes

Proteins

Disease

Underlying Basic Biologic Defect

Targeted Drug Therapy

Gene Therapy

Stem Cell Therapy

Prevention

Diagnostics

Pharmacogenomics
Several genetic variants on chromosome 12, within genes that regulate prostaglandins, play central role in risk for colorectal cancers (see H. Nan and colleagues JAMA 313(11):1133-1142, 2015)
Changing Knowledge & Therapy

Understanding at cellular level

My cancer

Personalized / Precision Health Care
Two Examples of Specific Mutations in One Gene that Produce Different Phenotypes

**FGFR2** fibroblast growth factor receptor 2

**BRACA1/2** tumor suppressor genes
Breast and Ovarian Cancer and \textit{BRCA1}/2 Genes

- Most cases of breast and ovarian cancer that occur in the general population are not the result of an inherited mutation in the \textit{BRCA1} or \textit{BRCA2} genes.
- Only about 3 out of every 100 women who develop breast cancer will have a \textit{BRCA1} or \textit{BRCA2} mutation.
- About 10 of every 100 women who develop ovarian cancer will have a \textit{BRCA1} or \textit{BRCA2} mutation (variable SNP in sequence determines expression).
- For women who have a \textit{BRCA1}/2 mutation, the risk for early breast cancer and ovarian cancer is greatly increased (SNP location in sequence).
- In some families, breast cancer or ovarian cancer will occur due to inherited mutations in genes other than \textit{BRCA1}/2. However, this is uncommon.

Craniosynostosis Syndromes and FGFR2 Gene Mutations

- Different mutations (SNPs) in different locations within the DNA sequence of FGFR2 gene produce different phenotypes - - -Crouzon, Pfeiffer, Apert and/or Beare-Stevenson syndromes ("one gene produces different phenotypes")
Precision Medicine and Type 2 Diabetes: Lessons from Genetics to Epigenetics

- Known genetic variability (common SNPs) do not account either for current epidemics of type 2 diabetes or for family transmission of this disorder
- Rather, environmental factors illustrate extraordinary impact on natural history and/or epidemiology of type 2 diabetes
- Epigenetic mechanisms may explain familial aggregation of type 2 diabetes; certain epigenetic changes can be transgenerationally transmitted
- Cytokines & other metabolites affect DNA methylation and acetylation that reprogram specific gene expression and contribute to the type 2 phenotype
The Promise of Precision Medicine

The promise of precision medicine is delivering the right diagnosis and treatments, at the right time, to the right person. It is through this promise that we are given one of the greatest opportunities for new medical breakthroughs that we have ever seen.

Sylvia Mathews Burwell, HHS Secretary 3/20/15
Convergence between the Biological and Digital Revolutions Meet Craniofacial Anomalies
From Fish to Philosopher: “Evo-Devo” Evolutionary & Developmental Biology Reveal Highly Conserved Craniofacial “Blueprint”

Slavkin *Birth of a Discipline: Craniofacial Biology*, Aegis Communications 2012
Highly Conserved Homeotic Genes Control Craniofacial and Body Form (discovered in 1980s)

From flies to pediatrics, HOX genes regulate the entire body segmentation plan, from head to toe.

Slavkin *Birth of a Discipline: Craniofacial Biology*, Aegis Communications 2012
“A Tipping Point:” Thalidomide Tragedy Informs Teratology & Craniofacial Birth Defects (1950s – 1970s; Accutane in 1980s)
From Chromosome Discovery (1842)

To Karyotyping (1930s-1970s)


To The Transcriptome, To Proteomics

To Metabolomics, To “The Diseaseome”

To Pharmacogenomics and Systems Approaches

To Biomimetics and Tissue Engineering

To Regeneration and Nano-bio-informatics

To Phenomics, Precision Medicine and Beyond…
Genesis of Craniofacial (Multidisciplinary) Teams

Genetics as a Paradigm for Studies of Human Craniofacial-Oral-Dental Diseases and Disorders

“With the exception of trauma, essentially all diseases and disorders have a major genetic component (single or multiple genes & gene-gene and gene environment interactions).”


From Nucleus to Genetic Variance Including Mutations in One or More Genes

Genetic Code = Triplets or Codons (CGG, ATA)
Slavkin *Birth of a Discipline: Craniofacial Biology*, Aegis Communications 2012
SNPs (single nucleotide polymorphisms) are tools to identify minor genetic variance within genome-wide scans.
Human Genomic Math: 21,000 genes & 19,000 pseudogenes
Human Genetic Variations, and Variation in DNA Sequences (less than 0.1% of Human Genome)

3.2 billion letters of human DNA encoded within 21,009 genes
1 Base per 1,000 Shows Single Nucleotide Polymorphism (SNPs)
Regulation of Gene Expression through Epigenetic Processes (Epigenome)

From Family Genetic Pedigree to Gene Identification & Positional Gene Cloning
Phenomics: Decoding the Human Genome and Assigning Phenotype with Specific Gene(s)

- TNFSF4: Heart Attacks
- LCT: Lactose Intolerance
- CLOCK: Evening Preference
- SLC6A3: Substance Abuse
- CHRNA6: Linked to Tobacco Addiction
- OCA2: Blue Eyes
Next Frontier

Integrating genome-wide transcriptome, DNA methylation, and histone modification data with gene network and phenotype analyses will reveal the consequences of human disease- and disorder-causing mutations and introduce rational or precise drug design for many conditions.
Who pays for health care in 2015?

The government pays for it

Annual Medicare Part A Surplus or Deficit

Public Spending accounts for more than half all health care spending

Based on 2009 & 2013 Annual Report of the Board of Trustees of the Federal Hospital Insurance and Federal Supplementary Medical Insurance Trust Funds and 2005 & 2013 GAO reports
Healthcare Becoming Unsustainable

National Health Expenditures as Percent of GDP (1960-2020)

- $2.57 Trillion
- 19.8% GDP

Only 4 other countries have entire economies bigger than what we spend on healthcare.

Major Challenge: US Declining Health

Is this the future for our children?

1/3 to ½ become obese

1/3 get type 2 diabetes

Earlier disabilities

Life expectancy ↓ 2-5 yrs
Key Components of Craniofacial Health Care

Cost

Access

Quality

Which do you want? Can we have all three?
Craniofacial-Oral-Dental Genomics! Will Clinicians Ride the Wave or Watch From the Beach? Now is the time!
A call for increased education in genetics for dental health professionals. Collins & Tabak, 2004 JDE

A call for increased education in genetics for dental health professionals. Collins & Tabak, 2004 JDE

“Education is about the future, not the past, and we are now entering the era in which genetics and genomics will play a vital role in both oral health research and dental practice.”
Calls To Action for “Personalized Craniofacial-Oral-Dental Health” (2012-2015)

Personalized Medicine: Will Dentistry Ride the Wave or Watch from the Beach? Kornman & Duff, 2012 JDR

Personalized Oral Health Care: Providing “–omic” Answers to Oral Health Queries. Glick, 2012 JADA


Patient Stratification for Preventive Care in Dentistry. Giannobile, Braun, Caplis, et al. 2013 JDR

Personalized Medicine Enters Dentistry: What Might This Mean for Clinical Practice? Giannobile, Kornman & Williams. 2013 JADA

Revising the scope of practice for oral health professionals in health care: Enter Genomics. The Santa Fe Group (Primary Author Slavkin). 2014 JADA

From phenotype to genotype: enter genomics and transformation of health care. Slavkin. 2014 J Dent Res
Human genetics very successful at explaining diseases caused by single gene mutation (Mendelian Inheritance)

Mendelian inheritance of “traits” is very much the exception, not the rule.
...but most “traits” or common diseases are caused by a combination of multiple genes, gene-gene and gene-environment interactions, and epigenetics...

Genotype

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Phenotype

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Environment
Enter personalized health care to improve diagnosis, risk, stratification of patients “at risk,” and treatment for specific diseases and disorders.
NextSeq 500 Desktop Sequencer (from Illumina, San Diego)

- Faster (complete genome 8-12 hrs)
- Cheaper ($1,000 per human genome)
- Smarter (precise, efficient, accurate)
- DNA and RNA sequencing
- FDA approved in late 2013
- In 2015, now utilized in inherited disease detection, genetic variance and risk assessments, stratification of patients within large populations, and cancer diagnostics for treatment/chemotherapy selections
The Decreasing Cost of Genotype Information

Examples of the Regulatory Genes that Control Craniofacial-Oral-Dental Morphogenesis

• Anhydrotic Ectodermal Dysplasia: TNF-alpha ligand (ectodysplasin-A1) and receptor genes

• A Novel Oligodontia: PAX9 transcription factor gene

• Cleidocranial Dysplasia (supernumerary teeth): CBFA-1 transcription factor gene

• Rieger Syndrome (tooth number, size and shape): PitX2 transcription factor genes

• 700 genes identified in mice and 200 in humans (see Inborn Errors of Development)
Phenotype of the X-linked Anhidrotic Ectodermal Dysplasia (ED) child
Can we correct single gene mutations?

- X-linked Anydrotic Ectodermal Dysplasia
- Human defects include sweat and lacrimal glands, hair, nails and teeth
- Mouse animal models
- Dog animal models
- Define and measure clinical phenotype features

Therapeutic Strategies
- Inject TNF-alpha (EDA) during pregnancy
- Inject TNF-alpha (EDA) after birth
- “Proof of Principle”
- FDA approvals
- Public/private partnerships
- First patient injected with ED1200 protein in 2013; with clinical trial in progress
Slavkin *Birth of a Discipline: Craniofacial Biology*, Aegis Communications 2012
1990, Jonathan Zonana and Juha Kere discovered XLHED the gene mutation for X-linked hypohidrotic (anhydrotic) ectodermal dysplasia.

2000-2009, Oliver Gaide and Pascal Schneider identified ED1200 protein and showed that this protein rescued mutant *Tabby* strain mice with HED.

2006-2009, Margaret Casal rescued HED in a dog strain

2010, FDA approval EDIMER COMPANY begins “replacement therapy” trials with National Foundation for Ectodermal Dysplasia

2012-2013 Studies to better define and quantitate phenotypes

2013 First ED infant injected with ED 1200

2015-present Clinical Trial continues
Biomimetics... (to "mimic" biology) --- design and fabricate biological processes and biomaterials
Tissue Engineering for Challenges of Craniofacial-Oral-Dental Birth Defects, Head and Neck Trauma, Head and Neck Cancers & Behavioral Sciences Applications
Mesenchymal Stem Cells

Mesenchymal progenitors

- Pre-adipocytes
  - C/EBPβ
  - C/EBPδ
  - PPARγ
  - C/EBPα

- Myoblasts

- Pre-chondrocytes
- Proliferating chondrocytes
- Prehypertrophic chondrocytes
- Hypertrophic chondrocytes

- Col-II
- Sox5,6,9
- STAT1
- Runx2
- Osx
- Mx2
- Dlx5/6

- Col-I
- BSP
- Pre-osteoblasts

- Col-X
- Col-I
- BSP
- Pre-osteoblasts

- Myocytes
- Adipocytes
- Osteoblasts

MRFs
MEF2
Biomimetic Approach for Nose Replacement: Stem Cells, Scaffolds, Tissue Engineering and Biomaterials
Biomimetic Solutions for Nasal Carcinoma
Design and Fabricate Human Roots Using Stem Cells

Dental implant

Stem cell-mediated Root/Perio-complex regeneration

Porcelain Crown

Bio-root implant

Songtao Shi 2006
Reducing Scarring After Surgery or Burn Injuries

Scarring is an unmet medical need:

- Correction of birth defects, e.g. cleft lip and palate
- Reconstruction after injuries from war fighting or accidents
- Repair of burn injuries
- Revision of hypertrophic scars and keloids

Progress included:

- Identification and characterization of peptide
- In vitro work in cell cultures
- Studies in small and large animal models
- Scarless Laboratories, Inc. formed
- Pre-IND meeting with FDA
- Pre-clinical package in progress

Exploratory Grant (2007):
A Novel Peptide Inspired by Nature - Fibromodulin

Small Business Phase I Grant: Anti-scar Peptide for Cleft Lip Repair

Small Business Phase II Grant: Anti-scar Peptide for Cleft Lip Repair

First in man trial targeted for 2016

Fast Track
Advanced Head & Neck Cancer Treatments

- Monoclonal Antibody with Radioisotope
- Gene Therapy
- Modified Virus
- Encapsulated Drugs
- Nanomolecular “smart drug”
- Targeted Drug
- Photodynamic Therapy
- Imaging (X-ray, MRI)
- Cancer Targeting Therapeutic
- Apoptosis Sensor
- Cause of Disease Sensor
New studies demonstrate that perivascular mesenchymal stem cells (MSCs) contribute to endochondral as well as intramembranous craniofacial bone turnover. These $Gli1^+$ cells are located within suture mesenchyme and give rise to bone formation during development as well as in response to injury in adults. Ablation of $Gli1^+$ cells results in craniosynostosis.

The Next Frontier: Changing & Emerging Opportunities

The Next Ten Years (2025)

- Science-Based Health Care (Biomedical & Behavioral)
- Major Revision of Health Care Professional Education as a Function of Societal Needs (Interprofessional education & clinic care)
- Advocacy For Health Promotion, Risk Assessment & Disease Prevention
- Improved Cost Effectiveness & Clinical Efficacy
- Human Genome-Wide Scans for less than $1,000 per person
- Cellular, Molecular, Tissue and Organ Regeneration
- Virtual Surgery and Nano-instrumentation
- Advanced Bio-imaging
- Therapeutics & Rehabilitation of “Aging Populations”
- Access to Quality, Integrated, Coordinated and Comprehensive Health Care for all People at Reduced Costs in USA and beyond