Clinical and Translational Science Institute
Translating Research Into Improved Health
Building Research Infrastructure

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Outline

• Challenges
  – Health of our Nation
  – The Translation Gap

• Opportunity
  – UF Clinical and Translational Science Institute
    • Resources and services
    • Linking patients to consent and samples
    • Clinical trials infrastructure
    • Implementation science: personalized medicine
The Cost of a Long Life

Average Life Expectancy vs. Per Capita Spending (International Dollars)

- Life Expectancy
- Per Capita Spending

Countries included in the graph: Japan, San Marino, Monaco, Switzerland, Australia, Sweden, Iceland, Andorra, Canada, France, Italy, Spain, Norway, Singapore, Israel, Luxembourg, New Zealand, Netherlands, Germany, Greece, Malta, Belgium, Finland, Denmark, United States, Cuba, Cyprus, Ireland, Portugal.

In 2005, the United States ranked 30th in infant mortality.

Figure 1. Infant mortality rates, selected countries, 2005

How Do We Build A Healthier America?
Factors That Drive Health Outcomes

Health Outcomes
- Mortality (length of life)
- Morbidity (quality of life)

Health Factors
- Health behaviors (30%)
  - Tobacco use
  - Diet & exercise
  - Alcohol use
  - Unsafe sex
- Clinical care (20%)
  - Access to care
  - Quality of care
- Social & economic factors (40%)
  - Education
  - Employment
  - Income
  - Family & social support
  - Community safety
- Physical environment (10%)
  - Environmental quality
  - Built environment

Adapted from County Health Rankings model © 2010 UWPHI
The Translation Gap for T1 Research
More $ ≠ More Output

THE TRANSLATION GAP

NIH research project grants by degree of principal investigator

PhD
MD
MD-PhD

Pharmaceutical industry spending and output

Indexed to 1996 value (% change)

R&D expenditure
New molecular entity output

Source: NIH; CMR International & IMS Health
The Productivity Gap
New Molecular Entities and Biologic License Applications

Average R&D cost for each approved drug = $1.3 billion

Nat Rev Drug Disc 2010;9:89-92
...both health providers and members of the public, are not applying what we know.

...we are not reaping the full public health benefits of our investment in research.

...there is plenty of evidence that "old" research outcomes have been lost in translation as well.
It takes 17 years to turn 14 per cent of original research to the benefit of patient care

Original research

Submission

Acceptance

Publication

Bibliographic databases

Reviews, guidelines, textbook

Implementation

- Negative results: 18%
- Negative results: 46%
- Lack of numbers: 35%
- Inconsistent indexing: 50%

E.A. Balas, 2000
This is Not a New Problem: The Case of Scurvy

- **1593** - Sir Richard Hawkins recommended the following treatment for scurvy: "That which I have seen most fruitful for this sickness, is sour oranges and lemons."

- **1601** - Lancaster shows that lemon juice supplement eliminates scurvy among sailors (non-randomized controlled trial)

- **1747** - Lind shows that citrus juice supplement eliminates scurvy

- **1795** - *(194 years after Level 2 evidence)* British Navy implements citrus juice supplement
In 2006, NIH developed the Clinical and Translational Science Award (CTSA)

The CTSA consortium vision:
- to improve human health by transforming research and training environment to enhance the efficacy and quality of clinical and translational research

National Strategic Goals:
- National Clinical and Translational Research Capacity
- T1 Translational Research
- The Training and Career Development of Clinical and Translational Scientists
- Consortium-Wide Collaborations
- The Health of our Communities and Nation

The 61 CTSA institutions are linked together to transform the local, regional, and national environment to increase the efficiency and speed of clinical and translational research
CTSA: The National Consortium
UF CTSI Organization

- UF CTSI
- Tracking and Evaluation
- Stakeholders Group
- External Advisory Committee
- Community Engagement
- Regulatory Knowledge and Research Support
- Clinical Programs
- Laboratory Programs
- Training Programs
- Research Design and Analysis
- Personalized Medicine
- Biomedical Informatics
- Communications Research
- Pilot Programs
The Translational Research Continuum at UF: An Expansion of T3 and T4 Research

**T1**
What works under controlled conditions? (Translation to Humans)

- **Basic Biomedical Discovery**
- **What is the effect on population health? (Translation to Population Health)**
- **Clinical Efficacy**

2008 (n=862)
- 16% T1
- 20% T2
- 37% T3
- 27% T4

2011 (n=912)
- 18% T1
- 14% T2
- 48% T3
- 21% T4

**T2**
What works in real world settings (Translation to Patients)

**T3**
How can we change practice? (Translation to Practice)

**T4**
What is the effect on population health? (Translation to Population Health)

**Clinical Practice**

- CTSI Study Registry includes 9,401 human subject research protocols across four IRBs (medical and non-medical)
- 4,497 / 9,401 are considered medical and/or health related protocols
- 3,422 / 4,229 are categorized as translational research (T1 – T4)
Services and Resources for Development of a Successful Clinical Research Project

• Study Design and development
  – Biostatistics, qualitative/quantitative analysis, ethics, community access

• Regulatory and submission help
  – Online IRB submission (myIRB)
  – Budget and pricing tool, fixed Medicare rates for research
  – Research navigators, clinicaltrials.gov support
  – IND/IDE submission support

• Database and software development and support
  – REDCap or custom

• Communications research consulting (College of Journalism)

• Recruitment and retention services
  – StudyConnect, HealthStreet, ResearchMatch
  – Research Subject Advocate
  – Integrated Data Repository: Consent2Share and cohort discovery
  – Community research associates

• Tissue and sample collection and storage
  – Biorepository
UF Health Research Connection

Bridging resources for patients, research and care

• Link patients to researchers
  – StudyConnect
• Link researchers to patients
  – Consent2Share
• Link patient samples and medical data
  – Integrated Data Repository
• Link populations to research community
  – HealthImpacts
  – HCV TARGET
• Translate Discovery into health
  – Implementation science
Study Registry and StudyConnect

Study Registry: All (9,700) human subject studies approved by 4 UF IRBs from 2008 to date.
StudyConnect: Web site with 400 active studies for potential research participants to find opportunities.
UF Consent2Share
Consent for Research Use of Tissue and Data

• Initiated on 9/11/12
• Consent form given with admissions packet (pt. specific bar code)
• Consent asks 2 questions
  – Can we store your excess tissue with PHI?
  – Can we re-contact you for a future research study?
• Collected by admissions clerk, data entered into EPIC, consent form scanned with other documents
• Patient’s physician can access pt response, answer questions
• Informed Consent Hotline to answer initial questions
  – CTSI patient research advocate for more detailed queries
• Results to date: > 4,600 patients completed consent
  – 79% consent for re-contact for research
  – 84% consent for storage of tissues/samples
Translational Technologies and Resources Program

• **Overarching Goal**
  – Develop and Provide basic science tools and services for research

• **Services**
  – CTSI Biorepository (M. Clare-Salzer)
  – Genotyping (J. Johnson)
  – Biobehavioral (S. Nixon)
  – Human Imaging (S. Lai)
  – Biomedical Mass Spectrometry (T. Garrett)
  – Global Metabolomics (D. Powell)
  – Quality Assurance, GCP, GLP (C. Abernathy)
  – Simulation (S. Lampotang)
CTSI Biorepository

- Biospecimen collection, processing and storage. Stored biospecimens can be used by any researcher with IRB-approved protocols.
- Prospective biospecimen collection to fulfill investigator needs for IRB-approved protocols.
- Storage for biospecimens collected by investigators. Stored biospecimens belong solely to the investigator.
- Oversight of the release of biospecimens from the UF Department of Pathology for other IRB-approved research protocols.
- Pathology services including those provided by the Molecular Pathology Core and confirmation of diagnosis by a board-certified pathologist upon request.

One of two Hamilton Storage Technologies' SAM -80°C automated sample management systems (Robotic freezers). The biorepository also has eight Forma Thermo Scientific -80°C Freezers with back-up CO₂ and sensaphone alarm systems including back-up storage space, centrifuge for basic bodily fluid processing, QiaCube for small volume RNA, DNA and protein purification, Agilent Bioanalyzer for RNA, DNA and protein quality control analysis, OnCore BioSpecimen Management
Cohort Identification
Integrated Data Repository (IDR)

- Investigators use the IDR (themselves, or staff-facilitated) to identify numbers of patients meeting entry criteria for trials or data-based studies.
- If PHI on the cohort is needed, researchers may request access to the de-identified data from the IRB.
- Approved requests result in availability of a research-specific data set to the researcher in a secure environment.

Current content: 297,613 pts, 1.5 million visits from 6/1/11 forward
- demographics, diagnoses, procedures, visit details,
- PMP, Biorepository, Consent2Share

For more information: idr.ahc.ufl.edu or ctsi.ufl.edu
Adding the **Consent Process and Biorepository** to i2b2 for cohort discovery

UF & Shands Data

- Includes informed consent status

Research begins approved research

Hospital / Clinic Environment

Research Environment

**Research data request**

IRB request and approval for PHI research data

Researcher

- The researcher can find out how many patients have agreed to be contacted for future research projects.

Remove PHI

- Informed consent status

CTSI Biorepository
UF Health Research Connection
Bridging resources for patients, research and care

PARTICIPANTS

HEALTH CARE PROVIDERS

UF&Shands
Integrated Data Repository

UF Consent2Share

UF CTSI
Biorepository

RESEARCHERS

UF StudyConnect
UF-Affiliated Research Networks

- **Local/Regional**
  - North Florida Pediatric Community Research Network (Jacksonville area)
  - Jacksonville Health Equity Research Organization Practice-Based Research Network (JaxHERO)

- **Statewide**
  - Health IMPACTS for Florida (UF-FSU statewide research network)
  - Florida Neonatal Neurologic Network

- **National**
  - NHLBI Cardiovascular Cell Therapy Research Network (Carl Pepine)
  - NIDCR Dental Practice-Based Research Network (Valeria Gordan)
  - Hepatitis C Therapeutic Registry and Research Network (HCV-TARGET, Nelson)
  - Network for Pancreatic Organ Donors with Diabetes (nPOD)
  - NIH Pharmacogenomics Research Network (Julie Johnson)
  - Sentinel Network for Community-Based Participatory Research (Linda Cottler)
UF-FSU Community Research Program

Goal:
- Test interventions in physician practices;
- Translate research findings into improved health care quality; and
- Mentor medical students and trainees in conducting research and implementing research findings in practice.

Two pilot projects:
- Sports related concussion surveillance and management (PI: Bauer)
- Health risk assessment among adolescents in primary care (PI: Shenkman)

Funding:
- UF/FSU ($500,000)
- State of Florida ($600,000)
- NIH ($473,000)
Clinical and Translational Research Buildings

CTRB
- CTSI, IOA, Biostats, Epi, Health Outcomes & Policy
- 120,000 ft$^2$ total
- 20,000 ft$^2$ patient research
- Open: March 2013

Lake Nona-Orlando
- CTSI + IOA
- Clinical research unit
- Community engagement
  - HealthIMPACTS
  - HealthStreet
- Center for Pharmacometrics and Systems Pharmacology
- SBRI and OH partnership
Hepatitis C Therapeutic Registry and Research Network

**ClinicalTrials.gov Identifier: NCT01474811**

- **Mission**: to establish a nationwide registry of patients undergoing treatment with new therapies for HCV at both academic and community practices

- **Specific aims**
  - Improve information of populations underrepresented in phase III trials
  - Identify and remediate educational gaps and adverse event management
  - Serve as a core for collaborative, translational studies

- **Structure**
  - Chairs:
    - Nelson (UF): clinical coordinating center and biorepository
    - Fried (UNC): data coordinating center (REDCap-based)
  - Trial network: 27 academic institutions and associated community engagement outreach; centralized data collection service

- **Highlights**
  - Partnership: academia + industry + FDA/EMA
  - Funding: ~$12 million
  - > 1,500 pts enrolled to date (approx 200/month)
HCV-TARGET
Overview

• Longitudinal, observational study
  – Prospective and sequential, retrospective cohorts enrolling

• Inclusion criteria:
  – Adult patients (≥ 18 years) being treated with or who have been treated with antiviral regimens that contain oral direct acting antiviral agents

• Exclusion criteria:
  – Inability to provide written informed consent unless waiver of informed consent granted by local IRB

• Biorepository: baseline DNA and serum at key timepoints
  – Baseline, EOT (protocol or breakthrough/relapse), follow-up SVR (12 or 24)
Primary Specific Aims

- Safety and efficacy in populations represented and underrepresented in phase III clinical trials
  - African Americans / Hispanics, cirrhosis, null responders, age > 65
  - Subgroup analyses to determine the cumulative influence of IL28B, fibrosis, viral subtype (1a vs 1b), other co-morbidities
- To refine point estimates and narrow confidence intervals
- Adverse event surveillance and management
  - Anemia, rash, anorectal, dysgeusia, etc
- Virologic breakthrough and resistance
  - Biorepository sample collection
- Impact of viral load measurement on treatment efficacy
  - Compliance / utility of current futility rules
  - Clinical relevance of “detectable / BLOQ” vs “undetectable”
- Evaluate/inform FDA pharmacometric modeling
  - Unstudied populations and dosing regimens
Implementation Science
UF&Shands Personalized Medicine Program

• Background
  – Human genome project completed in 2001
  – Collins (NIH): expectation that an individual’s personal genome will be part of their medical record, from which information can be pulled to determine disease risk or guide treatment decisions

• Challenge
  – Despite the substantial number of important genetic discoveries made, there are limited examples of clinical translation to practice

• UF Objectives for Personalized Medicine Program
  – Engage UF&Shands Health System as leaders in genetic-guided care
  – Pre-emptively genotype on broad panel (256 SNPs) to mimic eventual reality of genomic data in EMR
    • Prepare health informatics systems to handle increasing amounts of genetic data linked into EMR
    • Define when and how to use genetic data in patient care
Personalized Medicine Program—Launched June 25, 2012

 UF delvers promise of personalized medicine to heart patients

Personalized medicine — a concept in which an understanding of a patient’s genetic makeup is used to enhance treatment — has arrived at UF&Shands, the University of Florida Academic Health [ ... ]

Clinical Translation in Genomics and Pharmacogenomics

UF&Shands Personalized Medicine Initiative

Clopidogrel (Plavix): genetic polymorphism of CYP2C19 leads to reduced ability to activate clopidigrel and increased risk of cardiovascular complication.
UF CTSI’s Vision
Improving the health of Florida’s communities with a focus on prevention and an emphasis on team science

• Learning Health System
  – “one which progress in science, informatics, and care culture align to generate new knowledge as an ongoing, natural by-product of the care experience, and seamlessly refine and deliver best practices for continuous improvement in health and health care” (IOM, 2007)
  – Put CTS research to work on health system priorities: quality, effectiveness, safety

• Linkage as “One Florida”
  – Cultivating an ability to work together with public and private partners to develop statewide collaborations and networks
    • UM CTSA award and statewide initiatives

• Human Investment-Team Science
  – Develop and sustain current and future translational researchers and strengthen the research workforce
  – Team science approach as basis for both patient care and research