Division of Health Sciences & Linus Pauling Institute
Ignite Research Colloquium
Chronic Diseases: Prevention, Detection, Management, and Treatment

MAY 9, 2019

WELCOME AND PRESENTATIONS
3:30–5:00 PM

WINE/BEER RECEPTION
5:00–6:00 PM

Oregon State University
Welcome - DHS and LPI Ignite Colloquium

• F. Javier Nieto, Dean, CPHHS
• Richard B. van Breemen, Director, LPI

Moderators:
• Marie Harvey, Associate Dean, CPHHS
• Mark Leid, Associate Dean, COP
• Luiz Bermudez, Associate Dean, CVM
Ignite Agenda and Timeline

3:30 – 3:45  Welcome

3:45 – 4:25  Session I
5 presentations; Q&A
5 presentations; Q&A

4:25 – 5:00  Session II
4 presentations; Q&A
5 presentations; Q&A

5:00 – 6:00  Reception: wine, beer, hors d’oeuvres
SESSION I
Areas of expertise: nutrient metabolism, diet/gene interactions, epigenetics, cancer prevention, inflammation & immune function

Current ongoing projects:
1. Benefits of zinc in human health across the lifespan
   – Zinc status and its effects microbiome and age-related immune dysfunction.
   – Genetic & epigenetic function of zinc during development and sensitization to environmental toxins

2. Dietary factors for cancer prevention (prostate and breast cancer) – Focus on cruciferous vegetables
   – Dietary epigenetic modulators, such as sulforaphane, for prevention- chromatin/non-coding/DNA methylation
   – Canine lymphoma projects
   – Metabolomic biomarkers
   – Diet/microbiome and cancer prevention interactions

Low zinc levels in the immune cells of aged animals

Sulforaphane (SFN), from broccoli slows prostate tumor growth
How does diet affect microbiome and response to toxicants?
Is the microbiome a determinant of diet-based chemoprevention responses?

Zinc Adequate

Zinc Deficient

Gaulke et al. (2018) mSphere
Gene-Environment interactions and cancer risk/survival in large cohort studies for precision medicine

Yumie Takata, Cancer and Nutritional Epidemiologist at CPHHS

Pooled Analysis of almost 2 Million Adults Worldwide

SWHS: Shanghai Women’s Health Study
SMHS: Shanghai Men’s Health Study
JPHC: Japan Public Health Center-based Prospective Study
OSU, OHSU and Portland VA

WHI: Women’s Health Initiative
VITAL: Vitamins and Lifestyle study
IWHS: Iowa Women’s Health Study
PLCO: Prostate Lung Colorectal and Ovarian Cancer Screening Trial
AARP: American Association of Retired Persons study
SCCS: Southern Community Cohort Study
NHS: Nurses’ Health Study
HPFS: Health Professional Follow-up Study

EPIC: European Prospective Investigation into Cancer and Nutrition

R03 CA 183021
Gene x Environment (modifiable factors) interactions for cancer risk using large data (VA, cohort, etc)

My expertise

• Nutritional and molecular epidemiologist
• Cancer and chronic disease epidemiologist (lung, colorectal, prostate and breast cancers)
• Data scientist (data cleaning and management and statistical analysis)
• Advanced SAS programmer
Nanoparticle-mediated mRNA therapy for muscle wasting disorders

Polymer + mRNA → Nanoparticle

Control Treatment

Ventral Dorsal

% Change in lean mass from baseline

Nanomedicine platforms for image-guided surgery and phototherpay

cancer endometriosis

Temperature, °C

Tumor Only Tumor + SiNc-NP Laser "On" Laser "Off"

32 34 36 38 40 42 44 46 48 50

0 250 500 750 1000 Time, s
We know that:

- Biomarkers for chronic illnesses are typically associated with mortality risk.

- Psychosocial factors such as control beliefs and negative meaning are associated with health in late life (Lachman et al., 2011; Pargament et al., 2000).

  - Why?
    - Health behavior habits, medical adherence explain only some of the variance.

- *Can psychosocial factors moderate the relationships of biomarkers to health outcomes?*
Do Psychosocial Factors Moderate the Effect of Biomarkers on Survival in Older Patient Populations?

Control Beliefs Moderate the Effect of HbA1c on Survival Time in Patients with Diabetes

- Control beliefs better predictor of mortality than HbA1c; HR = .66, p < .001; Interaction HR = 1.13, p < .05*

Negative Meaning in Life Moderates the Effect of Ejection Fraction on Survival Time in Patients with CHF

- Negative meaning a better predictor of mortality than ejection fractions; HR = 1.16, p < .001. Interaction HR = .99, p < .05*
How do variations in the diet and microbiome impact our exposure to chemical carcinogens in our diet? AHR, Indoles and Benzo[a]pyrene
Areas of Collaboration Needed-
- **Metabolomics**- composition of indoles- profiles distinct for diet and bacterial versus host tryptophan metabolites
- **Microbiome**- GF versus controls; inoculation with human fecal microbiome; impact of diet on mouse/human microbiome
- **Biostatistician**-

**Role of Dietary Indoles- Cruciferous Vegetable Diets**

**Role of Microbiome**
- Germ-Free
- Human Fecal Microbiome

Pharmacokinetics of oral $[^{14}\text{C}]-\text{BaP}$

Oral micro-dosing of $[^{14}\text{C}]-\text{BaP}$ and pharmacokinetics with UPLC-accelerator mass spectrometry

David E. Williams, Ph.D.
Helen P. Rumbel Professor for Cancer Prevention
Linus Pauling Institute
Environmental and Molecular Toxicology
Q & A
Research on Healthcare Access, Quality and Costs—Building on What We Learn About Care Coordination and Impacts

- Study and employ interventions to improve health care and to understand impacts on care coordination, quality of care, timeliness, costs, and patient satisfaction
- To reimagine care coordination and self-care that utilizes new technologies, tools and data for personal health records and health monitoring.

Denise M Hynes, BSN, MPH, PhD, RN, Professor, College of Public Health and Human Sciences, and Director, Health Data and Informatics (HDI) Program, Center for Genome Research and Biocomputing (CGRB), Oregon State University Research Health Scientist, US Department of Veterans Affairs

University email: hynesd@oregonstate.edu

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1. At a population level (and without intervention), what are the predicted outcomes for each risk group (as determined by acuity tool)?
2. What is the effect of a risk group intervention (coordination resources assigned) on outcomes (reduced morbidity, mortality and/or cost)?
3. In the absence of intervention, what proportion of patients are categorized into the "wrong" risk group (proceed to have outcomes at a much different level than expected)?
4. What are the associations between coordinator services and "right care at right time"?
5. Even with coordinator services, what proportion of patients do not receive care needed ("wrong care")?
6. What is the effect of right care at right time on outcomes (reduced morbidity, mortality and/or cost)?
Implementation of a Care Coordination Review Team to Improve Patient Outcomes

• **What it is:** Standardized multidisciplinary team process to assess health and social care needs/risk and assign a lead care coordinator/case manager

• **Study Objective/Activities:** Implement and plan for expanded implementation
  • Evidence base moderate/ major national initiative underway to leverage
  • Will assess best implementation strategy including developing training, guidebooks, methods to ensure fidelity, etc.
  • Develop evaluation plan

• **Implementation sites for Phase 1:** two VA facilities in Portland & Spokane
  • Focus on high risk and/or new patients

• **Interest:** 1) Implementation science experts 2) Seeking a non-VA integrated health care provider plan willing to do same
OSU Mass Spectrometry Center
Directors: Claudia Maier, Fred Stevens

- Capabilities
  - Small molecule characterization and quantification;
  - Pharmacokinetic studies
  - Metabolomics and lipidomics
  - Multi-analyte LC-MRM assays
  - Proteomics and PTM analysis
  - Protein structural analysis
- Infrastructure
  8 (UP)LC-MS/MS platforms
  1 APGC-MS platform
  Bioinformatics software tools
- Output
  ~30 Publications/year
- Research opportunities for (under)graduate students, postdocs, and visiting scholars

https://mass-spec.science.oregonstate.edu/
google search: Oregon State Mass Spectrometry
Established 1973-Serving OSU, UoO, OHSU
OSU Mass Spectrometry Center
Directors: Claudia Maier, Fred Stevens

Metabolomics/Lipidomics

• Protocols for metabolite/lipid extractions from cells, tissues, fecal materials and bio-fluids
• Botanicals; functional annotation of bioactives
• Functional annotation of microbes; metabolism
• High res accurate mass measurements of precursors and fragment ions
• In house metabolite library (>700 compounds) and library of natural products (>300 compounds)
• Software/bioinformatics in place
• Isotope tracer metabolomics/lipidomics

NIH S10 Stevens; ABSciex 5600 tripleTOF

NIH S10 Maier; Waters Synapt G2 HDMS RERF & Institutional Funds

Elie et al. Environ. Res. 2015
Miranda et al., J. Food Bioactives: 2018
Paulina Kaiser

- Courtesy faculty/instructor in Epidemiology
- Research Development Manager at Samaritan since 2016

Samaritan Health Services

- Nonprofit regional healthcare system
  - 5 hospitals (3 critical access) + ~80 outpatient clinics
  - ~189,000 patients in 2018
  - 100+ residents & fellows
- Samaritan Pastega Regional Cancer Center
- Samaritan Health Plans
  - InterCommunity Health Network Coordinated Care Organization (IHN-CCO)
  - Commercial plans, Medicare Advantage
Research Opportunities

- Population health
  - Chronic disease management
  - Access to care
- Social determinants of health
  - Integration into clinical settings
  - Evaluating impact
- Clinical outcomes
  - Readmission
  - Mortality

Resources

- Existing data
  - Epic EMR
  - Claims data
- Support for prospective research
  - Scientific Review Committee
  - Clinical Research Department
- Funding
  - IHN-CCO Delivery System Transformation (DST) pilot projects
PPMO: Peptide-Conjugated Morpholino Oligomers

- Block translation of mRNA
- Modify splicing of pre-mRNA
- Block poly-A signal sequences
- Block riboprotein binding sites
- Inhibit ribozyme activity
- Block RNA base editing
- Probe an RNA sequence, including MOVIE visualization of transcription
- Block viral cyclization sequences
- Protect miRNA targets on mRNAs
- Inhibit lncRNA maturation or activity
- Cause frameshifts at “slippery” mRNA sequences
- Inhibit miRNA maturation and activity
- Block splice regulatory protein binding to pre-mRNA
- Block proteins mediating RNA translocation (e.g. zipcode sites)

Cell-penetrating
Targeting
Endosomolytic

Cleavable
Non-cleavable
Biologically stable
Sequence-specific
Very low toxicity

PMO (Morpholino)

A, C, G or T

Delivery Peptide

Antisense PMO

PPMO: Easy-To-Use and Versatile Agent for Studying Gene Function In Vivo
Hong Moulton, CCVM, hong.moulton@oregonstate.edu

PPMO: Peptide-Conjugated Morpholino Oligomers

- Cell-penetrating
- Targeting
- Endosomolytic

- Cleavable
- Non-cleavable
- Biologically stable
- Sequence-specific
- Very low toxicity
**In Vivo-PPMO: Easy One-Step Protocol with Any Administration Route**

- Highly specific gene-regulation reagents requiring **NO DELIVERY ASSISTANCE**
- Water-soluble
- Effective on cultured cells, ex-vivo tissues and in vivo, regularly used to perform transient in vivo knockdown
- Used in experimental systems and clinical applications
- Not available commercially. We make them in my lab at OSU.
  - Design Morpholino sequences for your targets and applications
  - Select delivery and/or targeting peptides, and linkers
  - Produce PPMO for your applications
  - Collaborate in grant proposals

* hong.moulton@oregonstate.edu
UK Biobank

- Data collected between 2006 and 2010
- ~10 million written invitations were mailed to individuals aged 40 to 69
- 22 geographically distributed assessment centres
- 500,000 people (5.5% response)
- Focus of data collection is on clinical and biomedical data

About 15 million aliquots of samples are stored in a freezer located in a laboratory building in near Manchester constructed specially for that purpose.
## Association of causal risk factors with cardiovascular disease mortality in UK Biobank and HSE-SHS cohort studies

<table>
<thead>
<tr>
<th>Exposure</th>
<th>N</th>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P_diff</th>
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<tbody>
<tr>
<td>Male sex</td>
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<tr>
<td>UK Biobank</td>
<td>502655</td>
<td>2251</td>
<td>3.78 (3.42, 4.17)</td>
<td>0.000</td>
</tr>
<tr>
<td>HSE/SHS</td>
<td>89895</td>
<td>1596</td>
<td>2.22 (2.00, 2.46)</td>
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<tr>
<td>Self-reported diabetes</td>
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<tr>
<td>UK Biobank</td>
<td>500038</td>
<td>2233</td>
<td>3.73 (3.38, 4.12)</td>
<td>0.360</td>
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<tr>
<td>HSE/SHS</td>
<td>89871</td>
<td>1596</td>
<td>3.43 (2.96, 3.96)</td>
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<td>Physically inactive</td>
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<tr>
<td>UK Biobank</td>
<td>495497</td>
<td>2162</td>
<td>3.40 (3.04, 3.80)</td>
<td>0.000</td>
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<tr>
<td>HSE/SHS</td>
<td>56703</td>
<td>933</td>
<td>2.33 (2.02, 2.68)</td>
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<tr>
<td>Hypertension</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>UK Biobank</td>
<td>494047</td>
<td>2179</td>
<td>1.89 (1.69, 2.11)</td>
<td>0.003</td>
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<tr>
<td>HSE/SHS</td>
<td>88193</td>
<td>1583</td>
<td>2.48 (2.14, 2.86)</td>
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<tr>
<td>Current or former cigarette smoker</td>
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<td></td>
<td></td>
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<tr>
<td>UK Biobank</td>
<td>499701</td>
<td>2224</td>
<td>2.04 (1.87, 2.24)</td>
<td>0.757</td>
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<tr>
<td>HSE/SHS</td>
<td>89766</td>
<td>1592</td>
<td>1.99 (1.78, 2.23)</td>
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<tr>
<td>Current non-drinker</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>UK Biobank</td>
<td>501152</td>
<td>2240</td>
<td>1.94 (1.72, 2.20)</td>
<td>0.037</td>
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<tr>
<td>HSE/SHS</td>
<td>89845</td>
<td>1592</td>
<td>1.59 (1.38, 1.83)</td>
<td></td>
</tr>
<tr>
<td>Age (per 5 years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK Biobank</td>
<td>502655</td>
<td>2251</td>
<td>1.65 (1.59, 1.70)</td>
<td>0.057</td>
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<tr>
<td>HSE/SHS</td>
<td>89895</td>
<td>1596</td>
<td>1.81 (1.75, 1.88)</td>
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<td>Obesity (BMI &gt;=30 kg/m2)</td>
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<tr>
<td>UK Biobank</td>
<td>499589</td>
<td>2204</td>
<td>1.68 (1.55, 1.83)</td>
<td>0.064</td>
</tr>
<tr>
<td>HSE/SHS</td>
<td>82656</td>
<td>1411</td>
<td>1.47 (1.31, 1.64)</td>
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</tbody>
</table>
SESSION II
Ling Jin

- Born in P.R China, Jiangsu Province, Xuyi City
- DVM & MS (Microbiology) at Nanjing Agricultural University
- Ph.D. (Virology) at University of Illinois at Urbana-Champaign
- Post-Doc at Cedar-Sinai Medical Center, University of California at Irvine, House Ear Institute
- Faculty at OSU since 2004
Research

• Latency of herpesviruses
  – HSV-1, RHV (LHV-4), KHV
  – Create mutants (deletion or insertion) to address the roles of viral genes during latency in animal models

• What is the mechanism of herpesvirus latency? How does dormant viral genome become active following stress?

• Stress/immune responses and DNA replication
Persistence of foot-and-mouth disease virus in African buffalo

FMDV is highly contagious! How does FMDV persist in its natural host? 3 serotypes.

COHORT STUDY
Herd of 60–70 buffalo
Capture every 2–3 months for 3 years
Monitor FMDV transmission

EXPERIMENTAL STUDIES
Infect buffalo with FMDV
Allow naïve animals to contact
Monitor FMDV transmission

MATHEMATICAL MODELING

Only acute transmission
=> Extinction!

With chronic transmission
=> SAT1: Persistence!
SAT3: Maybe

Other hypotheses:
SAT2: Antigenic shift
SAT3: Antibody loss

SAT1: $R_0 = 15.8$
SAT2: $R_0 = 7.5$
SAT3: $R_0 = 5.2$

time (0–1 y)

time (0–10 y)
The Sanders Laboratory: Zebrafish models of chronic infectious disease

• Mycobacteria
  • Rising rates of nontuberculous mycobacterial diseases

• *Toxoplasma gondii*
  • An estimated 1/3 of the world population is infected with *T. gondii*
  • Is the 2nd leading cause of death from foodborne illness in the U.S.
  • The most common retinal infection in the U.S.

• Intestinal nematode infections
  • Cause 5.2 million disability-adjusted life years globally

Department of Biomedical Sciences
Email: Justin.Sanders@oregonstate.edu
Objectives

1. Define the immunological impacts of chronic infections on *D. rerio*

2. Develop assays to measure functional immunological endpoints in zebrafish


Department of Biomedical Sciences
Email: Justin.Sanders@oregonstate.edu
Immunotherapy is now a first treatment option for many types of cancers

- Cytotoxic T cells can distinguish diseased cells from healthy cells.
- Most immunotherapies are designed to enhance T cell functions and numbers.

How do T cells recognize transformed cells?
Direct MHC class I antigen presentation: Peptide display at the cell surface reveals the intracellular proteome

What aspects of cellular biology alter antigen presentation?

Current Projects in the Lab
• Ubiquitin, UBL, and ubiquitin ligase activity
• The unfolded protein response
• Proteasome function
Gut-brain axis: emerging roles of gut microbiome in Autism

Maude David
Assistant Professor
Microbiology & Pharmaceutical Sciences
davidlab.science.oregonstate.edu
Computational Biology

Microbial Ecology
Metabolism

Clostridium celatum

Prokaryote: 16S, Metagenomes
Human Variant Analysis

Behavior Analysis
Elevated Plus Maze
Open field habituation
Prof. Kathy Magnusson

Eukaryote Cell Cultures
Enteroendocrine cells
- Vagus nerve
Prof. Pat. Chappell

ck labelled mice!

Electrophysiology
Dr. Kenton Hokanson

Transcriptomics

SBIR with Second Genome Inc & crowdsourced study
=> Microbial compounds

maude.david@oregonstate.edu
Vitamin C: magic bullet for alleviating complications of metabolic syndrome (MetS)?
Maret G. Traber

• MetS is diagnosed based on the presence of at least 3 of 5 cardiometabolic risk factors: hypertension, hyperglycemia, central obesity, hypertriglyceridemia or depressed high-density lipoprotein (HDL)

• MetS is associated with increased gut-derived endotoxin

• Metabolic endotoxemia
  • drives inflammation in MetS
  • increases the risk of more advanced disorders (e.g. type II diabetes, nonalcoholic fatty liver disease; NAFLD)
MetS is associated with impaired gut barrier function that increases gut-derived endotoxin (LPS), which is translocated via the portal circulation to the liver.

MetS is associated with impaired vitamin E bioavailability and low plasma vitamin C.
• Current collaborations via IGNITE - w/ Dr. Maude David - explore potential hormonal mimetics synthesized via gut microbiome.

• **Project 1**: Combination of two existing projects:
  • Neuroendocrine regulation of reproduction
  • Hormonal influence on osteosarcoma

• **Needs**:
  • Evaluation of osteoblast differentiation and osteoid production in vitro
  • Proteomic data interpretation/analysis

Chappell lab: Circadian Clocks, Reproduction, and Cancer
Dr. Patrick Chappell, Dept. of Biomedical Sciences
patrick.chappell@oregonstate.edu 541-737-5361

Weinman et al., BMC Cancer 2019
Herber et al., Nature Comm 2019
- **Project 2**: Effects of light-at-night exposure on mouse mammary tissue:
  - Epigenetic changes (methylation only so far)
  - Selected commensurate expression changes

- **Needs**:
  - Bioinformatic advice/help: have we done everything we can with the dataset?
  - Best *in vitro* model to use to pursue promising candidates
LEAP
Lifestyle | Eating | Activity | Progress
30-Day Lifestyle Medicine Intervention

Format
- Modeled after gold standard CHIP
- Pre & post-health screens and labs
- 3 hours, 3 evenings/week x 4 weeks

Content
- Health benefits of plant-based meals
- 60-90 minutes of instruction by RD & other professionals
- Interactive activities, group discussions & problem-solving

Homework
- Cooking class meals
- Book & DVD reviews
- Giving a food demo

Lab Results | Group support | Food Tasting | Education | Personal study | Practice

WHY IT WORKS

www.chiphealth.com
LEAP RESULTS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CHIP</th>
<th>LEAP</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight in pounds</td>
<td>-6.1</td>
<td>-5.3</td>
<td>0.34</td>
</tr>
<tr>
<td>BMI</td>
<td>-1.0</td>
<td>-1.0</td>
<td>0.41</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>-0.9</td>
<td>-1.0</td>
<td>0.33</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>-0.2</td>
<td>-0.2</td>
<td>0.35</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>-2.1</td>
<td>-2.0</td>
<td>0.29</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>-1.7</td>
<td>-1.3</td>
<td>0.48</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>-0.4</td>
<td>-0.3</td>
<td>0.25</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>-4.4</td>
<td>-4.0</td>
<td>0.21</td>
</tr>
<tr>
<td>Blood sugars (mg/dL)</td>
<td>-6.2</td>
<td>-0.2</td>
<td>0.044</td>
</tr>
</tbody>
</table>

Lifestyle Medicine

- Works as well as medications
- No negative side effects
- Favorable effects on multiple conditions
- People will accept it when they know it works
- CHIP is reimbursable by BCBS & Medicare
- Empowering to participants

Recommend that lifestyle medicine programs be used as the first step in reducing risk factors for chronic disease.

The greatest results were seen in those with the highest risk.

THANK YOU!

Stephanie Polizzi, MPH, RDN, CHES, FAND
Coos/Curry OSU Ext Family & Community Health
stephanie.polizzi@oregonstate.edu
1. Strategies to reduce risks of rx opioid misuse, opioid use disorder, and overdose

2. Economics of Drug to treat Multiple Sclerosis
Using linked administrative data to evaluate interventions to reduce risks related to opioid crisis in Oregon

Prescription Opioid Performance Improvement Metrics and Heroin Abuse [CDC 5U01CE002786-02]
- Study 1: Rx opioid dispensing patterns prior to heroin overdose
- Study 2: Rx opioid dispensing patterns prior to self-reported heroin initiation
- Study 3: Characterizing patterns of dose reduction in discontinuation among chronic opioid therapy patients

Reducing Overdose After Release from Incarceration (ROAR) [R01CE00300]
- Pilot study to evaluate opioid overdose prevention program for women with OUD released from OSP (Community navigator (CRM) plus MAT (naltrexone) upon release)
- Linked administrative data that includes: DOC, Medicaid, HDD, vital stats to estimate fatal and non-fatal od after release

Data Sources | Measures
--- | ---
MOTS | Demographics, diagnoses, enrollment
MMIS | Non-fatal hospitalization outcomes
MOTS | Prescription opioid and heroin-related treatment outcomes
Vital records | Prescription opioid and heroin-related fatalities
PDMP | Prescription opioid patterns of use
Thank you – Please join us at the reception!