Institute for Exposomic Research, Icahn School of Medicine at Mount Sinai

The Exposome & Precision Medicine

"*Everything that rises must converge*"
Flannery O'Connor

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Ethel H Wise Professor and Chairman

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Director: Mount Sinai Institute for Exposomics

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What is Precision Medicine?

- NRC Definition
  - Tailoring of medical treatment to the characteristics of each patient.
    - classify individuals into subpopulations that differ in their susceptibility to a disease, prognosis, or response to a specific treatment.
    - Interventions are concentrated on those who benefit, sparing expense and side effects for those who will not.

In essence, it means understanding the patient's *individual background*
- that influences disease severity, progression and response to treatment

Operates in a setting where the Probability of illness = 1 (i.e. prevention no longer matters)

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The promise of precision medicine

- *Pharmacogenomics*
  - *Increased drug efficacy & decreased toxicity*
  - *Decreased exposure to ineffective drugs*
  - *Target therapy to the most effective drugs*
  - *Targeting of behavioral modifications based on individual risk factors*
- Improved counseling and decision making
- Improved patient outcomes and satisfaction
- Improved tolerance of therapy → improve adherence

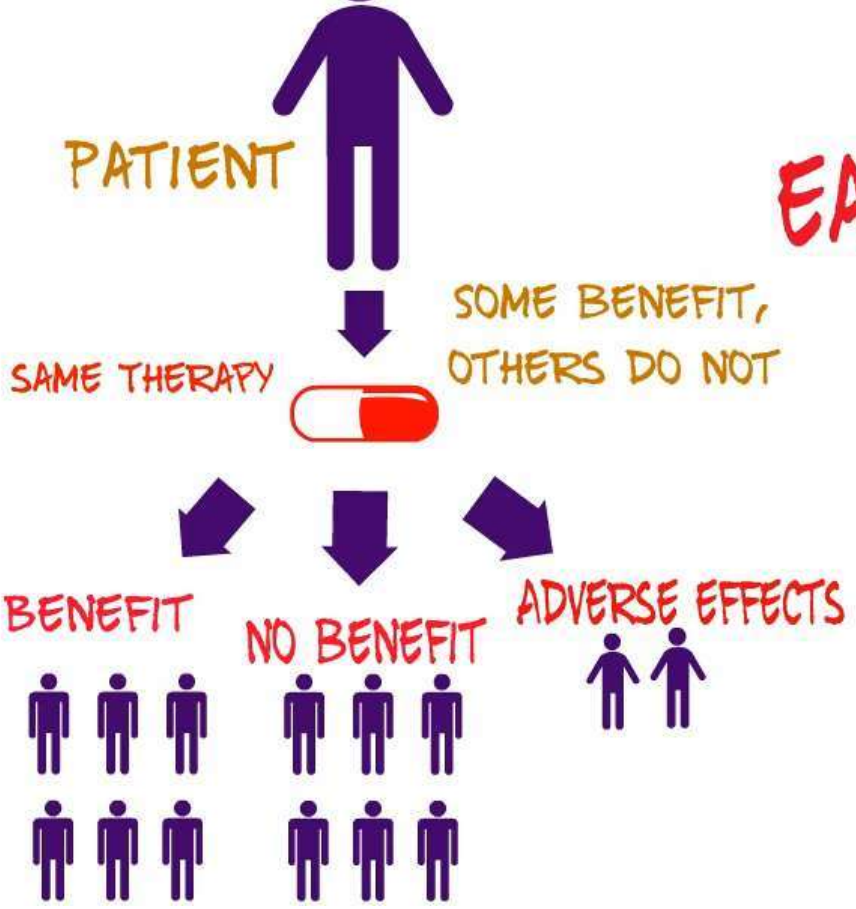**But we know that genetics is only 1 piece of a much bigger puzzle**

Genes
Behavior
Nutrition
Infections
Chemicals
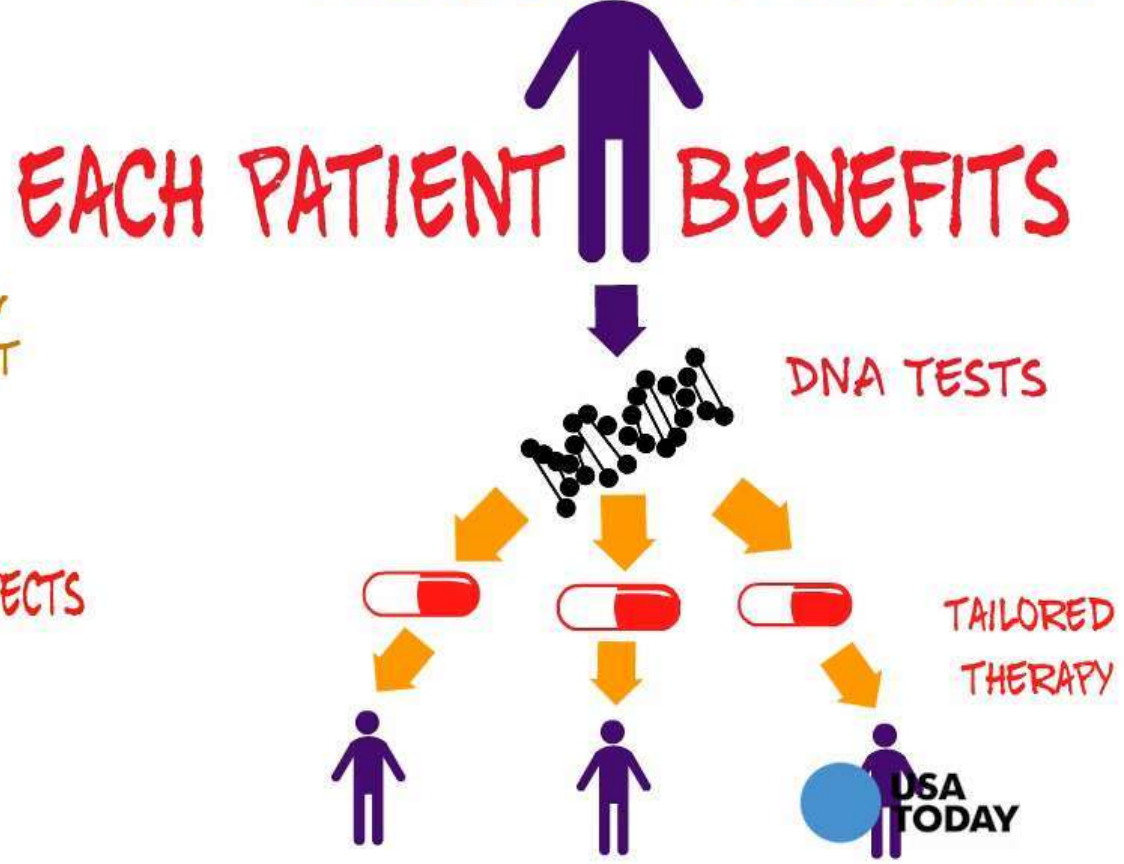Physical environment
Culture/society
Stress

Introduction to the special issue in Science was entitled:
"It's Not Just the Genes" Vol 296, 2002
Paula Kiberstis, Leslie Roberts

For many programs in Precision Medicine, there is no mention of environment

Complex Disease Research

"So, how did we get here?"
-David Byrne

ADHD, Obesity, Asthma, COPD, Parkinson's, Cancer etc.

- Etiology-mix of genetic/environmental risk factors
- Rising in prevalence/annual incidence
- Genetic main effects cannot explain rising rates
- Environmental risk factors largely unidentified
- Too much "Nature vs Nurture"
  - Heritability estimates
  - Genetics confers risk, not causation
  - Environment works on a genetic background

Why are Diseases called "Genetic" or "Environmental"?

- Genetic polymorphism low in prevalence, and environmental factor high in prevalence

  - disease appears genetic

- Environmental factor low prevalence, Genetic polymorphism high in prevalence

  - disease appears environmental

Example: Are Yellow Shanks genetic or environmental?

- Yellow shanks- discoloration of chicken "legs" with a particular genetic variant when fed yellow corn (as opposed to white corn) (Ken Rothman example)
  - Autosomal dominant

Farmer Jones

Inbred Chicken Flock
        All carry Variant for
        Yellow Shanks
Feeds White corn
Store Runs out
        Feeds Yellow corn
        all chickens get yellow
        shanks

Farmer Smith

Inbred Chicken Flock
        Do not Carry variant
        for Yellow Shanks
Feeds Yellow corn
New Mutation
        1 Chicken gets shanks
        ½ his offspring get
        Shanks and so on

Is Yellow Shanks Environmental or Genetic?
Is Cancer Environmental or Genetic?
Is Phenylketonuria Environmental or Genetic?

What is the heritability of Chicken Shanks?

All Genes operate in variable environmental backgrounds

The Exposome encompasses all environment

It's not just chemicals

- *The exposome is all of these*

And there are Many, Many Backgrounds

- Nutrition
  - Obesity
  - Vitamin/mineral deficiency
- Health
  - Disease states change metabolism
    - And increases risk of exposures to multiple drugs
- Sex
  - Hormones can change metabolism
  - Pregnancy
- Geography/culture
- Mixtures of chemicals

Why is this important?

- A 53 year old develops a DVT on a trans-pacific flight
  - Develops GI bleed after starting standard dose of warfarin

- A 17 year old child with autism has a notable increase in head banging and anger outbursts

  - Blood lead level is 73 ug/dL
  - His 3 year old brother's blood lead is 2 ug/dL.

Why is this important?

- A newborn infant in rural Iowa is cyanotic but behaving normally
  - Cardiac referral –Echo- normal heart
    - Methemoglobin level is 24%
    - 5, 10 year old siblings MHB <1%

- A 14 year old with GE reflux is treated with morphine for a fracture and develops respiratory failure.

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Precision Medicine- A Genocentric Science

- Why has Precision Medicine largely ignored Environmental Contributors to ?

  – Disease mechanism

  – Diagnosis of disease

  – Response to Treatment

Environmental Health: A Prevention Centric Science

- *Why has Environmental Health largely ignored*
  - *Role of Environment in Response to Treatment*
  - *Effects of environment on people "with" a disease*
    - *Disease severity or progression*
- *Largest vulnerable population to environment may be those with a chronic disease*
  - *But we rarely study them*

Medicine and Public Health "Ghost" each other

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Where are the roadblocks?

Medicine

- Individual level
- Diagnosis
  - Certainty a problem exists
- Treatment
  - Side effects
  - Outcomes

Environment and Public Health

- Population level
- Risk factors
  - If exposed will you get sick?
  - Probability of illness
- Prevention
- Susceptible populations

Medicine starts _after_ the person is sick, Public Health starts _before_; wants to discover "why" and to prevent

Medicine is not interested in "why"; medicine is interested in "how" to treat the situation that exists
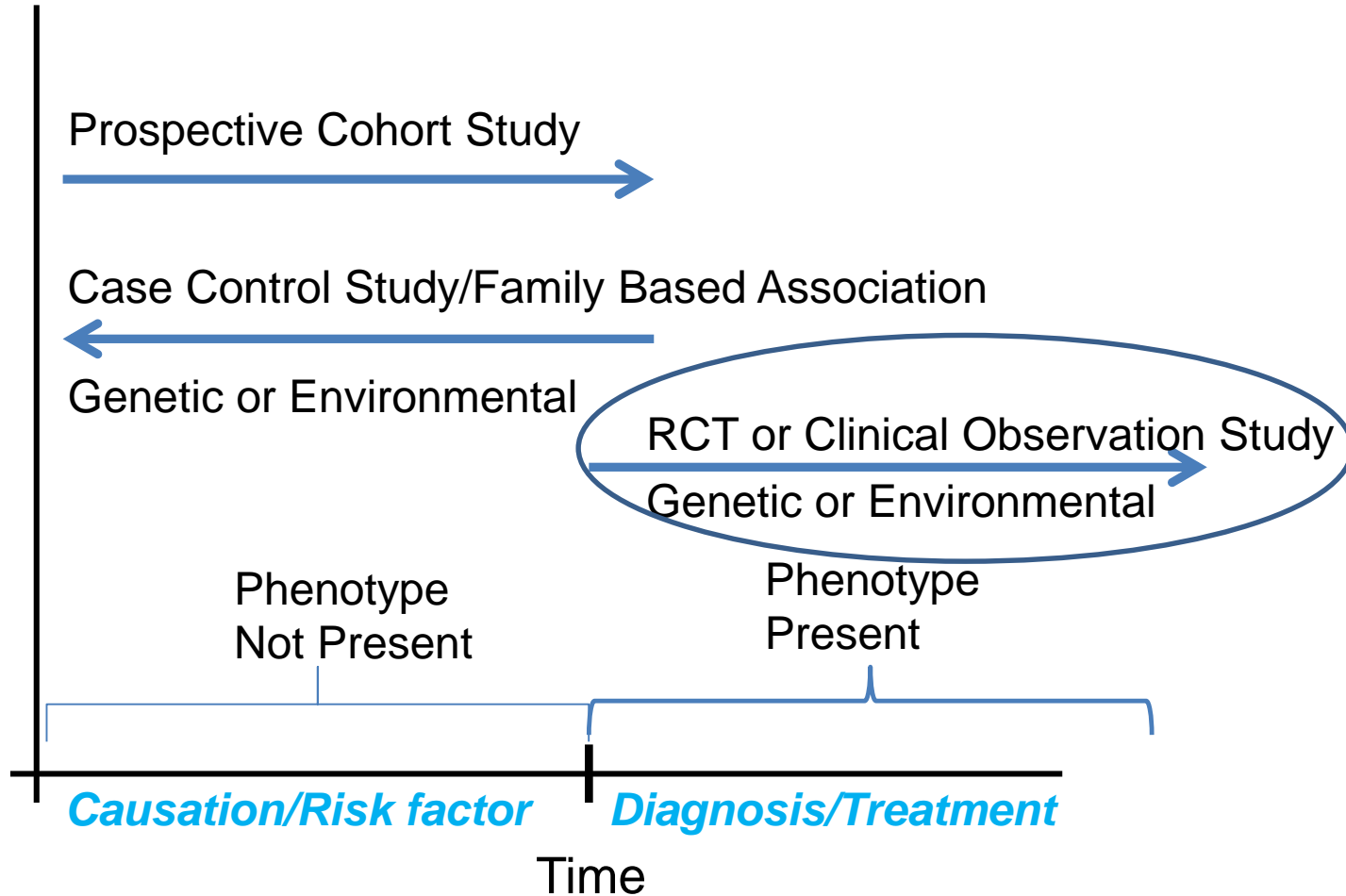
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The Medical Perspective

- Help me diagnose the patient
  - Exposomics in Epidemiology might help
    - Risk factors are a kind of weighted variable
- Help me treat the patient
  - Exposomics in Epidemiology doesn't help
    - I will ignore study results
    - Example
      - Smoking and lung cancer/heart disease

There are no right answers to wrong questions.

Ursula K. Le Guin

Public Health Research vs Clinical Research

Prospective Cohort Study

Case Control Study/Family Based Association

Genetic or Environmental

RCT or Clinical Observation Study

Genetic or Environmental

Phenotype
Not Present

Phenotype
Present

Causation/Risk factor   *Diagnosis/Treatment*

Time

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Precision medicine studies should start after disease onset and move forward in time.

What are the most important backgrounds in Precision Medicine?

- Not genes and not environment but *disease and treatment*

We need to do the studies that Physicians need to treat patients
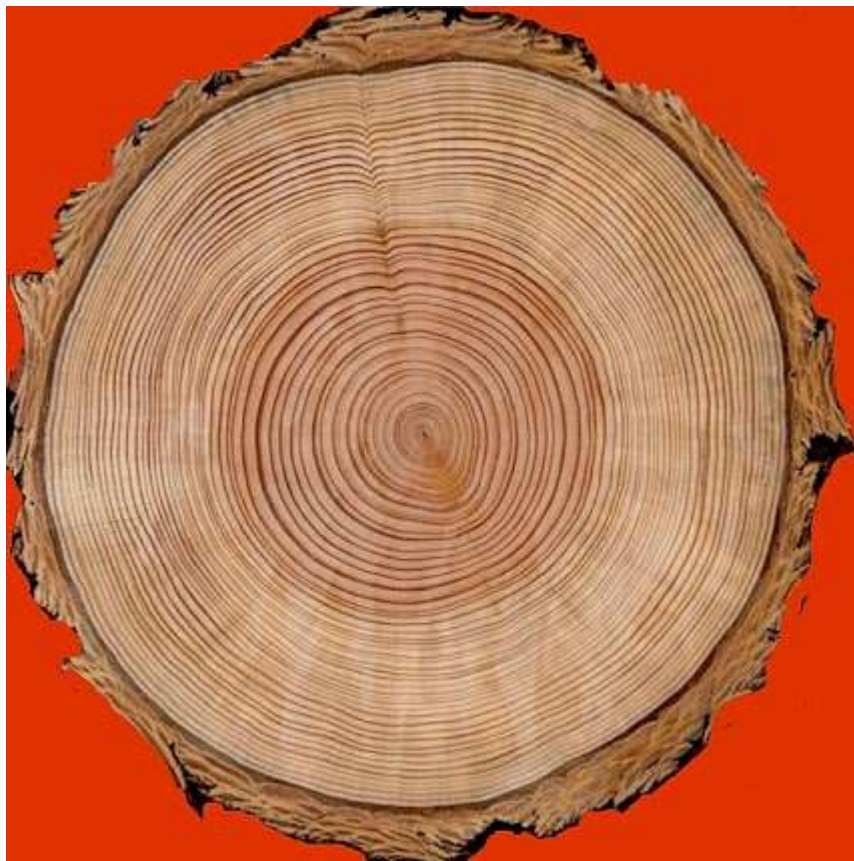
And right now we are not

Can the Exposome operate in the Medical World?

- Yes, if we believe that environment impacts
  - Diagnosis,
  - Treatment variability
  - Side effects
  - Disease Progression and prognosis
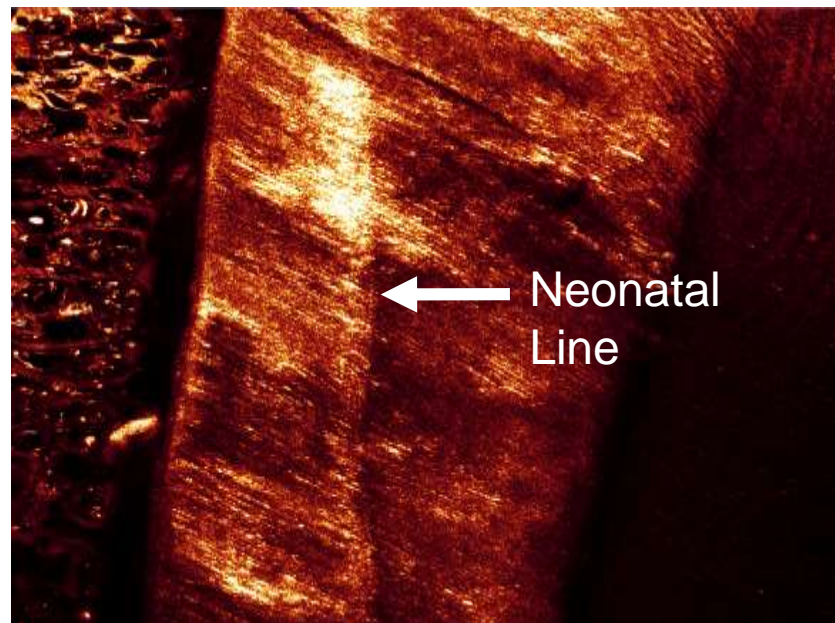
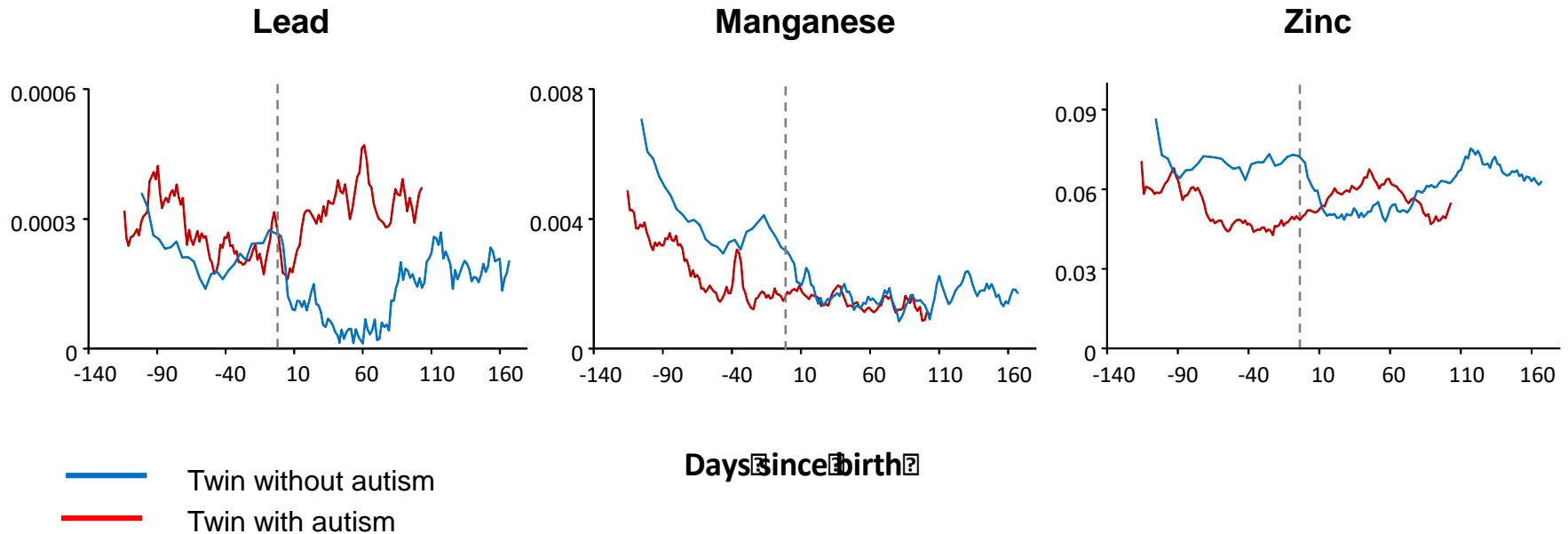# What if we could go back in time?

Growth rings in a tree

Growth rings in teeth

Manish Arora et al

Neonatal Line

How can we leverage this information clinically ?

Monozygotic Twins: discordant for Autism

Arora, M et al., Nat Commun. 2017

Lead   Manganese   Zinc

Days since birth

Twin without autism
Twin with autism

Greatest value may be in diagnostics (schizophrenia?)
Impacts on Treatment options?

Maybe, maybe not

Precision Exposomics: Medicine vs Public Health

- **Medicine**
  - "time travel" not necessary
  - Causation irrelevant
    - Nonspecific phenotypes might not matter
  - counsel people at individual level
    - Sick people listen
  - Sick people=higher recruitment and retention

- **Public Health**
  - "time travel" helps
  - Causation is goal
    - Many causes, many phenotypes/subphenotypes
  - counsel people at population level
    - Healthy people don't listen
  - Healthy people= harder to recruit and retain

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Barriers and Opportunities

- Clinical Diseases may be relatively rare
  - May require networks to identify sufficient patients
- Environment may be "place based"
  - Air pollution, pesticides, lead, etc
  - Networks may increase geospatial variability
- Few Physicians trained in Environmental health or epidemiology
  - Occ Med and PEHSU are exceptions
  - Know little about environmental health or toxicology
  - Most think genetics is more important than environment
- Few Env. Epidemiologists conduct Clinical research
  - Don't have easy access to patients
  - May know a lot of risk factors and little about treatment
- Partnerships are complementary

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Precision Exposomics: Why Now?

- Exponential advances made in exposure science in the last 10 years

  - Untargeted chemical assays
  - Higher dimensional chemical panels
    - Endogenous and exogenous chemicals
  - Satellite Remote Sensing
  - Public Database mining
  - EMR mining
  - Wearable devices
  - Big data computational infrastructure

Untargeted Assays

- May aid in diagnostics
- Cohort or case control
  - May or may not inform treatment/disease progression
  - Clinical cohort or RCT
    - May have predictive signatures
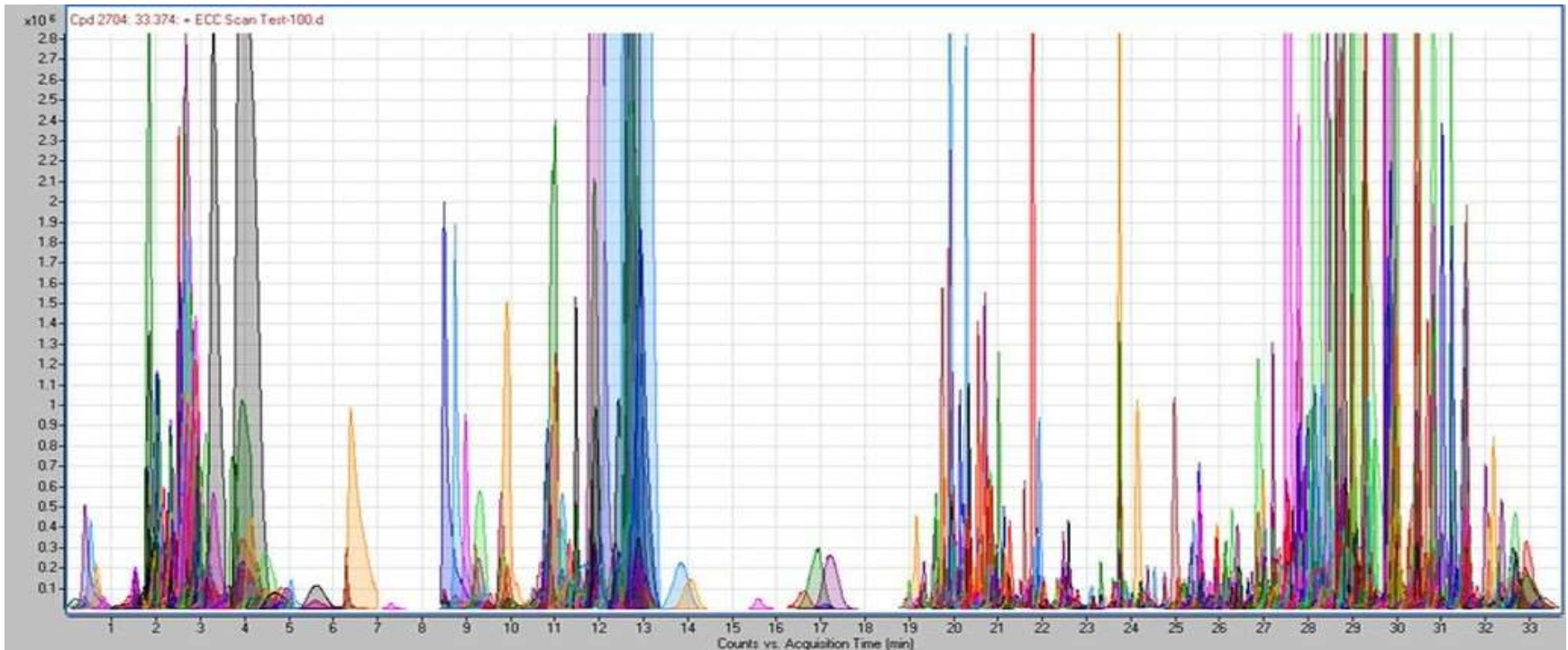
Operationalizing the Exposome in PMI: Untargeted Chemical Screens

- Case control study may be useful for diagnosis

- Untargeted Assays need to be run in cohorts of patients prospectively (RCT?)

  – Predict risk of complication(prior and during treatment)

  – Response to treatment (prior to starting)

Study Design matters when applying exposomic data

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Wearable Devices

- Wearable devices & "Internet of Things",
  - phone apps, cars, appliances sensors, etc.
    - Effectors enable objects to exchange data through the internet with other connected devices.
    - Download GPS and physiologic data directly

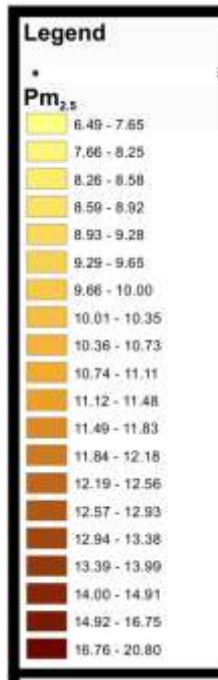Kuva 1. Internet of Things. Lähde: Huffington Post

'Smart Wristband'

Flexible sens

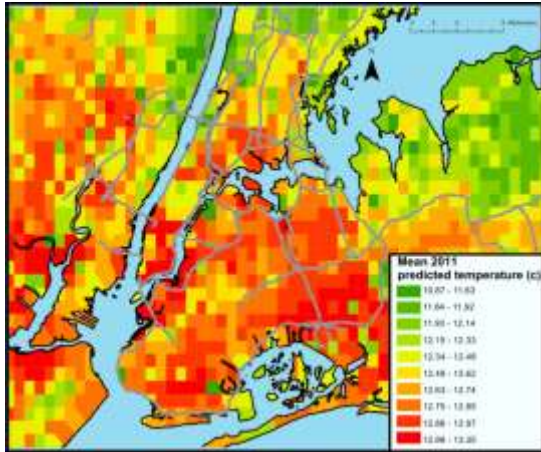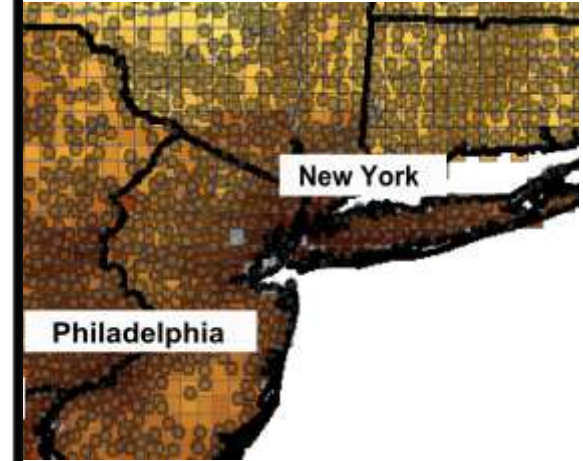Wireless flexible PCB

Wearable Devices

- Healthy people
  - Limited assistance in disease management
- Sick people
  - Track Response to treatment / disease progression
    - Track activity during chemotherapy, Parkinson's disease etc.
    - Heart rate variability and air pollution after coronary artery bypass
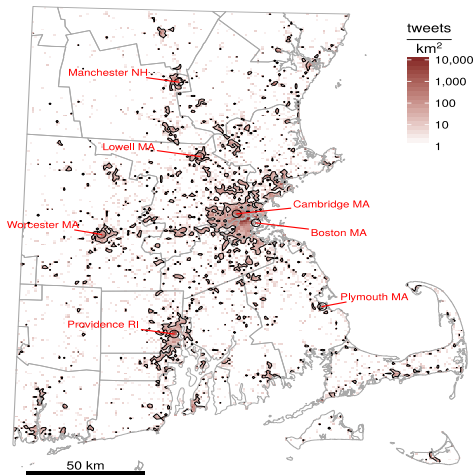
Leveraging GIS for the *External Exposome*

Daily Air pollution

Legend
Pm$_{2.5}$

6.49 – 7.65
7.66 – 8.25
8.26 – 8.58
8.59 – 8.92
8.93 – 9.28
9.29 – 9.65
9.66 – 10.00
10.01 – 10.35
10.36 – 10.73
10.74 – 11.11
11.12 – 11.48
11.49 – 11.83
11.84 – 12.18
12.19 – 12.56
12.57 – 12.93
12.94 – 13.38
13.39 – 13.99
14.00 – 14.91
14.92 – 16.75
16.76 – 20.80

New York

Philadelphia

Air Temperature/Climate

Exposure to green, natural areas

Social Media Content

Access to Healthy Foods

Traffic patterns
Noise

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Operationalizing the Exposome in PMI: Geomedicine

- Wearable device data
  - Activity, Air pollution, temperature, physiologic data
- Address history of residence
  - Back to childhood
- Occupational history
  - Job exposure matrix
    - Toxicology database
- Downloaded into a EMR at front desk
  - Output risks from exposure (crime statistics, chemicals, air pollution etc), death rates from diseases, etc

Barriers and Opportunities

- Clinical Disease may be rare
  - May require networks to identify sufficient patients
- Environment may be "place based"
  - Air pollution, pesticides, lead,
  - Networks may help with this as well
    - More geospatial variability
- Few Physicians trained in Environment
  - Occ Med and PEHSU are exceptions
- Few Env. Epidemiologists conduct Clinical research
  - Cohorts design common in order to get prospective exposure

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Examples of Environmental PMI projects include

- Air pollution (or indoor air quality) in cystic fibrosis disease severity and progression.

- Environmental obesogen exposure as a modifier of glucose control in diabetes

- Neurotoxic metals (Pb, Hg, As) as a modifier of autism severity

- Wearable devices to identify environmental triggers of acute asthma attacks

Examples of Environmental PMI projects include

- Role of indoor air quality in Surgical ICU outcomes

- Nephrotoxic chemicals as a modifier of nephrotic syndrome severity and progression

- Untargeted chemicals assays for development of diagnostic tests in newly diagnosed eating disorders (bulimia/anorexia)

- Toxic Metal exposures and Parkinson's Disease progression

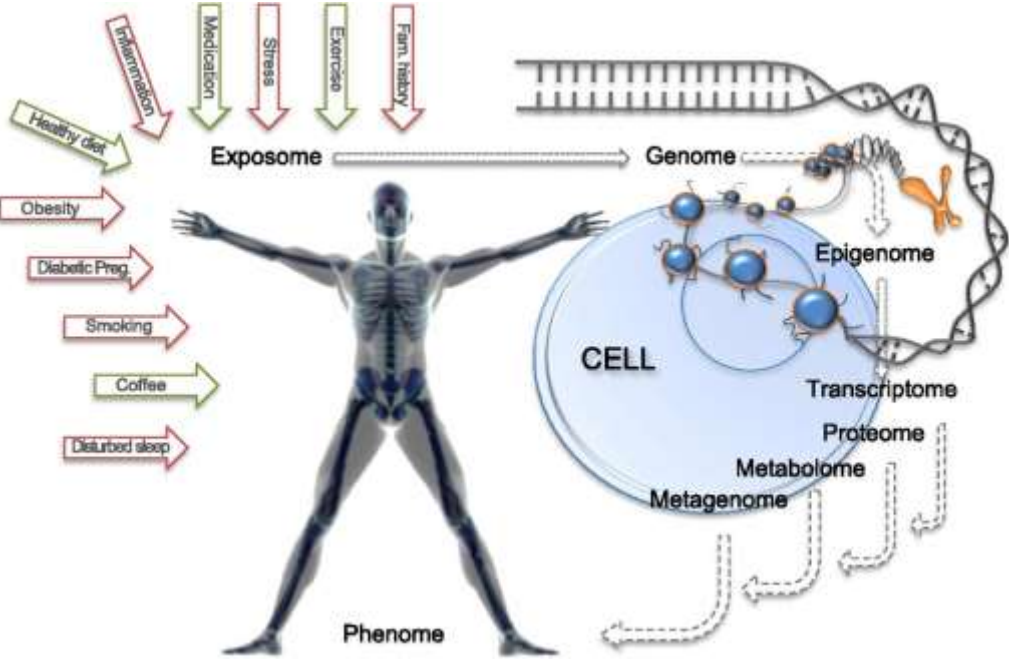# CHEAR/HHEAR offers a range of assays that can be combined *with Precision Medicine initiatives*
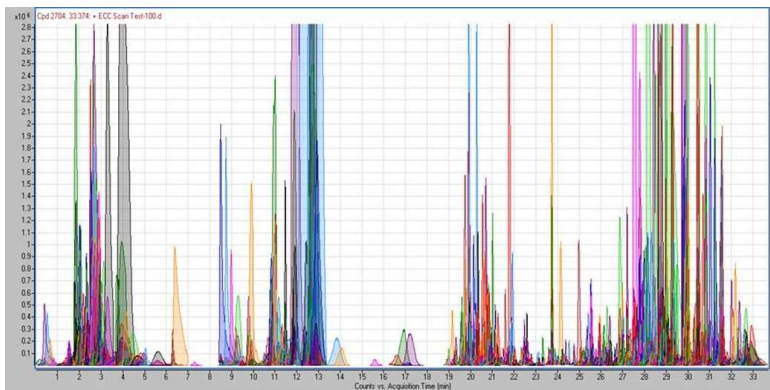
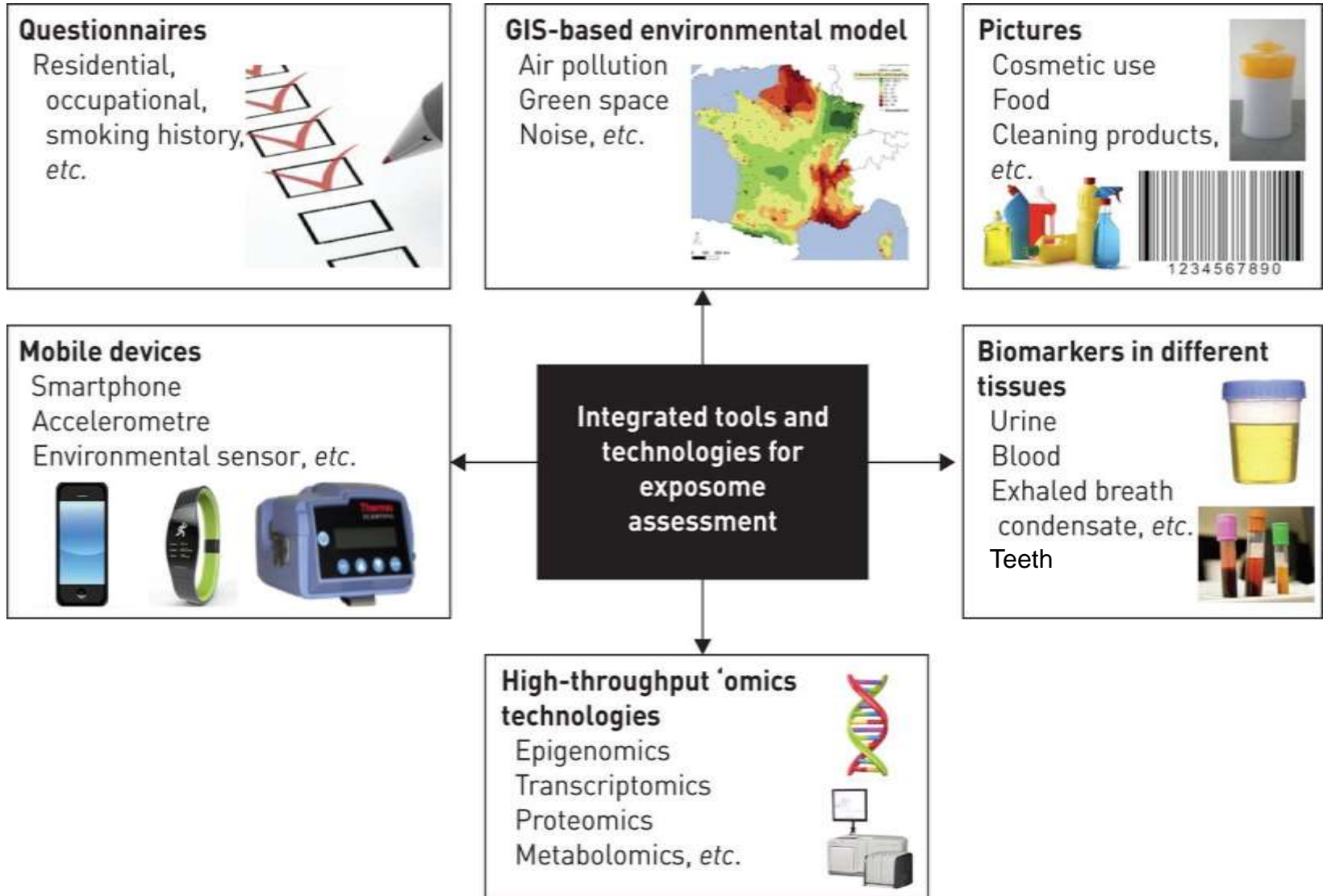Untargeted Chemical assays

Diet/metabolomics

Novel Biomarkers

Targeted Chemical assays

Exposomics Requires Integration of Multiple Data Types

Questionnaires
Residential, occupational, smoking history, etc.

GIS-based environmental model
Air pollution
Green space
Noise, etc.

Pictures
Cosmetic use
Food
Cleaning products, etc.

Mobile devices
Smartphone
Accelerometre
Environmental sensor, etc.

Integrated tools and technologies for exposome assessment

Biomarkers in different tissues
Urine
Blood
Exhaled breath condensate, etc.
Teeth

High-throughput 'omics technologies
Epigenomics
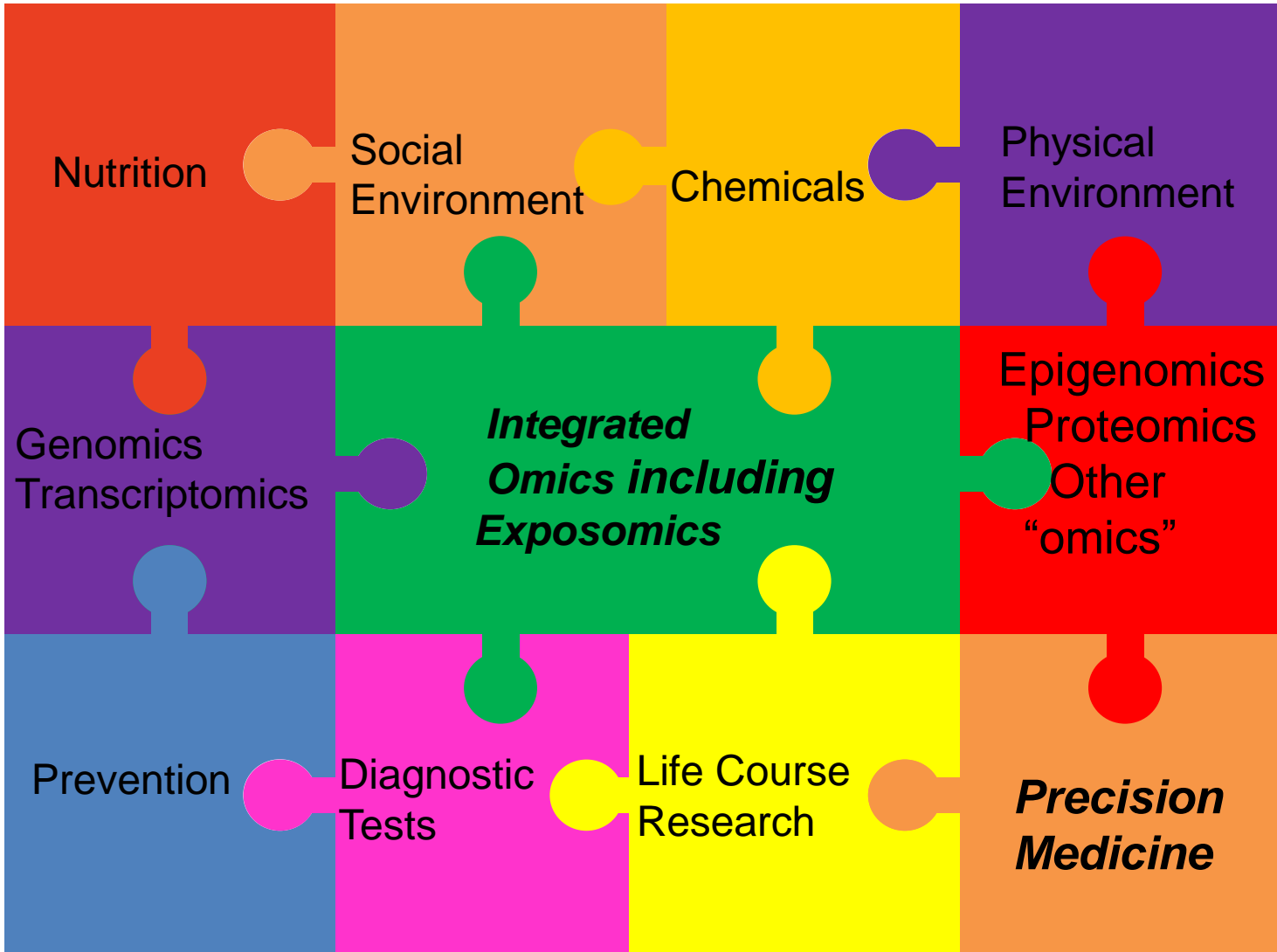Transcriptomics
Proteomics
Metabolomics, etc.

In The Future Exposomics in PMI will enable:

- Diagnostic tests
  - Subpopulations with varying prognosis
- The relationship between environment and treatments
  - Response variability due to exposure
  - Side effects
  - Compliance

Exposomics will complete the Complex Disease PMI puzzle

If we ask the Right questions

So the Precision Medicine Programs will look more like this: