Right Person, Right Drug, Right Time: Challenges and Opportunities

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Gary E. Marchant, Ph.D., J.D.
gary.marchant@asu.edu

CENTER FOR Law, Science & Innovation
ASU Sandra Day O'Connor College of Law Arizona State University
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Personalized Medicine

- Replace "one size fits all" paradigm
- Prediction, diagnosis, prognosis, and treatment tailored to the molecular profile of individual patient
- Other terms used:
  - Individualized medicine
  - Pharmacogenomics
  - Stratified medicine
  - Precision medicine

Precision Medicine Initiative

Announced by President Obama in 2015 State of the Union address

"the right drug at the right dose for the right person"

UK National Health Service: Personalised Medicine Initiative

- **Gearing up for one of the most fundamental changes in NHS history**
- 24 September 2015 – 13:03Sir Bruce Keogh has outlined an emerging strategy for Personalised Medicine in the NHS.
- NHS England's National Medical Director said it would entail a move away from a 'one size fits all' approach to the treatment and care of patients with a particular condition, to using diagnostics, genomics, data analytics and other emergent technologies to identify the underlying cause of disease.
- He told NHS England's Board this was the way to ensure the right patient gets the right treatment at the right time, leading to improved outcomes.
- **Sir Bruce Keogh said**: "The shift to personalised medicine is already underway – our role as a system leader and commissioning organisation is to consider how this transformation can be accelerated.

NHS England

Precision Medicine vs. Longevity Interventions: Tension?

Disease Categories
(e.g., breast cancer, cystic fibrosis)

More Specificity

Precise Molecularly-Defined Disease Subcategories

Basic Evolutionary-Conserved Functions

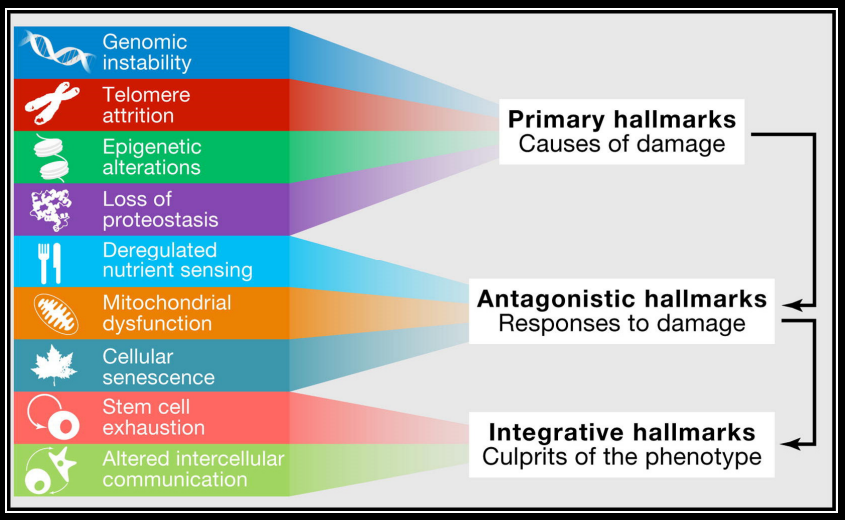
More Generality

Disease Categories
(e.g., cancer, arthritis)

Precision Medicine

Longevity Interventions

Hallmarks of Aging



López-Otín et al., 2013

Cell PRESS
Cell 2013 153, 1194-1217DOI: (10.1016/j.cell.2013.05.039)

Variations for Individually Targeting Aging Interventions

1. Genetic variants affecting lifespan/ healthspan
2. Variations in metabolizing drugs:
   - Pharmacokinetics
   - Pharmacodynamics
3. Gene-Environmental interactions/ Epigenetics

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Genetic Variants Affecting Lifespan/Healthspan

- Longevity appears to have about 20-30% heritability
- Has been many attempts to identify genes affecting aging in humans using candidate gene and GWAS approaches
  - modest success – a few significant gene variants identified (e.g., *APOE*, *FOX03A*)
  - "heritability gap"
- Future approaches:
  - Long-term prospective studies
  - Gene panels
  - Whole genome sequencing

Applications of Gene Variants Affecting Aging

- Personal lifespan prognosis
  - Do citizens want this? How will they respond?
  - Life insurers?
  - Tort damages?
- Targeted prevention measures?
- Identify potential pathways for interventions
- Selection? (PGD, NIPD)
- Gene therapy/editing?

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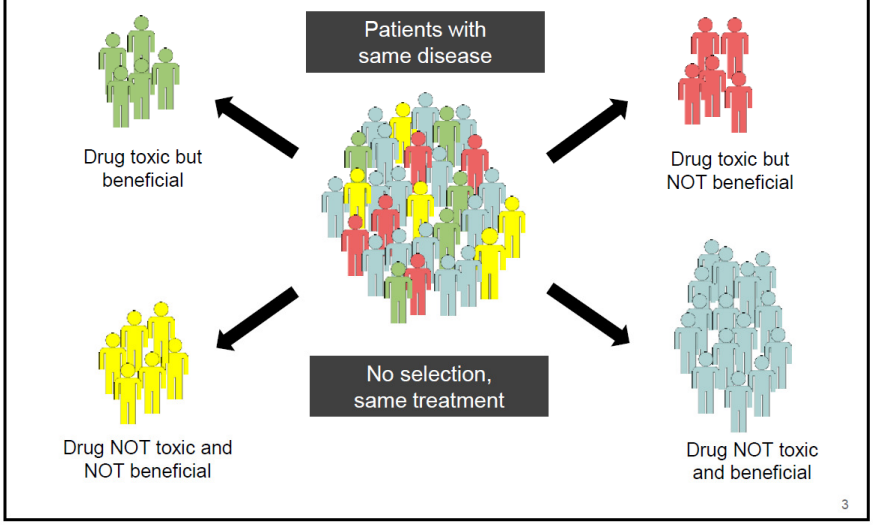

Source: Scott Ramsey

Applications of PGx Testing

- Limit availability of drug to certain genotypes or biomarkers to:
  - Limit adverse effects; and/or
  - Ensure efficacy
- Streamline drug trials
  - Stratify subjects by biomarker
  - Limit enrollment by biomarker
  - Retrospective analysis of data by genotype
- Drug labeling/warning

Examples of Conditions in Which Precision Medicine Has Been Used.

Table 1. Examples of Conditions in Which Precision Medicine Has Been Used.*

Medical Field	Disease	Biomarker	Intervention
Cancer	Chronic myeloid leukemia	BCR-ABL	Imatinib[4]
	Lung cancer	EML4-ALK	Crizotinib[3]
Hematology	Thrombosis	Factor V Leiden	Avoid prothrombotic drugs[5]
Infectious disease	HIV/AIDS	CD4+ T cells, HIV viral load	Highly active antiretroviral therapy[6]
Cardiovascular disease	Coronary artery disease	*CYP2C19*	Clopidogrel[7]
Pulmonary disease	Cystic fibrosis	*G551D*	Ivacaftor[8]
Renal disease	Transplant rejection	Urinary gene signature	Antirejection drugs[9]
Hepatology	Hepatitis C	Hepatitis C viral load	Direct-acting antiviral agents[10]
Endocrine disease	Multiple endocrine neoplasia type 2	*RET*	Prophylactic thyroidectomy[11]
Metabolic disease	Hyperlipidemia	LDL cholesterol	Statins[12]
Neurology	Autoimmune encephalitis	CXCL13	Immunotherapy[13]
Psychiatry	Alcohol-use disorder	*GRIK1*	Topiramate[14]
Pharmacogenomics	Smoking cessation	*CYP2A6*	Varenicline[15]
Ophthalmology	Leber's congenital amaurosis	*RPE65*	Gene therapy[16]

* In the biomarker column, proteins or genes that are probed to find the specific variants of interest are shown. AIDS denotes acquired immunodeficiency syndrome, HIV human immunodeficiency virus, and LDL low-density lipoprotein.

Jameson JL, Longo DL. N Engl J Med 2015;372:2229-2234.

The NEW ENGLAND JOURNAL of MEDICINE

Two Types of Variation

- Molecular variations create subcategories of disease
  - Breast cancer/HER+ (Herceptin)
  - Cystic fibrosis with R117H mutation (Ivacaftor)
  - NSCLC –EGFR mutation (Gefitinib)
- Molecular variations that affect drug metabolism:
  - Warfarin VKORC1/CYP2C9
  - Plavix
  - CYP2C19

Disease Heterogeneity | Drug Pharmacogenetics

Market Fragmentation

- Current "one size fits all" allows manufacturers to benefit from "blockbuster" drugs
- If patients with same disease are now stratified by genotypes or gene expression profiles, market for any one drug will be fragmented
- If market for a drug is constricted with no accompanying reduction in R&D and regulatory approval costs, fewer drugs will be economical to bring to market
  - "orphan genotypes"?

Personalized Medicine: Drug Selection Issues

- Most pharmacogenomic tests are probabilistic rather than yes/no
  - What must be the probability of efficacy (or toxicity) before a drug should be prescribed for a given genotype?
- What is patient refuses to have genetic test associated with a pharmacogenomic drug? Should doctor prescribe drug anyway?
- What if patient doesn't meet genetic profile for a drug, but patient wants drug anyway?

Insurers/Third Party Payers

- Will insurers (private and public) pay for pharmacogenomic testing? Under what conditions?
  - Costs of genetic testing must be offset by savings from avoided toxicity and costs of treating patients who will not benefit from drug
- Will insurers require pharmacogenomic test as a condition for paying for drug?

Need for Validated Biomarkers

- "Reliable diagnostic, prognostic, predictive, pharmacodynamic, and pharmacokinetic biomarkers are critical to assure correct patient selection, drug dosing, and monitoring for safety and efficacy of many therapies in clinical practice. Novel molecular and genetic markers are increasingly being used to guide treatment, although challenges exist in the validation and clinical uptake of newly discovered biomarkers."
  - Amur et al, Clin. Pharm. Therapeutics July 2015

Precision Medicine: The Hope/Hype

"Here's my sequence..."

New Yorker, 2000