PRECISION MEDICINE: THE FUTURE OF PRIMARY CARE?

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DISCLOSURES

I have received grant support from the NIH/NHLBI for the precision medicine related project Pulmonary Vascular Phenomics (PVDOMICS) project- 10% salary support and $1,439,250 for the UA site.
Precision Medicine: “Prevention and treatment strategies that take individual variability into account”

Collins and Varmus. NEJM. 2015;372:793.
Personalized Medicine

Precision Medicine
ABO Blood Typing: Personalized Medicine is an OLD concept
Outcome

Process
A CHANGE IN PERSONALIZED MEDICINE

Previously

Symptom based

Treatment guided by intuition, experience, and some research

Now

Pattern based

Evidence-based medicine, experience and intuition

Precision Medicine

- Big data sources
- Rapid processing systems
- Machine learning and deep learning
- New Platforms for OMIC analysis
Neoadjuvant chemotherapy for patients with locally advanced breast carcinoma

Hormone receptor +/−

HER2 ±

Konig et al. Eur Resp J. 2017; 50:1700391
HOW DOES PRECISION MEDICINE WORK?

Deep phenotyping of patients

Medical history
Lifestyle
Physical examination
Basic laboratory
Imaging
Functional diagnostics
Immunology/histology
Omics

Big data

Track 1
Preprocessing
Data mining

Track 2
Diagnostic and prognostic models

Track 3
Predicting treatment response

Dissemination and communication

Konig et al, Eur Resp J. 2017; 50:1700391
DEEP PHENOTYPING IS MUCH MORE THAN MOLECULAR TESTING

<table>
<thead>
<tr>
<th>Reference</th>
<th>Disease</th>
<th>Variable</th>
<th>Diagnostic and/or prognostic model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical history and physical examination</td>
<td>[9]</td>
<td>Asthma</td>
<td>Age and onset of disease</td>
</tr>
<tr>
<td>Lifestyle</td>
<td>[10]</td>
<td>Atopic eczema</td>
<td>Cat exposure and genetics</td>
</tr>
<tr>
<td>Basic laboratory tests</td>
<td>[11–14]</td>
<td>Severe asthma</td>
<td>Eosinophil counts</td>
</tr>
<tr>
<td>Imaging Functional diagnostics</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Immunology/histology</td>
<td>[15]</td>
<td>Asthma</td>
<td>Lung function and exhaled NO</td>
</tr>
<tr>
<td>Omics</td>
<td>[16]</td>
<td>Asthma</td>
<td>ADRB2</td>
</tr>
</tbody>
</table>

Konig et al. Eur Resp J. 2017; 50:1700391
“Tonight, I’m launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes — and to give all of us access to the personalized information we need to keep ourselves and our families healthier.”

— President Barack Obama, State of the Union Address, January 20, 2015
PVDOMICS

Six Clinical Centers:
- Brigham and Women's Hospital
- Columbia & Cornell
- Mayo Clinic Rochester

University of Arizona
Vanderbilt University
Johns Hopkins Univ.

One Data Coordinating and OMICs Center:
Cleveland Clinic

R24 (PHBI): University of Indiana (Geraci)
R24: Cincinnati Children's Hospital (Nichols)
Approach: To perform comprehensive phenotyping and endophenotyping across the WHO classified PH clinical groups 1 through 5 as well as intermediate phenotypes (including those without overt PH) in order to deconstruct the traditional classification and define new meaningful subclassifications of patients with pulmonary vascular disease.
DATA MINING AND PROCESSING: MACHINE LEARNING

- Invokes large quantities of data
- New patterns or refinements of old patterns by clustering techniques

Patient with HFpEF

History and Physical
Echocardiography
Lab
EKG
Omics

Phenomapping: Hierarchical cluster analysis

Lung congestion ✅
Pulmonary hypertension ❌
Chronotropic incompetence ❌
Skeletal muscle weakness ❌
Atrial fibrillation ❌

Source: MathWorks, Inc.
NEW HFPEF PHENOTYPES

FROM DEEP PHENOTYPING TO MODEL BUILDING

DECISION TREE ANALYSIS: ALGORITHMS BASED ON UNSUPERVISED DATA

Wang et al. J Heart Lung Transplant 2012;31:140–9
SYSTEMS BIOLOGY: A HOLISTIC APPROACH TO COMPLEX DISEASE
NEURAL NETWORKS: UNCOVERING NOVEL (UNEXPECTED) RELATIONSHIPS BEFORE CLUSTERING
NETWORK ANALYSIS: SOCIAL NETWORKS

1971 A sample of 1,000 people from the study includes many large groups of smokers.

2000 Nearly three decades later, groups of smokers tended to be smaller and more isolated.

Key:
- Male smoker
- Male non-smoker
- Female smoker
- Female non-smoker
- Friendship, marriage or family tie

Circle size is proportional to the number of cigarettes smoked per day.

Sources: New England Journal of Medicine; Dr. Nicholas A. Christakis, James H. Fowler

The New York Times
NETWORK ANALYSIS: MENTAL HEALTH INTERRELATIONSHIPS

NETWORK ANALYSIS: LAYERING IMPROVES PHENOTYPING

Barabasi NEJM 2007;357:404.
Deep learning algorithms to detect cancer cells.

Source: MathWorks, Inc.
Precision Medicine
TRIAL ENRICHMENT STRATEGY

Screen for Surrogate Marker(s)

Trial Subjects

- Subjects Excluded from Trial

+ Trial Subjects

Placebo

Active Drug
• PROGRAMMED DEATH RECEPTOR 1 MARKER PREDICTS TREATMENT RESPONSE TO IMMUNOTHERAPY FOR NSCLC.
• MERCK: EXAMINE A SUBSET OF NSCLC PATIENTS WITH HIGH PD-L1 EXPRESSION AND EVALUATE IF THEY RESPOND TO KEYTRUDA OVER STANDARD CHEMOTHERAPY.
• BMS: EXAMINE ALL NSCLC PATIENTS REGARDLESS OF EXPRESSION AND EVALUATE IF THEY RESPOND TO OPTIVO OVER STANDARD CHEMOTHERAPY.
• UNLIKE ONCOLOGY, TISSUES ARE NOT READILY AVAILABLE TO ENHANCE MOLECULAR CHARACTERIZATION AND GUIDE THERAPY

• DEEP PHENOTYPING GUIDES THE PROCESS

• CURRENT PHARMACO-GENOMIC TRIALS VS STANDARD CARE DO NOT FAVOR GENETIC TESTING
  • GENOTYPE-GUIDED WARFARIN DOSING (STERGIOPULOS ET AL. JAMA 2014;174:1330)
  • PHARMACOGENOMIC TESTING FOR MAJOR DEPRESSION (WINNER ET AL. DISCOV MED 2013;16:219)
THE STAKEHOLDERS

• PATIENTS
• CLINICIANS/RESEARCHERS
• REGULATORY
• INDUSTRY
A Patient is diagnosed with a chronic illness

OUTCOMES: REGULATORY AND PATIENTS VS CLINICIANS/RESEARCHERS

“Devastating”
“Anxiety about the future”
“Isolated”
“Sad/”Depressed
“Not Understood”
COMMENTARY ON PRECISION MEDICINE: METHODOLOGICAL ISSUES

• CODING BIAS
• SAMPLING BIAS
• IMPROPER VALIDATION
• NOT ALL PROGNOSTIC MARKERS ARE CAUSATIVE (E.G. CARDIAC ARRHYTHMIA SUPPRESSION TRIAL)-THE QUEST FOR SURROGATE MARKERS
• INADEQUATE COMPARISON TO THERAPEUTIC STANDARDS
COMMENTARY ON PRECISION MEDICINE

• STAKES ARE HUGE! OUR RESPONSIBILITY AND MORAL OBLIGATIONS ARE HUGE!

• WHO GETS THE INFORMATION?

• HOW DO WE ALLOCATE SCARCE RESOURCES?

• WHAT ARE THE LIMITS OF PRECISION MEDICINE- THE BORN VS UNBORN, THE USA VS NORTH AMERICA VS ?

• WILL PRECISION MEDICINE LEAD TO LOWER COSTS?
CONCLUSIONS

• PRECISION MEDICINE IS A **PROCESS** DEFINED BY A FOCUS ON IMPROVING OUTCOMES BY FOCUSING ON UNIQUE PHENOTYPES

• THE PROCESS STARTS WITH DEEP PHENOTYPING

• MACHINE LEARNING DEFINES NEW OR UNEXPECTED GROUPS WHILE MODEL BUILDING DEFINES THEIR IMPORTANCE

• NETWORK ANALYSIS ILLUSTRATES THE INTERRELATED/HOLISTIC QUALITIES OF COMPLEX DISEASE

• THIS PROCESS ALLOWS FOR ENRICHED TRIAL STRATEGY

• THIS PROCESS WILL AFFECT **EVERYONE** IN MEDICINE. IT HAS **HUGE** IMPLICATIONS!
THANK YOU!