Perspectives of biologists, epidemiologists and geneticists’ controversies in sciences and health systems’ reforms

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In the upcoming trends showing increase of the global Burden of diseases

  e.g. in dementia, the global burden of disease increases by 2 by 2030 and 3 to 4 by 2050

  (World Alzheimer reports, UN declaration on NCDs)

Urgent needs have to be addressed in order to help policy makers in dealing with societal costs of diseases.
Why to discuss scientific controversies in societies of telecare and ehealth?

• Epidemiological research is used for patient stratifications, possibly towards personalized and predictive medicine in many areas.

• Advances in «Omics» sciences lead to predictive or «precision» medicine and individualized care.

• The IT revolution also creates opportunities for new business models.

• BioIT vendors and lifescience companies compete for health care solutions, but need to ensure quality of care delivery systems for populations of patients.
IMPACT OF « OMICS » TECHNOLOGIES FOR IT SYSTEMS

- Impact on stratification of patients
- Impact on changes of codifications
  
  drug coders
  
  disease classifiers

Impact on computer adaptive platforms to integrate genetic predictive modeling diseases with evidence in development
Example of a computer platform development

AND

Partnership
AKP: Partners

Strategic Medicine

Mayo Clinic (Breast Cancer)

Gaps

MDlogix

Thomson Reuters Knowledge Bases

Endeplus

DI = Decision Index = \[ F(Q(I), \text{Physician Experience, Research Data, Clinical Trials, Cost Analysis}) \]

Strategic Medicine, 2010
Examples of scientific controversies
• Recent technologies help in particular to detect and prevent mild cases of cognitive impairments or integrate genomic medicine

• More and more individualized genetic traits and pedigrees can be used

• However, scientists disagree: recent study results from population base studies use population imaging (e.g. Breteler et al., 2011) versus integrative genomics approaches (e.g. Rhinn's 2013 and network biologists)
Controversy in asthma genetics between molecular biologists (Vercelli, 2011) and geneticists (Weiss et al., 2009)

They lead to:

- different predictive disease modeling
- different impact assessments of aging and environmental modifiers
SCIENCE in Transition and TRANSLATIONAL MEDICINE

- More bio individual data are integrated in Electronic Medical Records (EMRs)
- Genomic medicine increases needs for data interpretation
- Integration of data lead to new models and machine tools towards more individualized care

HOWEVER, Translational medicine also needs PROCESS RESEARCH
CONSTRAINTS IN PROCESS RESEARCH

• Issues of reproducibility

• Traditional models of production of scientific knowledge are not sufficient

• Traditional incentive systems for scientists do not work any more - no incentive for validation studies

• Impact factor scoring system for publications does not lead to validation of projects in other race/ethnic groups and organizational sites
Case of asthma corticosteroids
Controversy in asthma genetics

- Views from molecular biologists (Vercelli)
  
  focus on gene-environment interactions
  for individual genes- focus on role of epigenetics

- Views from geneticists (Weiss)
  focus on gene-gene interactions and
  holistic approach (epistasis), focus on drug response
Genetic models of asthma and the role of environmental modifiers (early systematic review)

- Exposure to **endotoxins** (e.g. Werner et al, Eder et al, 2004; Zambelli et al, 2005)
- Exposure to **viruses** (e.g. McIntire et al, 2003; Hoffjan et al, 2005)
- Exposure to **pets** (e.g. Gern et al, 2004)
- Exposure to **tobacco** (Wang et al, 2001; Colilla et al, 2003; Meyers et al, 2005)
- **Sex** and **early life exposure** (Nicolae et al, 2005)
SCIENTIFIC DISCOVERIES ON GENE DRUG THERAPY CAN IMPROVE EPIDEMIOLOGICAL MODELS:

- THEY IMPROVE **PATIENT STRATIFICATION** FOR DRUG RESPONSE

- THEY HELP TO CORRECT THRESHOLDS TO DECREASE THE RATE OF FALSE POSITIVE RESULTS IN SCREENING OF POPULATIONS
Example: Genes associated with medications for asthma: they do not meet all standards for replication of results

Ext from: « New approaches to personnalized medicine for asthma: where we are? »

Dr S Weiss, j Allergy Cli Immunol, Feb 2012

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Example of new scientific discoveries on integration of genetic variants from patients

(Study on corticosteroids pharmacogenetics, Tantisira et al., 2004)

Objective: to decrease the rate of non-responders to corticosteroids medications and intervariability of responses between individuals

Study: association of SNP and longitudinal response to corticosteroids
variation in the gene CRHR1 is consistently associated with enhanced response to therapy in three population groups: two adult groups with different disease severity, one children group; it also lead to less side effects

source: Tantisira, Lake, Palmer, Lazarus, Siverman, Liggett, Gelfand et als, 2004
Such results can address issues of intervariability: example of impact on outcome measures such as average lung function response (FEV).
Executive summary

Progress in asthma pharmacogenomics

- The first pharmacogenomic genome-wide association study of inhaled corticosteroids response in an asthma cohort identified a functional variant in *GLCCI1*, a glucocorticoid pathway gene.
- Gene–gene interactions of various candidate loci are associated with treatment response.

Systems biology

- Systems biology approaches seek to generate the best model of a biological network from large-scale `omics` data.

Systems biology approaches in asthma

- Bayesian networks and Random Forests are capable of modeling and accurately predicting phenotypic response from genomic and expression data.
- Integration of modeling with expression data provides a system-level view of asthma.
- Incorporating epistasis and directionality effects will improve the accurate prediction of pharmacogenomic phenotypes through utilization of clustering and network-based approaches.

Integrative pharmacogenomics

- Integrating genomic data with expression quantitative trait loci can identify candidate genes and infer biological networks associated with therapeutic response.

Conclusion

- Novel pharmacogenetic loci and gene pathways can be inferred using a systems biology approach.
CHALLENGES OF SCIENCE IN TRANSITION

- CAN WE TRUST STUDY RESULTS?
- ARE TECHNOLOGISTS AND GATEKEEPERS ABLE TO CONTROL CHANGING ECOLOGICAL COMPLEX SYSTEMS?
- WHEN AND HOW CAN WE INTEGRATE GENETICS INTO PREDICTIVE DISEASE MODELING, WITH LIMITED REPLICABILITY STUDIES?
REATIONS OF NIENTISTS - COALITION MOVEMENTS

• INTERNATIONAL LEVEL: AAAS Chicago meeting February 2014

• NATIONAL INITIATIVE/ Exemple In Netherlands: SCIENCE in TRANSITION

www.scienceintransition.nl

Raise awareness of current limitations in scientific discovery especially in translational space!

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Conclusion for feasibility studies - incident reports and timing of use of evidence in translation

- Use of positive and negative narratives
- More research on narratives in decision tools
  patient decision aid developer
  decision tools for physicians
- Development of more good practices and use of taxonomies for validation studies