The Impact of New Technologies on the Science of Clinical Care and Drug Development

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"For over 40 years, imaging has significantly added to noninvasive clinical assessment of disease and determining therapeutic success."

Key Messages

- Ongoing information boom resulting from scientific and technological advances
- Ultimate goal of new information is to explain heterogeneity in response to therapeutics
  - Right dose of right drug at right time for right patient
- Challenges in routine and efficient utilization for this purpose
- A collaborative, multidisciplinary, effort from Pharmacoimaging, Pharmacogenomics, and Pharmacometrics FGs

Imaging – Pharmacology is Now "Visible"

- Advances in cancer identification, measures of tumor kill, cardiac performance, and identity of brain and endocrine disorders, among others
- Driven by advances in molecular biology, tracer chemistry, computational physics, and material sciences
- Interesting, specific examples classified as *predictive, prognostic, diagnostic, or dosimetric* markers

Table 1. Biomarker Classes for Imaging Biomarkers: Examples of Clinical Use
Many imaging systems are now available, and these examples are not intended to be exhaustive but rather to describe a marker class. Table is adapted from Moyer and Barrett.[3]

MARKER CLASS	DEFINITION	EXAMPLE
Predictive	A biomarker available before a drug or action is applied to a target.	MRI: In Multiple Sclerosis the brain exhibits physical changes in the white matter structures related to water relaxivity (the magnetization of water hydrogen can be detected as emission of radiowaves).
Prognostic	A biomarker available after a drug or action is applied and which predicts a subsequent increase in risk of injury or change in pathologic state.	PET/SPECT: C-11 ß-CFT uptake in dopamine-rich regions of the substantia nigra is significantly reduced following exposure to the neurotoxin MPTP, a byproduct of improper chemical synthesis of methamphetamine.
Diagnostic	A biomarker available at the time of symptoms (pathology) or following a drug or action on a target.	PET: C-11 PIB and F-18 Amyvid serve to measure amyloid deposition in the brain of suspected Alzheimer disease patients. PET and SPECT: Imaging of suspected lung cancer with standard uptake value (SUV) of >5 using F-18 FDG, or ischemic myocardium viewed as cine gated images where regional uptake and wall motion are measured. Optical: Bioluminescence/Ultrasound/MRI/PET/SPECT/Thermal: Blood flow changes; metabolic changes; shape changes; etc. fMRI : rCBF (regional cerebral blood flow) in regions of the brain during thought or physical movement—using BOLD (blood oxygen level dependent) techniques to localize flow change from a stroke.
Dosimetric	A biomarker available after a drug or biologic imposes an action applied on a target and which a response can be related to the dose (or proportionality of an action) relative to a negative control.	Imaging: Microscopy: Chromosomal aberrations (dicentrics) using microscopic imaging (radiation dosimetry). MRI: Apparent diffusion (weighted) coefficient MRI in tumor responses (necrosis) to chemo- and radiotherapy. SPECT: Application of In-111 for cell trafficking white blood cells recognizing changes in tissues, i.e., cytokines to elicit natural killer cell proliferative dose response following chemo- or radiotherapy.

Genomics

- Recent examples of utilization
  - Differences in response to peg-INFa + ribavirin treatment for HCV due to both viral genotype and SNP in human host
  - Development of targeted therapeutics, for e.g, trastuzumab, in breast cancer patients over-expressing HER2
  - VKORC1 and CYP2C9 genes in warfarin dose adjustment
  - Susceptibility to Stevens-Johnson syndrome in HLA-B*1502- positive subjects treated with carbamazepine included in label

- FDA website for examples of genomic markers included in drug labels

Dashboard Systems

- Addressing heterogeneity in drug response- a common goal of PK/PD modeling and personalized medicine
- Lack of decision-support tools to integrate biomarker data with other patient-specific information to generate a treatment recommendation
- *Dashboard*- a Web-based interface to integrate PK/PD models with patient-specific inputs for visualizing data and generating and updating predictions and recommendations
- Aided by increase in computational power

Dashboards in Clinical Care

- Medical care systems are not consistently equipped to collect and manage the volume and complexity of new patient-centric information- addressing this is the next level of patient care
- IBM's Watson is being evaluated as a diagnostic tool at Memorial Sloan Kettering Cancer Center- helps avoid anchoring bias leading to misdiagnoses
- Examples of dashboards to facilitate decisions for individual dose adjustments needed for narrow TI drugs, pediatric populations, and biologics that lose efficacy due to immunogenicity
- Improved individualized dosing may be advantageous to drug manufacturers and payers as well

Dashboards in Drug Development

- Potential for facilitating decision-making as a component of Model-based Drug Development
- May be used as in clinical practice when individualized or adaptive dosing is performed in clinical trials
- Potential to co-develop with companion diagnostics, especially for drugs requiring co-development of a TDM assay

Barriers

- Successful implementation requires multi-disciplinary interactions (biologists, technologists, pharmacometricians, clinicians, and others) within and between academic centers, regulatory agencies, drug companies, and clinical care centers.

- Lack of communication and common understanding of available tools and technologies

- Differences in how stakeholders think of health care

What Next?

- Potential multi-disciplinary workshop among key stakeholders?
- Educational opportunities
  - Expansion of pharmacometrics training for effective communication with clinicians?
- Increased communication and awareness of changes in health-care utilization and how AAPS can impact