Imperatives for Imaging in the Era of Personalized Medicine

Academy CIBR Luncheon
Tuesday, March 28, 2017

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Duke University Medical Center
Definition of Precision Medicine

Precision medicine (PM) is an evolving approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person.

It is in contrast to a "one-size-fits-all" approach, in which disease treatment and prevention strategies are developed for the average person, with less consideration for the differences between individuals.
Precision Medicine

“The initiative will encourage and support the next generation of scientists to develop creative new approaches for detecting, measuring, and analyzing a wide range of biomedical information.”

Precision Medicine

• Tools employed in PM can include molecular diagnostics, imaging, and analytics/software.

• PM is dependent on information from molecular profiling tests (genome, proteome, microbiome, etc.), and the knowledge bases available to assist clinicians in taking action based on test results.

• Biomarkers are the key to precision medicine.
NAM Recommendations RE: PM

• 2. **Accelerate clinical data integration and assessment.** Advancing precision medicine and achieving a greater understanding of the complexities of human health and disease will require aligning and integrating diverse, often unstructured datasets into a comprehensive knowledge network.

  • Realizing the Full Potential of Precision Medicine in Health and Health Care A Vital Direction for Health and Health Care
  • National Academy of Medicine; September 19, 2016
In PM, there are six major clinical areas of interest: oncology, brain disorders, infections, cardiovascular disorders, metabolic disorders, and other inflammatory disorders.

The area of medicine in which PM is most advanced is cancer (Precision Oncology), and this is the “near-term” focus of the Federal Initiative.
Precision Medicine Skepticism

- Early PM success in oncology PM may not be broadly transformative to other disorders.
- PM depends on AI of massive amounts of data. “Multiple comparisons problem” will be a factor (signal-to-noise problem).
- Cannot do all possible trials, so will need to rely on observational data and modeling (need to continuously collect and assess real-world patient data for continuous learning).
- Overdiagnosis and overtreatment maybe issues.
- Impact of PM on overall cost of healthcare is uncertain.
- Timescale may be decades.
Basics of TNM Staging System
AJCC Cancer Staging Manual Editions

- Global standard
- Focuses on prognosis and appropriate treatment at time of presentation.

<table>
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<th>Publication</th>
<th>Effective dates for cancer diagnoses</th>
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<td>8th</td>
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Average: 5.6 years
The 8th Edition

Complete Cancer Staging Manual released October 1, 2016

8th Edition effective with cases diagnosed January 1, 2018
8th Edition: New Features

• Building a bridge from a population-based to a more precision-based (individualized) approach.

• Imaging section in each chapter.
AJCC Vision

The Transition from Population-Based to a more “Personalized” Approach

Cancer Stage → Comprehensive Cancer Profile

- AJCC/UICC TNM Stage (Basic Classification)
  - TNM

- AJCC Prognostic Stage Groups (Advanced Clinical Relevance)
  - TNM + Prognostic Factors

- AJCC “Personalized” (Advanced Clinical + Personalized Relevance)
  - TNM + Prognostic Factors + Risk Assessment Models + Clinical Trial Stratification

Population Survival Outcomes → Personalized Survival Outcomes
Example of Increased Complexity in Prognostic Stage Groups; Imaging is Integral

Table occupies one section of one page; 19 groups.

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Complexity mandated to keep stage information clinically relevant

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**MultiGene Panel** – Oncotype Dx® Recurrence Score Less Than 11

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**Example of Increased Complexity in Prognostic Stage Groups; Imaging is Integral**

8 Ed Breast Cancer

Tables fill 4 pages; ~187 groups.
Implications of PM for Imaging
(What do we need to do to optimize imaging for PM?)

1. Enhance imaging information (molecular, functional or anatomic) that reflects the individual’s biological basis of disease

2. Focus on therapeutic implications or options as opposed to primarily focusing on diagnosis

3. Extract objective, quantitative information that is reproducible and can be incorporated into decision-support algorithms
1. Examples of Imaging to Enhance Biological Information for PM

- Image-guided biopsies, for “high-content” tissue.
- Whole-body PET/CT for staging, or eligibility for a trial.
- FDG-PET or other radiopharmaceuticals (e.g., F-18-FES) for monitoring response or dose-finding (e.g., F-18-FDHT for a prostate cancer drug).
- Theranostics (e.g., Ga-68/Lu-177-DOTATATE for neuroendocrine tumors)
- Functional imaging approaches in MR, CT and ultrasound.
- Radiomics or radiogenomics
Challenges for Molecular Imaging

• From a developmental cost perspective, need to identify markers that have a reasonably broad utility. This is inherently at odds with the concept of PM.

• Molecular imaging agents must be accurate, reliable, properly validated and appropriately implemented.

• Resources for clinical trials of imaging agents (to accomplish the above requirements) are scarce.

• Reimbursement for imaging agents is low. Therefore commercial ROI is unfavorable.

• The science is hard; the business case is formidable.
4. Develop innovation-oriented reimbursement and regulatory frameworks. The current reimbursement environment does not reward innovators for the value created by their diagnostic tests. Rather than being value-based, reimbursement for diagnostics is typically cost-based and discourages the translation of innovative tests and therapies. Incentives to develop the evidence base and the economic model that support precision medicine will be crucial.

- Realizing the Full Potential of Precision Medicine in Health and Health Care A Vital Direction for Health and Health Care

- National Academy of Medicine; September 19, 2016

(E.g., reimbursement for Oncotype DX is ~$4000. Reimbursement for most imaging contrast agents is < $1000.)
2. Focus on Therapy

- Reports from imaging studies need to focus on implications for choosing the optimum therapy.
- An effective treatment cannot be considered “precise” unless treatment efficacy is correlated with a biologically sound and validated biomarker that can effectively distinguish the responder from the nonresponder.
- Because imaging can be done repeatedly, an important role is to assess response to current therapy on serial studies.
Edwin Silverman, MD, PhD
Assoc Professor of Medicine
Brigham & Women’s Hosp, Boston

James Crapo, MD
Professor of Medicine
National Jewish Health, Denver

Co-PIs, COPDGene Study, NHLBI

“We need quantitative information from CT scans to help us manage patients with COPD.”
3. Quantitative Imaging Biomarkers

- Treating physicians want quantitative results.
- They prefer numerical probabilities to ambiguous qualitative descriptors.
- Evidence-based medicine and QA programs depend on objective data.
- Decision-support tools require objective input data.
Examples of Consumer Expectations Re: Quantification

- 94% of oncologists expect some or all tumors to be measured at the time of standard initial clinical imaging. (Jaffe T, AJR 2010)
- Pulmonologists want CT-derived quantitative measures in COPD and asthma pts. (ATS/ETS Policy statement, AmJRespCritCareMed 2010)
- Hepatologists want quantitative measures of liver fat infiltration (Fitzpatrick E, World J Gastro 2014)
- Rheumatologists want quantitative measures of joint disease (Chu C, JBJS 2014)
- Neurologists and psychiatrists want quantitative measures of brain disorders (IOM Workshop, Aug 2013).
- U.S. Regulatory agencies (FDA & CMS) want more objectivity in imaging scan interpretations.
• Variation in clinical practice results in poorer outcomes and higher costs.

• **One** approach to reduce variability in radiology is to extract objective, quantitative data from scans.
**Dept of Radiology Chest CT Report:  March 28, 20xx**

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<td>Bone Density</td>
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<tr>
<td>Lung Nodule Volume</td>
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</table>

Background discussion: Yadda, yadda, yadda ...

**Conclusion:**

- Probability of disease $m$ is: $x$ %
- Response to current management $n$ is: $y$ %
- Positive predictive value for therapy $q$ is: $z$ %

(Adapted, with permission, from D. Yankelovitz)
Quantitative Imaging Biomarkers Alliance (QIBA)

• Started by RSNA in 2007

• Mission: Improve the value and practicality of quantitative imaging biomarkers by reducing variability across devices, patients, and time.
  
  • “Build imaging devices that are also measuring devices”
  
  • “Industrialize imaging biomarkers”

• http://rsna.org/QIBA.aspx
Toward Quantitative Imaging

Clinical Value of QI Data

Data showing Clinical Value

Accurate, reproducible QI Data
Qualitative Imaging => Biomarker Assays

Assays are characterized by their:

- **Technical Performance**
- **Clinical Performance**
  - Clinical validation (How the biomarker performs in a human population, e.g., sens/spec)
  - Clinical utility (How the biomarker affects outcomes)
Overall Goal of QIBA

Problem

Measure = 7 ± 6

Goal

Measure = 7 ± 2

Analysis

Sources of Variance

Differences in:
- Patient Handling
- Acq. Protocols
- Reconstruction
- Segmentation

Solution

When all participating actors conform...

Requirements for:
- Acquisition Params
- Recon Params
- Resolution
- Processing Params
- Patient Prep & Operation
- Segmentation
- Calibration

Image compliments of Kevin O’Donnell
QIBA Process

Write a Profile (systems-engineering, technical standards document)

- Claim
- Specifications

Key technical parameters to characterize for an imaging biomarker are:

- Bias
- Precision
- Linearity

NIH
NIBIB
NIST
FDA
## 2017 Fleischner Society Guidelines for Management of CT Pulmonary Nodules

**A: Solid Nodules**

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<th>Nodule Type</th>
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<th>Comments</th>
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<td>No routine follow-up</td>
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<tr>
<td></td>
<td>6–8 mm (100–250 mm³)</td>
<td>CT at 6–12 months, then consider CT at 18–24 months</td>
</tr>
<tr>
<td></td>
<td>&gt;8 mm (&gt;250 mm³)</td>
<td>Consider CT at 3 months, PET/CT, or tissue sampling</td>
</tr>
</tbody>
</table>

Nodules <6 mm do not require routine follow-up, but certain patients at high risk with suspicious nodule morphology, upper lobe location, or both may warrant 12-month follow-up (recommendation 1A).
FDG-PET SUV Example

Single scan:
- Patient preparation
- Scan acquisition
- Image reconstruction
- Image analysis
- Image interpretation → SUVx measure

Scan 1 → time → Scan 2:
- Patient preparation
- Scan acquisition
- Image reconstruction
- Image analysis
- Image interpretation
   Compare for biomarker assessment
Concerns about Inter-Vendor Reproducibility in FDA-Approved Software Packages

- Coronary calcium scoring (CT)
- Coronary artery plaque burden (CT)
- Stroke perfusion (CT)
- Cartilage in osteoarthritis (MR)
- Lung density: COPD (CT)
- Tumor volume measurements (CT and MR)
- Tumor glycolysis (PET)
- Amyloid burden (PET)
- …
Poor Reproducibility has Clinical Implications


• “Among individuals at intermediate cardiovascular risk, state-of-the-art CT scanners made by different vendors produced substantially different Agatston scores, which can result in reclassification of patients to the high- or low-risk categories in up to 6.5% of cases.”


• “Indeed, intervendor variability, even with state-of-the-art equipment, seems to be the largest contributing factor to differences in plaque volume measurements at coronary CT angiography. A similar phenomenon has been observed for CAC scoring”

• Oberoi S, et.al. Reproducibility of noncalcified coronary artery plaque burden quantification from coronary CT angiography across different image analysis platforms. AJR. 2014 Jan;202(1)

• “Currently available noncalcified plaque quantification software provides ...poor interplatform reproducibility. Serial or comparative assessments require evaluation using the same software. Industry standards should be developed to enable reproducible assessments across manufacturers.”
Poor Reproducibility of Stroke Perfusion Methods


  “…persistent lack of standardization of perfusion imaging, the direct comparison of different processing algorithms, and evidence on which methodology will prove most appropriate for patient selection and for predicting clinical outcome.”

Poor Reproducibility of Cartilage Composition Methods


• “Mosher, et. al., investigated reproducibility across different vendor platforms and found fairly limited reproducibility with RMS CVs ranging from 7% to 19% for femorotibial joints.”
QIBA FDG-PET Digital Reference Object (DRO) Specifications

• The DRO is based on the NEMA / MITA Image Quality phantom
  • PET and CT sets of DICOM images
  • Also can be generated with smoothing and noise
• SUV values in general are either 0, 1.0, or 4.0, except
  • A single voxel in ROI 3 is set to 4.11
  • A single voxel in ROI 4 is set to -0.11
  • A checkerboard pattern is used to provide a deterministic test for calculation of the standard deviation in 2D (ROI 5) and 3D (ROI 6)

CT (transmission) PET (emission)

ROIs used for reporting values
PET DRO results: 13 sites, 18 display systems

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blue = okay, yellow = ?, pink = borderline, red=wrong
5 MB harddrive being shipped by IBM - 1956
The Earliest Radiology Reports (1896)

The radiology report began as a letter between colleagues, describing what the images showed—analogous to reports from other clinical subspecialty consultations and strikingly similar to the narrative format we see today. These “reports” first became commonplace in the early 20th century, as radiography facilities began to proliferate in U.S. hospitals.

Anyone familiar with the pitfalls of modern radiology practice will note familiar elements of Dr. Morton’s practice. Work flow issues (“I only got the negative today and could not therefore report earlier”) and hedging related to image quality (“The picture is not so strong as I would like...”) had early origins. Another harbinger of things to come: Dr. Morton’s fee for a simple
Standardization of Image Acquisition and Reporting

• Variability due to qualitative and ambiguous terms in radiology reports is a recognized problem

• Initiatives to address the problem:
  • RSNA Structured report templates; Radreport.org, RadLex
  • ACR Appropriateness criteria; ACR RADS systems (e.g., BI-RADS, LI-RADS, PI-RADS)

• Challenges:
  • Radiologists worry about commodification and loss of creativity
  • RIS’s don’t facilitate structured reporting
  • EHR’s don’t facilitate structured radiologic reporting
Imaging in Prostate Cancer

- PubMed search (3/18/17): 12638 results
- Filter for “staging”: 2208 results
Page 719: Although imaging could one day potentially improve clinical staging accuracy, interobserver reproducibility, issues with patient selection, and contradictory results have limited the utility of imaging in clinical staging, and imaging alone cannot replace DRE as the clinical staging standard. Thus, for local T category assignment, no imaging test is explicitly required.
Although imaging could one day potentially improve clinical staging accuracy, interobserver reproducibility, issues with patient selection, and contradictory results have limited the utility of imaging in clinical staging, and imaging alone cannot replace DRE as the clinical staging standard. Thus, for local T category assignment, no imaging test is explicitly required.

(DRE = digital rectal examination)
Can We Improve the Reproducibility of Quantitative Multiparametric Prostate MR Imaging Metrics?

Edward Johnston, FRCR, and Shonit Punwani, MRCP, FRCR, PhD
UCL Centre for Medical Imaging, 5th Floor, Wolfson House, 4 Stephenson Way, London NW1 2HE, UK. E-mail: johnston@nhs.net

DOI: http://dx.doi.org/10.1148/radiol.2016161197

We read with interest the article by Carrozzo et al. [1] in the July 2016 issue of Radiology, whereby quantitative metrics derived from multiparametric magnetic resonance (MR) imaging were combined by using generalized linear models to differentiate tumors with an American Joint Committee on Cancer score of at least 7 in a multiple imager study. The authors describe extracting metrics that included T2-weighted signal intensity normalized to the obturator internus (OI) muscle and skewness and kurtosis from histograms. We wish to offer two constructive comments regarding this.

Absolutely! We CAN ... and we MUST!
Basic Research

Clinical Implementation
Implications of Precision Medicine for Imaging

1. Imaging information that reflects biochemical phenotype
2. A focus on therapy
3. Objective, reproducible, quantitative information, presented in a structured format.
Implications of Precision Medicine for Imaging

1. Imaging information that reflects biochemical phenotype

2. A focus on therapy

3. Objective, reproducible, quantitative information, presented in a structured format.
Thank you.