The Translation of QI to Clinical Research and Precision Medicine - Goals and Challenges

When and Why is Quantitative Imaging (QI) Important? in Clinical Practice (in this era of Precision Medicine)

Daniel C. Sullivan, M.D.
Duke University Medical Center

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."

Francis S. Collins, M.D., Ph.D., and Harold Varmus, M.D. A New Initiative on Precision Medicine, N Engl J Med 2015; 372:793-795, February 26, 2015

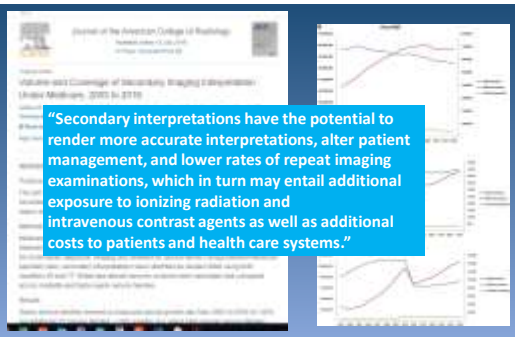
Basic Premise Supporting QI

The variability inherent in subjective, qualitative radiologist interpretations is a huge problem.

Editorial Comment:

- "…variation in reporting can lead to confusing recommendations to referring physicians on the same patient, eroding referrer confidence and jeopardizing referrals.
- …further expose radiology as a root cause of unnecessary increases in health care costs."
- "Individual patients, referring physicians, and society as a whole cannot possibly accept this degree of variability.

Macari & Megibow, Radiol, Apr 2011



"Secondary interpretations have the potential to render more accurate interpretations, alter patient management, and lower rates of repeat imaging examinations, which in turn may entail additional exposure to ionizing radiation and intravenous contrast agents as well as additional costs to patients and health care systems."

Premise

- Variation in clinical practice results in poorer outcomes and higher costs.
- Treating physicians want quantitative results. They prefer numerical probabilities to ambiguous qualitative descriptors.
- One approach to reduce variability in radiology is to extract objective, quantitative data from scans.

Definition of Quantitative Imaging

- Quantitative imaging is the development, standardization, and optimization of anatomical, functional, and molecular imaging acquisition protocols, data analyses, display methods, and reporting structures in order to permit the validation of accurately and precisely obtained image-derived metrics with physiologically relevant parameters, and the use of such metrics in clinical research and patient care.

Quantitative Imaging Biomarker

a characteristic derived from an *in vivo* image and objectively measured on a *ratio or interval scale* as an indicator of normal biological processes, pathogenic processes or a response to a therapeutic intervention.

Types of Variables (Stevens, 1946)

- Ratio:
- Interval:
- Ordinal:
- Nominal:

Types of Variables (Stevens 1946)

- **Ratio:** ratios are meaningful; Tumor volume, PET SUV
- **Interval:** differences are meaningful, but ratios are not; k-trans
- **Ordinal:** order of values has meaning, but actual values do not; Bi-Rads
- **Nominal:** numbers are assigned for convenience, but neither the order nor the values have meaning; Feature categories

Precision Medicine

Six major clinical areas of PM interest:
- oncology
- brain disorders
- cardiovascular disorders
- infections
- 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.

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Signs & Symptoms of Brain Disorders

- Abnormal -
  - Thoughts
  - Emotions
  - Behaviors

"DSM ...standardizes psychiatric diagnostic categories and criteria.
Critics, including the National Institute of Mental Health, argue the DSM represents an unscientific and subjective system. There are ongoing issues concerning the validity and reliability of the diagnostic categories; the reliance on superficial symptoms; the use of artificial dividing lines between categories and from "normality"; possible cultural bias; and medicalization of human distress."

Global Burden:
Probably 1 billion people.
In 2010, the global cost of mental disorders was estimated to be approx US$2.5 trillion; by 2030, that figure is projected to go up by 240%, to US$6.0 trillion.

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Quantitative Cardiovascular Imaging

- Cardiologists have extracted quantitative measures from clinical images for more than 40 years.
  - SPECT/PET
  - Echocardiography
  - CT (e.g., calcium scores; CT angiography
  - MR
- Assessing bias and precision has been a more recent focus.
- Threshold between "normal" and "abnormal" has been an ongoing debate.

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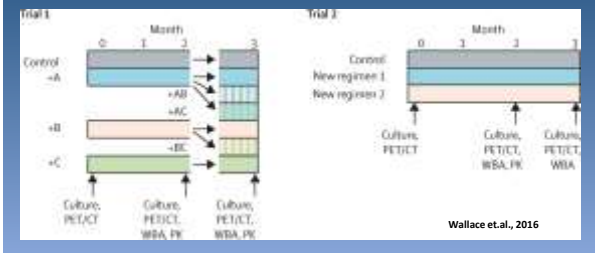
QI in Infection

- "Infection triggers a host response with the aim to destroy the pathogen, and this response can be measured."
- "Reliable biomarkers for infection should assist with earlier diagnosis, improve risk stratification, or improve clinical decision making."
- Esp – imaging can be an alternative to biopsy:
  - Tuberculosis
  - Hepatitis
  - Abdominal infections
  - Fungal infections
  - Osteomyelitis
  - Sepsis
  - Diabetic foot
- Quantify drug distribution

- "Tuberculosis is the leading infectious cause of death worldwide, with 9·6 million cases and 1·5 million deaths reported in 2014.
- Progress in tuberculosis-specific biomarkers (including culture conversion, PET and CT imaging, and gene expression profiles) can support this innovation.
- PET with CT combination could be an important non-invasive method to assess disease activity, response to therapy, and risk of relapse."

"Proposed plan for the development of three new MDR tuberculosis drugs. Figures is based on two 3-month trials. A, B, and C represent new drugs."



Wallace et.al., 2016

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Non-alcoholic fatty liver disease (NAFLD)
Progressive form = non-alcoholic steatohepatitis (NASH)

- **Affects 1 billion people worldwide**
- **"Gold standard" = liver biopsy**
  - **which is simply not practical as a routine component of clinical management.**

"Accurate, objective, quantitative, reproducible, precise biomarkers are needed to detect the presence of hepatic steatosis, NASH, stage of fibrosis and presence of advanced fibrosis, to risk stratify patients who need to be referred and treated by hepatologists."

- **MRS**
- **MRI-PDFF**
- **Conventional ultrasonography (CUS)**
- **Controlled attenuation (Ultrasound) parameter (CAP)**
- **Vibration controlled transient elastography (VCTE)**
- **Acoustic resonance forced impulse imaging (ARFI)**
- **Shear wave elastography (SWE)**
- **MR Elastography (MRE)**

Table 2. **Comparison between elastographic modalities.**

Modality	Cost	Accuracy	Point of care	Quality criteria	Caveats
VCTE	+	++	Yes	Standardised	Increased variability in morbid obesity and cirrhosis
ARFI/SWE	+	++	Can be	QIBA* is working on it	Increased variability in morbid obesity and cirrhosis
MRE	++	+++	No	QIBA* is working on it	Excellent accuracy in obesity and cirrhosis May fail in the setting of iron overload

ARFI, acoustic radiation forced impulse imaging; MRE, magnetic resonance elastography; QIBA, Quantitative Imaging Biomarkers Alliance; SWE, shear wave elastography; VCTE, vibration controlled transient elastography

Loomba, J Hepatol 2018

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Inflammatory Conditions for which QIBs are Needed

- **Rheumatoid arthritis**
- **Osteoarthritis**
- **Idiopathic pulmonary fibrosis**
- **Autoimmune disorders**
- **Neurodegenerative disorders**
- **Inflammatory bowel disease (IBS)**
- **Asthma**

Implications of Precision Medicine for Imaging

1. Objective, reproducible, quantitative information.
2. Standardization in imaging acquisition and structured reporting.

Thank you.