Quality standards for imaging studies

3rd International NASH Biomarkers Workshop
Washington, DC May 18, 2018

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Performance quantitative

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Resoundant

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Acknowledgements
Performance standards for quantitative imaging

Background
• Quantitative imaging
• Biomarker
• Quantitative imaging biomarker (QIB)

QIB Validation
• Concepts

Technical Performance
• Bias, linearity
• Precision
• Measuring interval
Quantitative imaging =

The extraction of quantifiable features from medical images

These features are called “quantitative imaging biomarkers” or QIBs
Biomarker =

Objectively measured characteristic as an indicator of normal biological processes, pathogenic processes, or a response to a therapeutic intervention.

Quantitative Imaging Biomarker (QIB) = Objectively measured characteristic as an indicator of normal biological processes, pathogenic processes, or a response to a therapeutic intervention derived from an in-vivo image.

Objectively measured characteristic as an indicator of normal biological processes, pathogenic processes, or a response to a therapeutic intervention.
The true value of a QIB is unknowable in vivo.

Stiffness

Ability to resist deformation from external pressure.

Diagram:
- Soft Object
- In between
- Stiff Object

Pressure from all sides.
Quantitative imaging “measures” the QIB value
Quantitative imaging “measures” the QIB value.

- “Measured” QIB value
- “QIB Measurement”
- QIB “Measurand”
- Actual QIB value

The “Truth”
Quantitative imaging = multiple components

<table>
<thead>
<tr>
<th>Quantitative Imaging</th>
<th>Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Site</td>
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<tr>
<td></td>
<td>Device</td>
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<tr>
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<td>Image acquisition technique</td>
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The same QIB can be measured by more than one quantitative imaging method.

- Magnitude CSE-MRI
- Complex CSE-MRI
- PDFF
- Multi-echo STEAM MRS
QIB validation has 3 elements

For a given quantitative imaging method

1. Technical performance/validation
   How well does the estimated QIB measure the actual QIB?

2. Clinical performance/validation

3. Clinical utility/usefulness
QIB validation has 3 elements

For a given quantitative imaging method

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## QIB validation has 3 elements

**For a given quantitative imaging method**

1. **Technical performance/validation**
   - How well does the estimated QIB measure the actual QIB?

2. **Clinical performance/validation**
   - How well does the estimated QIB detect, diagnose, stratify, monitor, etc.?

3. **Clinical utility/usefulness**
   - What is actionable value of estimating the QIB for clinical or regulatory outcomes?
QIB validation has 3 elements

For a given quantitative imaging method

1. Technical performance/validation
   - Bias, linearity
   - Precision: repeatability, reproducibility
   - Measuring interval

2. Clinical performance/validation

3. Clinical utility/usefulness
QIB validation has 3 elements

1. Technical performance/validation
   - Bias, linearity
   - Precision: repeatability, reproducibility
   - Measuring interval

2. Clinical performance/validation
   - AUROC
   - Sensitivity, specificity

3. Clinical utility/usefulness

For a given quantitative imaging method
| 1. Technical performance/validation | Bias, linearity  
|                                  | Precision: repeatability, reproducibility  
|                                  | Measuring interval |
| 2. Clinical performance/validation | AUROC  
|                                  | Sensitivity, specificity |
| 3. Clinical utility/usefulness    | Aggregated evidence  
|                                  | Biomarker qualification |
## Today

### 1. Technical performance/validation
- Bias, linearity
- Precision: repeatability, reproducibility
- Measuring interval

### 2. Clinical performance/validation
- AUROC
- Sensitivity, specificity

### 3. Clinical utility/usefulness
- Aggregated evidence
- Biomarker qualification
| Bias                  | Degree of systematic measurement error: difference between “measured” QIB values and their
|                      | • “true” values (if truth is known) OR
|                      | • “reference” values (if truth is unknown) |

| Linearity            | Degree of proportionality between between “measured” QIB values and their
|                      | • “true” values (if truth is known) OR
|                      | • “reference” values (if truth is unknown) |
If the “true” QIB value is known (i.e., phantom)...

“If there is perfect agreement (concordance) between “measured” and actual values...
If the “true” QIB value is known (i.e., phantom)...

“Measured” QIB Values (Investigational Imaging Method)

If there is some scatter in the “measured” values
If the “true” QIB value is known (i.e., phantom)... If there is some scatter in the “measured” values AND bias.

“Measured” QIB Values (Investigational Imaging Method)
If the “true” QIB value is known (i.e., phantom)...

“Measured” QIB Values
(Investigational Imaging Method)

No bias

Actual QIB Values (phantom)
If the “true” QIB value is known (i.e., phantom)...

“Measured” QIB Values (Investigational Imaging Method)
If the “true” QIB value is known (i.e., phantom)...

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Actual QIB Values (phantom)
If the “true” QIB value is known (i.e., phantom)...

“Measured” QIB Values (Investigational Imaging Method)
If the “true” QIB value is known (i.e., phantom)...

“Measured” QIB Values (Investigational Imaging Method)

No bias
Constant bias
Proportional bias
Constant + proportional bias
Nonlinear bias

Actual QIB Values (phantom)
If the “true” QIB value is known (i.e., phantom)...

“Measured” QIB Values (Investigational Imaging Method)

- No bias
- Constant bias
- Proportional bias
- Constant + proportional bias
- Nonlinear bias
- Nonconstant bias
If the “true” QIB value is unknown (i.e., no appropriate phantom)
If the “true” QIB value is unknown

“Measured” QIB Values (Investigational Imaging Method)

Reference QIB Values (Established Reference Method)
If the “true” QIB value is unknown

“Measured” QIB Values (Investigational Imaging Method)

Imperfect Reference QIB Values (Established Reference Method)
If the “true” QIB value is unknown

“Measured” QIB Values (Investigational Imaging Method)

Imperfect Reference QIB Values (Established Reference Method)

No bias
If the “true” QIB value is unknown

“Measured” QIB Values (Investigational Imaging Method)

Imperfect Reference QIB Values (Established Reference Method)
Several metrics of bias and linearity

Several graphical display approaches

(Beyond scope)
Precision refers to the variability in repeated QIB measurements on same “experimental unit”
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<td><strong>Real-world clinical scenario</strong></td>
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Reproducibility studies should vary the conditions likely to be varied in clinical care or trials

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Several metrics of repeatability and reproducibility

Several graphical display approaches (Beyond scope)
The measuring interval =

range of actual (or reference) QIB values over which measured QIB is linear with low bias and high precision
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range of actual (or reference) QIB values over which measured QIB is linear with low bias and high precision.
How good is good enough?
Summary

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