An analysis of patient-reported outcomes in breast cancer patients through item-response theory pharmacometric model
Patient-reported outcomes (PROs)

- Reports of the status of health-related quality of life that come directly from the patient
  - Collected as questionnaires
  - Inform on
    - Physical status
    - Disease-related symptoms
    - Symptomatic adverse effects

- Therapeutic areas:
  - Oncology
  - Diabetes
  - Respiratory
  - CNS
  - Auto-immune/auto-inflammatory

- Increasing interest from the regulatory agencies
Example of PRO questionnaire
Functional Assessment of Cancer Therapy-Breast (FACT-B)

- 36-item questionnaire
- 5 aspects of well-being:
  - Physical
  - Social/Family
  - Emotional
  - Functional
  - Breast-cancer related
- For each item: score 0 to 4 (ordered categorical data)
Analysis of multi-item PROs
Classical statistical approach

- Relies on the sum of scores
- Easy to conduct
- Individual items are not considered
- Requires imputation of missing answers
- Ignores correlations between items

Time to symptom worsening (drop in 5 points)

<table>
<thead>
<tr>
<th></th>
<th>Median (months)</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cap + Lap</td>
<td>4.6</td>
<td>445</td>
</tr>
<tr>
<td>T-DM1</td>
<td>7.1</td>
<td>450</td>
</tr>
</tbody>
</table>

Stratified HR=0.796 (95% CI, 0.667–0.951)

P=.0121
Analysis of multi-item PROs
Item response theory (IRT) approach

- IRT in a pharmacometric framework to describe composite scores
  - Alzheimer’s disease\(^1\), Parkinson’s disease, multiple sclerosis, schizophrenia, etc.

- Assumes that the score for each of the items depends on a latent variable (not directly observable)

\[ f_1(\Psi_i) \rightarrow (\Psi_i) \rightarrow f_2(\Psi_i) \rightarrow f_3(\Psi_i) \rightarrow f_4(\Psi_i) \rightarrow f_5(\Psi_i) \rightarrow f_6(\Psi_i) \rightarrow f_7(\Psi_i) \]

- I have a lack of energy
- I have nausea
- I feel ill
- I am forced to spend time in bed
- I have trouble meeting the needs of my family
- I am bothered by side effects of treatment
- I have pain

\(^1\text{Ueckert et al. Pharm Res (2014)}\)
Analysis of multi-item PROs
IRT model structure

- Describes the probability of each score $m$ for each item $j$ as a function of:
  - Patient-specific well-being $\Psi_i$
  - Item-specific parameters
    - $a_j$: 1 per item
    - $b_{jm}$: 4 per item
  
  \[ P(Y_{ij} \geq m) = \frac{1}{1 + e^{-a_j(\Psi_i - b_{jm})}} \]
  
  180 parameters for FACT-B

- Item characteristic curves
FACT-B data
EMILIA study

- Randomized, open-label, international phase III study

**HER2+ locally advanced or metastatic breast cancer**
N=991

Prior taxane and trastuzumab

Progression on treatment for LABC/MBC, or within 6 months of adjuvant treatment

1:1

**Ado-trastuzumab emtansine (T-DM1)**
(3.6 mg/kg IV q3w)
N=495

**Capecitabine** (1000 mg/m² PO bid, days 1-14, q3w) +
**Lapatinib** (1250 mg/day PO qd)
N=496

Adapted from Welslau et al. Cancer (2013)
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- Prior taxane and trastuzumab

- Progression on treatment for LABC/MBC, or within 6 months of adjuvant treatment

**1:1**

**Ado-trastuzumab emtansine (T-DM1)**

- (3.6 mg/kg IV q3w)
- **N=495**
- 2655 FACT-B, median 24 weeks

**Capecitabine** (1000 mg/m² PO bid, days 1-14, q3w)

+ **Lapatinib** (1250 mg/day PO qd)

- **N=496**
- 2192 FACT-B, median 18 weeks

**Treatment cycles**

1 2 3 4 5 6 7 8

FACT-B

Adapted from Welslau et al. Cancer (2013)
Objectives

• To characterize FACT-B data in breast cancer patients following treatment with T-DM1 using an IRT pharmacometric approach

• To investigate potential exposure-response relationships

• To compare the response of T-DM1 to the reference treatment (capecitabine and lapatinib)
T-DM1 arm data
IRT model development

HER2+ locally advanced or metastatic breast cancer (N=991)
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Progression on treatment for LABC/MBC, or within 6 months of adjuvant treatment

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Ado-trastuzumab emtansine (T-DM1)
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Model development
A 3-step modeling approach

**Step 1: base IRT model**
- Item score data used as dependent variable
- Probability of a given score is a function of well-being $\Psi$ and item-specific parameters
- Well-being $\Psi$ predicted for each visit and patient

**Step 2: longitudinal well-being model**
- Empirical Bayes estimates of $\Psi$ from step 1 used as dependent variable
- Effect of time, covariates and drug exposure on longitudinal well-being are investigated

**Step 3: longitudinal IRT model**
- Longitudinal item score data used as dependent variable
- Models from step 1 and 2 are combined
Step 1: Base IRT model

Describes the probability of each score for each item as a function of a well-being variable $\Psi$. 

Latent variable

FACT-B item data = dependent variable

Well being $\Psi$

Score Phys 1  ⋮  Score Phys 7  
Score Soc 1  ⋮  Score Soc 7  
Score Emo 1  ⋮  Score Emo 6  
Score Func 1  ⋮  Score Func 7  
Score Breast 1  ⋮  Score Breast 9
Step 1: Base IRT model
Describes the probability of each score for each item as a function of five correlated well-being variables $\Psi$
Step 1: Base IRT model
Item characteristic curves
Step 1: Base IRT model
Item characteristic curves
Step 1: Base IRT model
Reassignment of breast cancer specific items

- Reassignment to other subscales
  - Based on likelihood ratio tests
  - Significantly improved the fit of the base IRT model (dOFV=-1138)

<table>
<thead>
<tr>
<th>Breast cancer specific item</th>
<th>Reassigned to</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short of breath</td>
<td>Physical</td>
</tr>
<tr>
<td>Arms swollen or tender</td>
<td>Physical</td>
</tr>
<tr>
<td>Self-conscious about the way I dress</td>
<td>Emotional</td>
</tr>
<tr>
<td>Bothered by hair loss</td>
<td>Emotional</td>
</tr>
<tr>
<td>Bothered by change of weight</td>
<td>Emotional</td>
</tr>
<tr>
<td>Worry that family members get the same illness</td>
<td>Emotional</td>
</tr>
<tr>
<td>Worry about effect of stress on illness</td>
<td>Emotional</td>
</tr>
<tr>
<td>Feel like a woman</td>
<td>Functional</td>
</tr>
<tr>
<td>Feel sexually attractive</td>
<td>Functional</td>
</tr>
</tbody>
</table>
Step 1: Base IRT model
Describes the probability of each score for each item as a function of four correlated well-being variables $\Psi$.
Step 2: Longitudinal well-being model
Describes the **time-course of well-being** and investigates the effect of covariates and drug exposure.
Step 2: Longitudinal well-being model
Base model: structure

- **Best model**: asymptotic function of time

\[ \Psi(t) = \Psi_0 + \Psi_{ss} \cdot \left(1 - e^{-\frac{\ln(2)}{T_{1/2}} \cdot t}\right) \]

- \( \Psi_0 \): baseline well-being
- \( \Psi_{ss} \): steady-state well-being
  - \( \Psi_{ss} = 0 \): stable
  - \( \Psi_{ss} > 0 \): improvement
  - \( \Psi_{ss} < 0 \): worsening
- Additive inter-individual (IIV) and inter-subscale (ISV) variability on \( \Psi_{ss} \)
- \( T_{1/2} \) common to all subscales

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Typical value (RSE%)</th>
<th>Variability - SD (RSE%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Psi_{ss, physical} )</td>
<td>0*</td>
<td>IIV: 0.57 (6) ISV: 0.20 (20)</td>
</tr>
<tr>
<td>( \Psi_{ss, social} )</td>
<td>-0.18 (19)</td>
<td></td>
</tr>
<tr>
<td>( \Psi_{ss, emotional} )</td>
<td>0.32 (10)</td>
<td></td>
</tr>
<tr>
<td>( \Psi_{ss, functional} )</td>
<td>0*</td>
<td></td>
</tr>
<tr>
<td>( T_{1/2} ) (days)</td>
<td>52 (21)</td>
<td>111% CV (11)</td>
</tr>
</tbody>
</table>

* fixed
Step 2: Longitudinal well-being model
Base model: visual predictive checks

![Graph showing changes in well-being over time for Physical, Social, Emotional, and Functional aspects.](image_url)
Step 2: Longitudinal well-being model
Covariate model: investigated relations

- Covariates tested additively on $\Psi_0$ and $\Psi_{ss}$

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Disease status</th>
<th>Prior therapies &amp; T-DM1 exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age</td>
<td>• Baseline tumor burden</td>
<td>• Treatment line</td>
</tr>
<tr>
<td>• Region</td>
<td>• Baseline ECOG</td>
<td>• T-DM1 AUC&lt;sub&gt;cycle1&lt;/sub&gt;</td>
</tr>
<tr>
<td>• Ethnicity</td>
<td>• Site of disease involvement</td>
<td>• T-DM1 C&lt;sub&gt;min,cycle1&lt;/sub&gt;</td>
</tr>
<tr>
<td>• Race</td>
<td>• Hormone receptor status</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Liver, bone, lung, brain metastases</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Measurable disease</td>
<td></td>
</tr>
</tbody>
</table>

ECOG: Eastern Cooperative Oncology Group functional status.
Step 2: Longitudinal well-being model
Covariate model: significant relations

- Race (Asian vs non-Asian) affects baseline social and functional well-being

Demographics
- Age
- Region
- Ethnicity
- Race
  - $\Psi_{0,\text{social}}^*$
  - $\Psi_{0,\text{functional}}^*$

Disease status
- Baseline tumor burden
- Baseline ECOG
- Site of disease involvement
- Hormone receptor status
- Liver, bone, lung, brain metastases
- Measurable disease

Prior therapies & T-DM1 exposure
- Treatment line
- T-DM1 $\text{AUC}_{\text{cycle1}}$
- T-DM1 $\text{C}_{\text{min,\text{cycle1}}}$
- No exposure-response

ECOG: Eastern Cooperative Oncology Group functional status. * $p<0.001$
Step 3: Longitudinal IRT model
Combining models from step 1 and 2

**Explanatory variables**
- Time
- Covariates (Race)
- Drug exposure

**Latent variables**
- $\Psi_{\text{physical}}$
- $\Psi_{\text{social}}$
- $\Psi_{\text{emotional}}$
- $\Psi_{\text{functional}}$

- **FACT-B item data**
  - $\text{FACT-B item data} = \text{dependent variable}$

- $\text{Score Phys 1} \ldots \text{Score Phys 9}$
- $\text{Score Soc 1} \ldots \text{Score Soc 7}$
- $\text{Score Emo 1} \ldots \text{Score Emo 11}$
- $\text{Score Func 1} \ldots \text{Score Func 9}$
Step 3: Longitudinal IRT model
Visual predictive checks of the items’ average score

- **Lack of energy**
- **Have nausea**
- **Meeting needs family**
- **Have pain**
- **Bothered by side effects**
- **Feel ill**
- **Spend time in bed**
- **Short of breath**
- **Arms swollen or tender**
- **Close to friends**
- **Emotional support from family**
- **Support from friends**
- **Family accept illness**
- **Family comm. about illness**
- **Close to partner**
- **Sex life**
- **Feel sad**
- **Satisf. coping with illness**
- **No hope with fight vs illness**
- **Feel nervous**
- **Worry about dying**
- **Condition get worse**
- **Way I dress**
- **Bothered by hair loss**
- **Family mbr get same illness**
- **Effect stress illness**
- **Bothered change weight**
- **Able to work**
- **Work fulfilling**
- **Enjoy life**
- **Accept my illness**
- **Sleeping well**
- **Usually do for fun**
- **Quality of life**
- **Sexually attractive**
- **Feel like a woman**

**Axes:**
- **Y-axis:** Average score
- **X-axis:** Time (days)

**Legend:**
- Blue line: Average score for the observed data
- Gray shaded area: 95% CI of the average score for the simulated data

*Items originally in breast cancer subscale*
Step 3: Longitudinal IRT model
Asian patients typically have lower baseline social and functional well-being
Reference arm data
IRT model applied and refined

- HER2+ locally advanced or metastatic breast cancer (N=991)
- Prior taxane and trastuzumab
- Progression on treatment for LABC/MBC, or within 6 months of adjuvant treatment

1:1

- Ado-trastuzumab emtansine (T-DM1)
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  (N=495)

- Capecitabine (1000 mg/m2 PO bid, days 1-14, q3w) +
  Lapatinib (1250 mg/day PO qd)
  (N=496)
Step 1: Base IRT model

- The base IRT model developed with T-DM1 data was applied to the reference arm data

- Empirical Bayes estimates of $\Psi$ were obtained and used in Step 2
Step 2: longitudinal well-being model
Using parameter estimates obtained with T-DM1 arm model
Step 2: Longitudinal Well-being Model
Re-estimating Model Parameters

- Physical
- Social
- Emotional
- Functional

Change in well-being ($\psi$) from baseline vs. time (days)

- Median of the observed data
- 95% CI for the median of the simulated data
- 5th and 95th percentiles of the observed data
- 95% CI for the 5th and 95th percentiles of the simulated data
Step 3: longitudinal IRT model
T-DM1 vs reference

\[ \Psi(t) = \Psi_0 + \Psi_{ss} \cdot \left(1 - e^\frac{-\ln(2) \cdot t}{T_{1/2}}\right) \]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>T-DM1 arm</th>
<th>Reference arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Psi_{ss,\text{physical}} )</td>
<td>0*</td>
<td>-0.341</td>
</tr>
<tr>
<td>( \Psi_{ss,\text{social}} )</td>
<td>-0.0987</td>
<td>-0.115</td>
</tr>
<tr>
<td>( \Psi_{ss,\text{emotional}} )</td>
<td>0.428</td>
<td>0.338</td>
</tr>
<tr>
<td>( \Psi_{ss,\text{functional}} )</td>
<td>0*</td>
<td>-0.0243</td>
</tr>
<tr>
<td>( T_{1/2} ) (days)</td>
<td>77.4</td>
<td>28.7</td>
</tr>
<tr>
<td>Influence of Asian on ( \Psi_{0,\text{social}} )</td>
<td>-0.536</td>
<td>-0.482</td>
</tr>
<tr>
<td>Influence of Asian on ( \Psi_{0,\text{functional}} )</td>
<td>-0.195</td>
<td>-0.250</td>
</tr>
</tbody>
</table>

* fixed
Step 3: longitudinal IRT model
T-DM1 vs reference
Conclusions
EMILIA study

• The IRT pharmacometric framework well-characterized FACT-B item-level data in both T-DM1 and capecitabine/lapatinib treated patients.

• No T-DM1 exposure-response relationships were identified for FACT-B.

• Differences between Asian and non-Asian may exist in baseline social and functional well-being.

• T-DM1 arm showed similar or better typical well-being than reference arm for all physical, social, emotional and functional aspects.
Conclusions
Methodological achievements

- **First application** of IRT pharmacometric modeling to PRO data
- Handles missing values **without imputation**
- Accounts for **correlations between items**
- Describes the **multi-dimensional** nature of the questionnaire
- Provides insight into the **questionnaire structure**
- Can **easily be extended** to binary data and count data
Acknowledgements

• All T-DM1 team members at Genentech

• All colleagues at Uppsala University
• Clinician-rated adverse events

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Capecitabine + Lapatinib</th>
<th>T-DM1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any grade</strong></td>
<td>Diarrhea (80%)</td>
<td>Nausea (39%)</td>
</tr>
<tr>
<td></td>
<td>Hand-foot syndrome (58%)</td>
<td>Fatigue (35%)</td>
</tr>
<tr>
<td></td>
<td>Nausea (45%)</td>
<td>Thrombocytopenia (28%)</td>
</tr>
<tr>
<td></td>
<td>Vomiting (29%)</td>
<td>Diarrhea (23%)</td>
</tr>
<tr>
<td></td>
<td>Fatigue (28%)</td>
<td>Elevated AST (22%)</td>
</tr>
<tr>
<td><strong>Grade 3 or above</strong></td>
<td>Diarrhea (21%)</td>
<td>Thrombocytopenia (13%)</td>
</tr>
<tr>
<td></td>
<td>Hand-foot syndrome (16%)</td>
<td>Elevated AST (4%)</td>
</tr>
</tbody>
</table>

Adapted from Welslau et al. Cancer (2013)