Predicting stroke recovery

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Predictors of stroke outcome

- Stroke severity
- Age
- Co-morbidities
- Stroke lesion volume
- Leuokariaosis

Predictors of motor recovery and outcome

<table>
<thead>
<tr>
<th>Modified Rankin Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
</tbody>
</table>
Recovery and Outcome

Different recovery
Same outcome
Impairment and Function

**Impairment**
- Voluntary movement
- Fugl-Meyer scale (FM)

**Function**
- Task completion
- Action Research Arm Test (ARAT)
- Functional Ambulation Category (FAC)
Today

Predicting recovery from impairment

Predicting functional outcomes
Recovery from impairment

Fugl-Meyer scores increase by 70% of the available improvement for most patients

Prabakaran et al., NNR, 2008
Winters et al., NNR, 2014
Feng et al., Ann Neurol, 2015
Buch et al., Neurology, 2016
Recovery and Outcome

Same *proportional* recovery
Different outcome
Recovery from impairment

Fugl-Meyer scores increase by 70% of the available improvement for most patients

Prabhakaran et al., NNR, 2008
Winters et al., NNR, 2014
Feng et al., Ann Neurol, 2015
Buch et al., Neurology, 2016
Recovery from impairment

Biomarkers of the corticospinal tract can be useful

Functional integrity
  Transcranial magnetic stimulation

Structural integrity
  Magnetic resonance imaging
Recovery from impairment

FM scores increase by 70% of the available improvement for patients with a functional corticospinal tract

Byblow et al., Ann Neurol, 2015

\[ \beta = 0.45, \text{ 95\% CI } = 0.39 - 0.50 \]
Recovery from impairment

Excitability of the stroke M1 also increases by 70% of the available improvement

Recovery from impairment is not related to therapy dose

$\beta = 0.74$, 95% CI = 0.64 – 0.85

Byblow et al., Ann Neurol, 2015
Recovery from impairment

FM scores increase by 70% of the available improvement
for patients with a functional corticospinal tract

Stinear et al., Stroke, 2017

\[ \beta = 0.63, \text{ 95\% CI} = 0.55 - 0.70 \]
Recovery from impairment

Recovery from impairment is not related to therapy dose

Stinear et al., Stroke, 2017
Recovery from LL impairment

Lower limb Fugl-Meyer scores increase by 70% of the available improvement for all patients, regardless of MEP status

Recovery from lower limb impairment is not affected by therapy dose

Smith et al., Stroke, 2017
Recovery from impairment reflects a spontaneous neurobiological recovery process with which current doses of therapy do not interact.
What does this mean?

**Clinical research**
Aim to increase the proportion above 70%
If patients have less residual impairment, they will have greater function, independence, and quality of life
Use TMS to select patients for UL trials

**Clinical practice ?**
Most patients are left with residual impairment
Patients with severe UL impairment can recover proportionally if MEP+
Current therapy helps patients learn to function as well as possible
The big picture

Eight multi-centre RCTs of motor rehabilitation since 2011
   Acute and sub-acute stage
   Total 1,795 patients
   Variations of current practice
   All neutral

How can we increase sensitivity to intervention effects at the sub-acute stage?
   Greater contrast
   Patient selection
How does better prediction of functional outcomes help?

TAILOR REHABILITATION GOALS

MANAGE PATIENT EXPECTATIONS

USE TIME AND RESOURCES TO BRING THE BEST OUTCOME FOR THE PATIENT
How good are we at predicting now?

> 31,000 patients discharged from > 900 US hospitals

There is a 3-fold variation in discharge rates to SNF and IRF after stroke, even after adjusting for clinical characteristics and geographic availability

Zian et al. Stroke 2017;48:2836-42

“This marked variation could reflect the lack of an evidence-based algorithm...”
How good are we at predicting now?

Predicting ARAT score at 6 months
(Action Research Arm Test)

<table>
<thead>
<tr>
<th>6 month prediction</th>
<th>Correct</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>86%</td>
</tr>
<tr>
<td>10 - 56</td>
<td>47%</td>
</tr>
<tr>
<td>57</td>
<td>61%</td>
</tr>
<tr>
<td>Overall</td>
<td>59%</td>
</tr>
</tbody>
</table>

Nijland et al., Physical Therapy, 2013
Functional recovery and outcomes

Patients who have initially similar clinical scores can have very different recoveries and outcomes
Functional outcomes

Biomarkers of the corticospinal tract can be useful

Functional integrity
  Transcranial magnetic stimulation

Structural integrity
  Magnetic resonance imaging
**PREP2 algorithm**

PREP- Previously developed and validated

Revised with data from 207 patients

Median age 72 y (18 – 98 y)
  - 50% female
  - 10% ICH
  - 13% previous stroke

Recruited within 72 h of stroke symptom onset
Usual care, therapy dose recorded

Primary endpoint: ARAT score 3 m post-stroke
**PREP2 algorithm**

Hypothesis-free cluster analysis of ARAT scores at 3 m to identify four levels of upper limb function

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mean</th>
<th>Median</th>
<th>Minimum</th>
<th>Maximum</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>56</td>
<td>57</td>
<td>50</td>
<td>57</td>
<td>113</td>
</tr>
<tr>
<td>Good</td>
<td>43</td>
<td>42</td>
<td>34</td>
<td>48</td>
<td>55</td>
</tr>
<tr>
<td>Limited</td>
<td>22</td>
<td>22</td>
<td>13</td>
<td>31</td>
<td>16</td>
</tr>
<tr>
<td>Poor</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>23</td>
</tr>
</tbody>
</table>

Classification and regression tree (CART) analysis to create a decision tree for predicting outcome, including factors:

- age
- gender
- hand affected
- SAFE score
- thrombolysis
- previous stroke
- NIHSS score
- MEP status (MEP+, MEP-)
- UL therapy dose
- PLIC FAAI
- CST lesion load (%)
- SMT lesion load (%)
- stroke type (LACI, PACI, TACI, POCI, ICH)
- stroke location (subcortical, cortical/subcortical)
PREP2 algorithm

SAFE ≥ 5
3 days

SAFE score out of 10
PREP2 algorithm

SAFE ≥ 5
3 days

< 80 y

< 80 y

EXCELLENT
PREP2 algorithm

SAFE ≥ 5
3 days

SAFE ≥ 8
3 days

< 80 y

EXCELLENT
PREP2 algorithm

SAFE ≥ 5
3 days

SAFE ≥ 8
3 days

SAFE < 8
3 days

< 80 y

EXCELLENT

GOOD
PREP2 algorithm

- SAFE ≥ 5
  - 3 days

- SAFE ≥ 8
  - 3 days
  - EXCELLENT

- SAFE < 8
  - 3 days
  - GOOD

- < 80 y
PREP2 algorithm

- SAFE ≥ 5
  - 3 days

- < 80 y
  - SAFE ≥ 8
    - 3 days
  - SAFE < 8
    - 3 days

- MEP+
  - 4 – 7 days

- EXCELLENT
- GOOD
PREP2 algorithm

SAFE ≥ 5
3 days

SAFE ≥ 8
3 days

SAFE < 8
3 days

< 80 y

MEP+
4 – 7 days

NIHSS < 7
3 days

EXCELLENT

GOOD

LIMITED
PREP2 algorithm

Accurate for 75% of patients
PREP2 algorithm

Also accurate for 75% of patients
PREP2 algorithm

Excellent - Promote normal use

Good - Promote function

Limited - Promote movement

Poor - Promote compensation
What happens when you use it?

PREP information changed therapist perceptions and behavior

Therapist confidence
  Higher with PREP information $p = 0.046$
What happens when you use it?

**PREP information altered therapy content**
- Less passive movement for patients with Excellent prognosis
- Less task specific training for patients with Limited or Poor prognosis

**PREP information did not alter therapy dose**
- Lower therapy dose for Excellent patients, \( p < 0.001 \)
- No effect of PREP information, \( p = 0.295 \)

As intended
- PREP altered therapy content but not dose
- PREP did not result in rationing
What happens when you use it?

**PREP information shortened length of stay**

Stroke severity: Longer stays for more severe stroke, $p < 0.001$

PREP: Shorter stays with PREP information, $p = 0.005$

*Median decrease of 6 days, 95% CI = 1 – 12 days*

*No background change, $p = 0.843$*
What happens when you use it?

No effects of PREP information on clinical outcomes

- Similar ARAT scores at 12 weeks, \( p = 0.51 \)
- Similar mRS scores at 12 weeks, \( p = 0.85 \)
- Similar MAL scores at 6 months, \( p = 0.25 \)
- Similar SIS scores at 6 months, \( p = 0.38 \)

Patients tended to exceed expectations with PREP information
What happens when you use it?

PREP algorithm information gave therapists more confidence.

More focused upper limb rehabilitation, tailored to the recovery potential of individual participants, may have contributed to shortened length of stay by around 1 week.

PREP information may increase rehabilitation efficiency, with no negative effects on patient outcomes.
Walking function after stroke

60% of patients need help to walk

Independent walking is the most frequent goal

Determines WHEN a patient will be discharged from rehabilitation and WHERE they will go

Marie-Claire Smith
A freshly-minted PhD!
Predictors

Balance
Strength
Age
Comorbidities
<table>
<thead>
<tr>
<th>FAC</th>
<th>Functional Ambulation Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Not walking or 2 assist</td>
</tr>
<tr>
<td>1</td>
<td>Mod-max 1 assist</td>
</tr>
<tr>
<td>2</td>
<td>Minimal 1 assist</td>
</tr>
<tr>
<td>3</td>
<td>Supervision only</td>
</tr>
<tr>
<td>4</td>
<td>Independent on level surfaces</td>
</tr>
<tr>
<td>5</td>
<td>Independent on stairs, slopes, uneven surfaces</td>
</tr>
<tr>
<td>Demographics and stroke characteristics (n = 41)</td>
<td></td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Age (median, range)</td>
<td>72 (43-96)</td>
</tr>
<tr>
<td>Female</td>
<td>24 (59%)</td>
</tr>
<tr>
<td>First stroke</td>
<td>37 (90%)</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>6 (15%)</td>
</tr>
<tr>
<td>tPA</td>
<td>6 (15%)</td>
</tr>
<tr>
<td>Stroke severity</td>
<td></td>
</tr>
<tr>
<td>Mild (NIHSS &lt;5)</td>
<td>7 (17%)</td>
</tr>
<tr>
<td>Moderate – severe (NIHSS ≥ 5)</td>
<td>34 (83%)</td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
</tr>
<tr>
<td>------------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Ambulation</td>
<td></td>
</tr>
<tr>
<td>Non-ambulatory (FAC = 0)</td>
<td>33 (80%)</td>
</tr>
<tr>
<td>Dependent ambulation FAC (1,2,3)</td>
<td>8 (20%)</td>
</tr>
<tr>
<td>Motricity index LL (median out of 100, range)</td>
<td>48 (0-92)</td>
</tr>
</tbody>
</table>
Study timeline

Variables entered into analysis: age, sex, stroke classification (Oxfordshire), NIHSS, stroke type (motor, motor-sensory, motor-sensory-hemianopia), comorbidities, FAC, MRC grades, Motricity Index, Trunk Control Test, therapy dose, therapy intensity (minutes per day), MEP status, MRI lesion load.
TWIST algorithm

TCT > 40

6 WEEKS
Trunk Control Test

0 points = requiring assistance
12 points = indep but abnormal movement pattern
25 points = indep and normal movement pattern

1) Roll to weak side
2) Roll to strong side
3) Lie to sit
4) Sitting, feet off floor 30 seconds
TWIST algorithm

Accurate for 95% of patients
Predicting Recovery of function

Baseline clinical scores alone are poor predictors of UL functional outcome
- The PREP2 algorithm can accurately predict upper limb functional outcome for 75% of patients
- TMS is essential for patients with a SAFE score < 5

Clinical scores may be reasonable predictors of independent walking
- The TWIST algorithm might accurately predict whether and when patients will recovery independent walking, but needs validation
- TMS might not be needed
What does this mean?
Clinical practice

• For Upper limb:
  • You can make an accurate UL prediction for 2/3 of patients with SAFE score and Age
  • If on day 3 SAFE < 5, get NIHSS score and book TMS
  • Tailor therapy according to predicted outcome

• For Lower limb:
  • You might be able to make an accurate prediction for most patients with TCT and hip extension
  • Manage discharge planning and patient expectations
What does this mean?

Clinical research

Match treatment and control groups based on predicted outcome, not just baseline characteristics
Conclusions

Biomarkers for patient selection in trials

Biomarkers in clinical practice

Personalised rehabilitation

Better outcomes
Thanks

www.presto.auckland.ac.nz

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Marie-Claire Smith
Dr Victor Borges
Professor Alan Barber

Anna McRae
Ben Scrivener
Kathryn Quick
Emma Monigatti
Claire Valentine
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