What can affect the value of precision medicine?

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Example of stratified medicine: genotype-guided dosing of warfarin

- Two RCTs of **genotype-guided dosing** of coumarin derivatives (including warfarin) to treat atrial fibrillation or venous thromboembolism.
- These RCTs involved different comparisons:
  1. In England and Sweden:
     - Genotyped-guided dosing vs. standard care ("one-dose-fits-all")
  2. In The Netherlands and Greece:
     - Genotyped-guided dosing vs. clinical dosing algorithm ("low-tech stratified medicine")

Main conclusions (according to editorial by Furie NEJM, 2013): “these trials indicate that … pharmacogenetic testing has … at best, marginal usefulness, given the cost and effort required to perform this testing.”

HOTEVER, improved safety remains important.

Opportunities exist in:

a. **formal dosing algorithms**, without concern for genotype;

b. **patient adherence** and possibly more responsibility to patients;

c. increased **diligence** by … personnel in testing, monitoring, and dosing.
Is personalised medicine always better?

Oral anticoagulants (OACs)

New oral anticoagulants (NOACs)

Other options

NOACs: apixaban, dabigatran, rivaroxaban

Other: left atrial appendage occlusion
Consider all treatment options!

Figure 1 Base-case efficiency frontier depicting costs and QALYs for 8 stroke prevention strategies

Cost-Effectiveness Analysis

Lee et al, TCT 2014

Which intervention is cost-effective?
Which interventions are not?

Genotype-guided dosing

$4,568 per QALY gained

$6,298 per QALY gained
What is needed to assess the value of precision medicine?

1. Is a particular test accurate for the target condition?
2. Does diagnostic test use result in adverse effects or harms?
3. Does diagnostic use improve patient management?
4. Do treatments change intermediate health outcomes (e.g., biomarker levels, tumor size, mobility)?
5. Do treatments/health interventions result in adverse effects?
6. Are changes in intermediate outcomes associated with changes in health outcomes?
7. Does treatment improve health outcomes?
8. Is there direct evidence that predictive, screening, or diagnostic test use improves health outcomes?
What data is needed to assess precision medicine?

1. Test characteristics (sensitivity/specificity, costs)
2. Treatment strategy (given a positive or negative test)
3. Prognosis (health) with true positives, false positives, true negatives, false negatives.
   - need to consider later treatments and their effects (e.g., what happens with a false positive result?)
4. Costs associated with true positives, false positives, true negatives, false negatives.

➢ In addition, we need to assess the quality of the data
Where do we find the data that we need?

<table>
<thead>
<tr>
<th>Data needed</th>
<th>Possible sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test accuracy and costs</td>
<td></td>
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<tr>
<td>Side-effects of a test (plus probabilities, costs)</td>
<td></td>
</tr>
<tr>
<td>Treatment strategy with positive or negative test</td>
<td></td>
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<tr>
<td>Health outcomes (prognosis) if patient is true positive;</td>
<td></td>
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<tr>
<td>also if the patient is false positive, true negative, false negative)</td>
<td></td>
</tr>
<tr>
<td>Costs associated with true positives, false positives, true negatives, false negatives</td>
<td></td>
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<tr>
<td>Prior probability of positives (e.g., HER2-positive)</td>
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<tr>
<td>Utility values of different outcomes</td>
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<tr>
<td>Etc.</td>
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</tbody>
</table>

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Components of (precision) medicine

**QUESTIONS**
- Disease susceptibility: increased risk of disease?
- Prognosis: future course of disease?
- Companion diagnostic: treatment response to a particular medicine?

**METHODS**
- Demographics, history, etc.
- Physical examination
- Histology
- Clinical chemistry
- Genetics & -omics
- Other
- Combination

**DECISIONS**
- Decision to use a drug (effectiveness)
- Decision not to use a drug (lack of safety)
- Decision about drug dosage
- Decision amongst drugs
- Decision about which treatment (e.g., drugs, surgery, etc.)

Many combinations relate to precision medicine (personalised medicine, stratified medicine, etc.)!
HER2 & trastuzumab (Herceptin)

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An example of precision medicine (Herceptin/trastuzumab)

Different treatment strategies are available. Is the test-first approach the most cost-effective option?
The cost-effectiveness of precision medicine vs. the alternatives depends on different factors.

“Value” (HER2 positive) Test-first approach
Diagnostic test: where is the threshold between a responder and a non-responder?

Possible results amongst people with the disease:
- TP (true-positive)
- FN (false-negative)

Possible results amongst other people:
- TN (true-negative)
- FP (false-positive)

A threshold (D₂) determines which results are positive (abnormal) and which are negative (normal)
Conclusions regarding precision medicine and trastuzumab (Herceptin)

- The cost-effectiveness of a stratified medicine approach using Herceptin depends on various factors, including:
  1. The prevalence of HER2-positive tumours
  2. Test characteristics (sensitivity, specificity, costs)
  3. Treatment strategy with a positive/negative test
  4. Prognosis with/without treatment (health outcomes)
  5. Costs of treatment and disease

**AND**: Whether healthcare professionals and patients will do what they’re supposed to do!
What can possibly go wrong in daily practice?

- Consider how well the treatment strategies will work in the ‘real world’.
  - Precision medicine is like a fine watch
    It may be sophisticated ...
    but a simpler approach
    may actually work better in practice
Reasons why precision medicine won’t be more cost-effective than one-size-fits-all

1. **Incorrect comparator** is used (cetuximab, warfarin)
2. **Costs** of testing are too high (warfarin)
3. **Costs** of active treatment are too high (e.g. cetuximab)
4. **Costs** of active treatment are low (e.g., statins)
5. **Test accuracy** is insufficient
6. **Effectiveness of active treatment** is insufficient even when it works! (warfarin)
7. **Patient heterogeneity** is too low (prior probabilities are too low or high)(trastuzumab)
8. **Quality of care** factors: e.g., tests are used incorrectly (wrong patient, wrong time)
Is ‘precision medicine’ intrinsically the best?

- Precision medicine **MAY** improve health and **MAY** even reduce costs.
- **BUT:**
  - its theoretical value depends on many factors
  - its real-world value depends on many more
- Precision medicine is **not always cost-effective** vs. one-size-fits-all approaches!