Should personalised medicine be funded in low and middle-income countries?

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Key questions

- What is personalised medicine?
- Is there evidence that it provides benefit to patients?
- How much does it cost?
- Should it be funded in low and middle income countries?
- Should it be funded anywhere except as a research project?
What is “personalised medicine”

There are many definitions but most would consider “personalised medicine” to involve:

1. Molecular analysis of a sample of a patient’s tumour (and normal tissue)
2. Determination of molecular/genetic characteristic(s) of that tumour that promote survival and proliferation of the tumour cells
3. Individualised treatment of that patient with drugs that inhibit those key molecular pathways
... but people wiser than me have questioned whether this approach will lead to major advances in cancer treatment

Jim Watson: DNA revealed the causes, it may never reveal a cure

Nobel laureate Jim Watson is calling on the cancer community to take a long hard look at what has been achieved by blocking the molecular signals that drive individual cancers

by Anna Wagstaff

So, the first step for personalised medicine, as for any scientific approach, is to review evidence and not to believe blindly in a new hypothesis.
For personalised medicine to be of value to patients requires:

- Tumours to have a limited number of common driving mutations that can be targeted
- Infrastructure to characterise these mutations
- Availability of multiple targeted agents that are effective for cancer patients with a known “target”
- Targeted agents with less toxicity than chemotherapy so that they can be given in combination
- No or delayed resistance after initial response to targeted agents
- Common genetic changes in cells within a given tumour (i.e. minimal intra-tumour heterogeneity)
How effective are targeted agents for cancer patients with a known “target”? 

There are some successes

- Imatinib for CML (targets the BCR/ABL translocation, expressed in ~90% of CML)
- Trastuzamab for HER2+ breast cancer (targets HER2, expressed in ~20% of breast cancers)
- Vemurafinib for BRAF+ melanoma (targets BRAF, mutated in ~50% of melanomas)
Imatinib is effective

This is the poster child – the last really effective targeted agent – licensed in 2001.

It is the exception, not the rule

May 30, 2001
Trastuzumab is a useful drug for HER2+ breast cancer

For metastatic disease:
Slamon et al, NEJM 2001;344:783-92

As adjuvant therapy:
Perez et al, JCO 2011;29:336-73
Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation


Paul B. Chapman, M.D., Axel Hauschild, M.D., Caroline Robert, M.D., Ph.D.,
Important questions for personalised medicine

- How effective are targeted agents for cancer patients with a known “target”? Not very effective
- Do cancers become resistant after initial response to most targeted agents? Yes, very rapidly
- Are targeted agents less toxic than chemotherapy so that they can be given in combination?
Toxicity of these targeted agents was substantial; they inhibit pathways that are also essential for many normal cells.

58% of potentially fatal adverse events are not in the initial FDA drug label, and 39% are not reported in any published randomized trial.

Can they be used in combination?
Multiple clinical trials have shown that it is very difficult to combine targeted agents because of toxicity.
Important questions for precision medicine

• How effective are targeted agents for cancer patients with a known “target”? Not very effective
• Do cancers become resistant after initial response to targeted agents? Yes, very rapidly
• Are targeted agents less toxic than chemotherapy so that they can be given in combination? No
• Do tumours have a limited number of common driving mutations?
• Are the genetic changes similar in cells within a given tumour?
The causes and consequences of genetic heterogeneity in cancer evolution

Rebecca A. Burrell¹*, Nicholas McGranahan¹,²*, Jiri Bartek³,⁴ & Charles Swanton¹,⁵

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Inter tumour heterogeneity

Subclone 1

Intratumour heterogeneity

Subclone 2

Subclone 3

Clonal heterogeneity

Intercellular genetic and non-genetic heterogeneity
Tumour heterogeneity in the clinic

Philippe L. Bedard¹,², Aaron R. Hansen¹,², Mark J. Ratain³ & Lillian L. Siu¹,²

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Trial designs for interpatient heterogeneity

Trial designs for intratumour heterogeneity

Exploring the impact of intratumour heterogeneity in a therapeutic context adds a further layer of complexity. Even if current technologies such as minimally invasive multiregional sampling of metastases or molecular imaging are able to identify functional tumour subpopulations that are geographically distinct, the design of clinical trials to interrogate these subpopulations is challenging.
Important questions for precision medicine

• How effective are targeted agents for cancer patients with a known “target”? Not very effective
• Do cancers become resistant after initial response to targeted agents? Yes, very rapidly
• Are targeted agents less toxic than chemotherapy so that they can be given in combination? No
• Do tumours have a limited number of common driving mutations? No
• Are the genetic changes similar in cells within a given tumour? No there is great heterogeneity

28/09/2014 ESMO, Madrid
Are there any clinical trials that show personalised treatment to be superior to standard therapy?

I have not been able to locate any such trials.

The only evidence that I can find consists of anecdotal reports of individual patients having a very good response to a selected drug.
Is personalised medicine expensive and logistically difficult?

YES, it requires:

• (Image-guided) biopsy and molecular analysis (e.g. sequencing of multiple genes) with rapid turn-around

• Substantial infrastructure for conducting clinical trials according to GCP

• Availability of multiple drugs to target multiple pathways, etc.
So personalised medicine ...

... is a field of research, not an established method for treatment of cancer

... has multiple real and theoretical problems making it unlikely that it will lead to substantial improvements in patient outcome

... is very resource-intensive
How, and where, should personalised medicine be investigated?

• In a very small number of large cancer centres in high-income countries, preferably in cooperation.

• Already too many cancer institutions are “jumping on the bandwagon”
Should personalised medicine be funded in low and middle-income countries?

**NO** — there are much better uses for limited resources...

...and it should only be funded in a few centres in high-income countries as part of a well designed research project.