Challenges in the development and reimbursement of personalized medicine:

Next Generation Sequencing: An HTA perspective on the implications for drug reimbursement?

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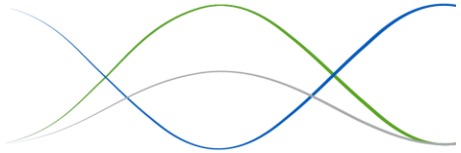
Agenda



- What is Next Generation Sequencing (NGS)?
- Potential uses and value of NGS
- Are we ready or not quite yet in oncology?
- Hypothetical examples of NGS in practice
- What value can NGS offer in HTA terms?
- Where will the evidence of clinical utility come from?
- Organising to get the best value from NGS
- Summary points

Definition: What is Next Generation Sequencing?

A substitute for the currently more common Sanger sequencing[1].

What is new in Next Generation Sequencing?

They are distinguished by their ability to rapidly examine many genes simultaneously, using a single test.

The main clinically relevant forms of NGS are[2]:

- Exome and targeted sequencing: targeted at specific genome locations.
- Whole genome sequencing: sequence of the entire genome.

The four main **advantages of NGS** over classical Sanger sequencing are[1]:

- Speed; cost of sequencing; sample size; accuracy.

Sources:[1]The Wellcome Trust (2014), [2]The European Bioinformatics Institute (2014)

What are the potential uses and value of NGS? (1) [1]

NGS is often seen as a disruptive innovation because of the significant decreases in cost of analysing many gene sequences in parallel substituting for a range of "traditional" tests

Three drivers of the cost of NGS:

1. The pre-analytics and assay
2. The bioinformatics platform. The assay generates a set of data, which is then visualised and analysed using the software developed to provide the informatics platform.
3. Evidence base for clinical utility and the need to convey the information to the patient and make treatment choices

Currently only the cost of component 1. is clearly declining.

Source: [1]Adapted from Deverka, P. A., & Dreyfus, J. C. (2014)

What are the potential uses and value of NGS? (2)

The value of NGS is partly dependent on the use that one makes of it.

NGS can be used for[1]:

1. Diagnosis
2. Treatment decisions and monitoring
3. Detection of future risk (although this raises ethical and data security issues as well as economic issues)
4. Reproductive planning (preconception and prenatal screening)
5. Newborn screening (which could also raise issues)

We look at disease/treatment targeted gene panels (1.& 2.)

Source: [1]Phillips, K. et al., (2014)

What are the potential uses and value of NGS? (3)

NGS more generally thought about as covering:

1. Targeted sequencing
2. Whole exome sequencing
3. Whole genome sequencing

I focus only on 1.

2. and 3. give rise to issues of:

- "Big Data" analytical challenges
- Storage, privacy, and data management
- Ethical issues, e.g. secondary findings

Source: [1]Phillips, K. et al., (2014)

NGS in clinical decision making: are we ready or not quite yet? The example of Oncology

- "Although many of the therapeutic implications of NGS involve clinical trial participation, **NGS is ready for the clinic**. Some clinicians would argue it already is in the clinic. Our focus now should turn to bringing this revolutionary, therapy-altering and prognostic technology to all patients in an efficient, affordable way." *Kathleen Harnden and Kimberly Blackwell*
- "Accordingly, **for today's clinical practice, single gene assays suffice**. However, as NGS become cheaper, it may be a simpler way to perform diagnostics on the small number of tumours in which several mutations, translocations or deletions are of proven benefit in decision-making, such as lung cancer or haematological malignancies." *Debu Tripathy*
- "In summary, then, somatic mutation profiling by **NGS is not necessary** for deployment of approved genomically-directed treatments and **is not yet at the point where it can be used to direct off-protocol treatment**. Profiling may be useful as a screening tool to determine trial eligibility but, for most patients". *Mark Robson*

Source: [1]Tripathy, D., Harnden, K., Blackwell, K., & Robson, M. (2014).

What could NGS look like in practice? (1)

Treatment selection in Lung cancer[1]:

- KRAS Mutation: have been associated with response or resistance to particular therapies
- EGFR Mutation: predicts for sensitivity to EGFR tyrosine kinase inhibitors (TKIs)
- ALK translocation: presence of an ALK translocation strongly predicts for sensitivity to ALK tyrosine kinase inhibitors
- MET amplification: recognized as one of the potential molecular mechanisms of acquired resistance to EGFR-TKIs
- ROS-1 fusions: can be used to offer targeted treatment with criozitinib.

Source: [1]Korpanty, G. J., Graham, D. M., Vincent, M. D., & Leighl, N. B. (2014)

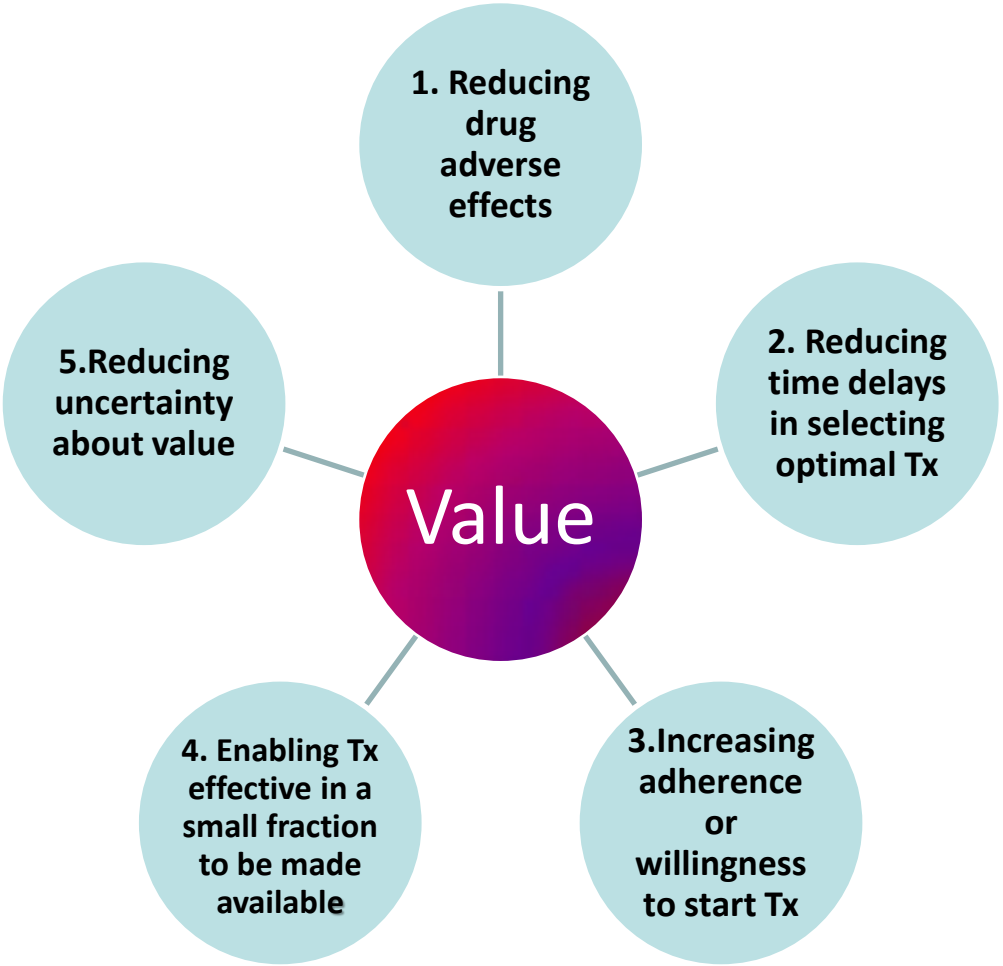
What could NGS look like in practice? (2)

Dosage adjustments and treatment selection in Schizophrenia:

- CYP450[1]: information about CYP450 genotype can be used to group patients in ultra rapid, moderate and slow metabolisers adjusting the treatment dose of drugs such as risperidone accordingly.
- COMT[2]: polymorphisms in the COMT gene determine likelihood of response to certain antipsychotics.
- SULT4A1-1 Haplotype 1[3]: identifies a subset of patients with lower risk of hospitalisation when treated with certain drugs compared to others.

Sources: [1]Ravyn, D., Ravyn, V., Lowney, R., & Nasrallah, H. A. (2013). [2]Gupta, M. et al. (2009). [3]Liu, Q. et al. (2012).

What are the potential sources of HTA value from use of NGS to select treatment options? (1)



Source: Garau et al. (2013)

What are the potential sources of HTA value from use of NGS to select treatment options? (2)

Reduced assay test costs, increased speed and accuracy

- Replaces a suite of tests – but we may not have needed them all
- Some reduction in time – this matters
- May avoid starting on the incorrect therapy
- Increased accuracy enables better patient stratification, fewer false positives and false negatives

Health and cost implications unclear. Positive health gain but higher costs? Is it cost effective?

Challenge: where will the evidence of clinical utility come from?

Evidence from the 9 case-studies

- Predominant funders are the *drug developers* (as part of the Rx development) and *public research bodies*
- Less clear role from Dx manufacturer

Sponsor	n	Case studies	Main study design
Drug Developer	6	Her2-BCa; EGFR-NSCLC; KRAS-CRC; BCR-ABL-CML; HIV, and Hep-C	RCT
Public Research	5	GenProfiling-Bca; KRAS-CRC; CYP2C19; Hep-C, and PreDx DRS	RCT
Dx Developer	2	GenProfiling-Bca; CYP2C19, and PreDx DRS	Retrospective
Payer	1	CYP2C19	Prospective observational

Towse A., et al. (2013)

Table 1. Sources of clinical utility evidence for decision-making in the nine case studies.

Marker	Main Study Design	Study size (patient numbers)	Sponsor	Decision-making Impact
Breast cancer recurrence (a) Oncotype DX® and (b) MammaPrint® (Prognostic/predictive in BrCa)	Retrospective RCT cohorts	(a) 688 [4] +651 [5] +895 [6] (b) Prognostic: 117 [9] +295 [10] +307 [11] +123 [12] , Predictive: 241 [13]	Diagnostic manufacturer Public research body	Generating clinical utility can yield inclusion in clinical guidelines and positive reimbursement decisions at a favourable price for test developers.
	RCTs	(a) 11248 [7] (b) 6600 [14]	Public research bodies	
HER2 (Trastuzumab in metastatic and early stage BrCa)	RCTs	469 [16] 3676 [19]	Drug developer Drug developer	Positive reimbursement decision for drug-diagnostic in a specific subpopulation based on health gains and cost-effectiveness.
EGFR mutations (1st line TKI treatment in NSCLC)	RCTs RCTs	1217 [25] 165 [26] 173 [27]	Drug developer Drug developer	Drug rescued because of a predictive, *ex post* companion diagnostic. Obtained first line indication
KRAS mutations (Anti-EGFR monoclonal antibodies in CRC)	Retrospective cohort analysis of an RCT	1198 [39]	Drug developer and Public research body	Decision-makers are willing to consider evidence generated *ex post* as sufficient to change recommended treatment protocols.
BCR-ABL transcript (TKI treatment in CML)	RCT	1106 [42]	Drug developer	Actionable, clinical information allowed for full incorporation into clinical guidelines; however, issues with inter- and intra-laboratory variability may impact patient management thus health outcomes.

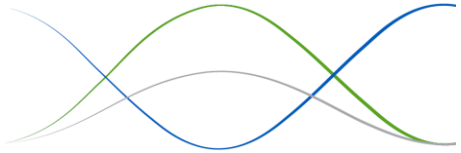
Table 1. *Cont.*

Marker	Main Study Design	Study size (patient numbers)	Sponsor	Decision-making Impact
CYP2C19 (Clopidogrel in ACS)	Retrospective RCT cohort+Healthy volunteers Prospective cohort study Proof-of concept RCT	1477+162 [52] 4471 [57] (Terminated early) 187 [58]	Public research body Payer Diagnostic manufacturer	The clinically significant and validated predictive effect would allow for health care efficiencies in the treatment of ACS. New POC test could improve implementation in clinical practice.
HLA-B*5701 (ABC in HIV)	Retrospective case control RCT	408 [59] 1956 [59]	Drug developer Drug developer	Prospective screening for first-line treatment is cost-effective in specific sub-populations. Treatment guidelines recommend abacavir only if patients have tested negative for HLA-B*5701.
Viral load (Pegylated interferon and ribavirin in hepatitis C)	Retrospective analyses of RCT data	1016 [61] 260 [62]	Drug developer Public research body	Testing becomes fundamental for predicting treatment outcome, reducing treatment side-effects and avoiding futile treatment and subsequent costs in non-responding patients.
PreDx® DRS (Risk in Type 2 diabetes)	Retrospective analysis of a sub-cohort of a lifestyle interventional trial	6784 [67,68]	Assay developer (trial funded by a public research body)	Although the score has been proven significantly better than other available methods and similar to the gold standard, uptake has been very limited. Data may not be generalisable to the whole population, and payers may not want to cover the test in addition to fasting glucose testing.

Organising to get the best value from NGS

- Need to have HTA of NGS where accuracy and clinical utility are assessed
  - "Home brews" present a quality challenge. Certification and inspection are key.
  - Willingness to use commercial "kits" is important if they offer better value.
- If NGS value is there in theory it is likely that it is only realised in practice in a few specialised treatment locations
- Need to introduce HTA for NGS and MDx

Summary Points



- There are some advantages of NGS compared with current practice in terms of speed, cost, sample size needed and accuracy.
- But NGS is not (yet?) transformative. The value of NGS does not come from multiple testing, but from the informatics and evidence of clinical utility. These costs are not falling.
- Demonstrating clinical utility is likely to be a challenge for NGS providers.
- However, use of NGS may well enable drugs to be better targeted, reducing use of ineffective drugs and adverse events, saving time, and improving health gain. But costs may go up.
- Need HTA for NGS and MDx – pay for value
- Using NGS effectively may well involve some concentration of cancer service provision in specialist centres.

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