Novartis Oncology

Industry Perspective: The challenges & opportunities of personalized/stratified medicine from a development and patient access perspective

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Presentation flow

- What is stratified medicine?
- Stratified medicine in Development
- Stratified medicine in Patient Access
- Summary and close

Rather than a lecture, points for discussion and food for thought from someone who works in the pharmaceutical industry and has clinical experience

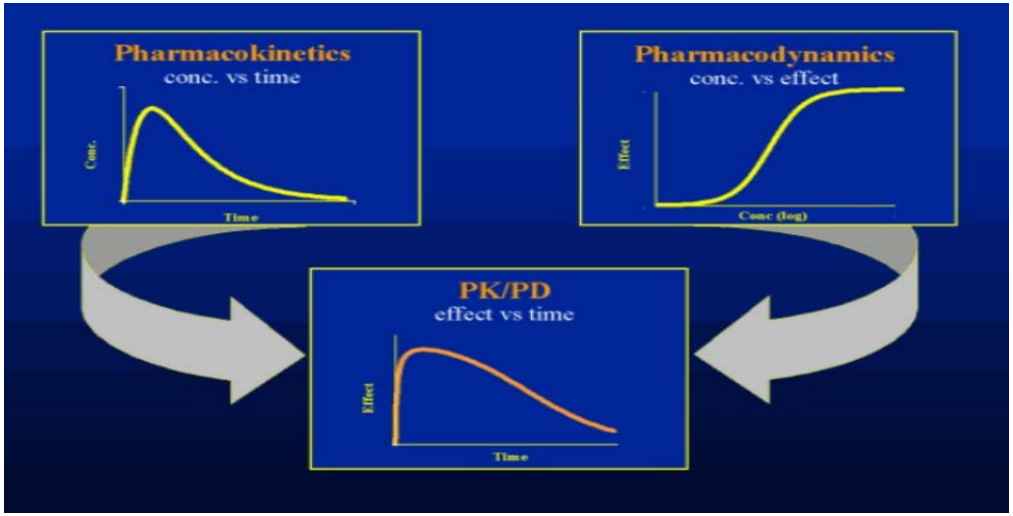
A cheerful start

"If it were not for the great variability among individuals, medicine might as well be a science, not an art"

William Osler

Stratified medicine- an attempt of a definition

- Prospectively, identifying (groups) of patients who benefit (or will have side effects) and who are unlikely to benefit (or wont have side effects)
  - Stratifying patients or disease, or both?
  - Pharmaco-genetics, pharmacogenomics or both

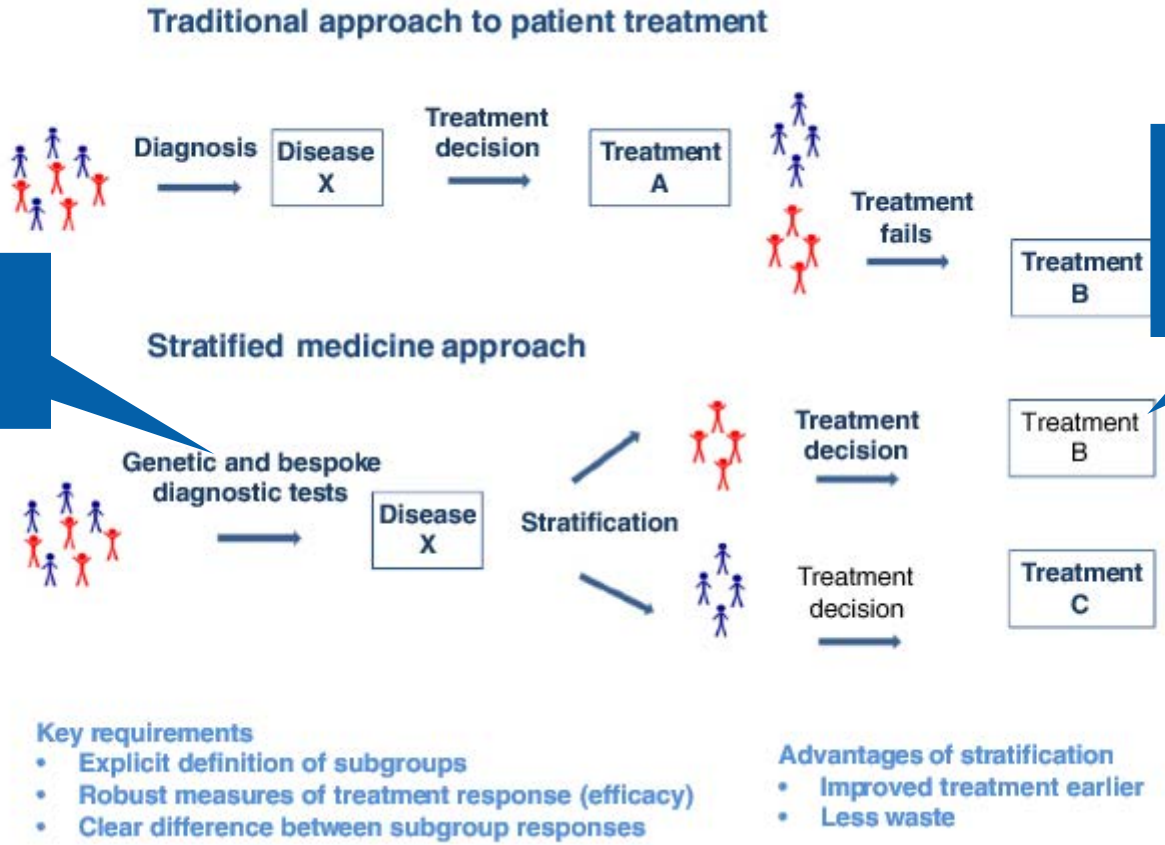


Dumontier, M https://www.slideshare.net/micheldumontier/personalized-medicine-5853949, accessed 18/09/2018 2340

Stratified medicine- an attempt of a definition

- A step towards personalized medicine
- A synonym for precision medicine
  - Or should it not better be “ more precise medicine”
- To treat precisely one has to diagnose precisely
  - How many types of hypertension are there?
  - Genomics and Proteomics may turn every disease into a are disease
- Is Stratified medicine a step forward?

How is it practically done?



Could be several tests

Could be more than one treatment and potentially at different doses

Lonergan, M. et al, Drug Discovery Today. Vol 22(1). 2017

Examples of Stratified Medicine*

- Genomic assays-no therapy, endocrine or chemotherapy
- Her-2 testing and trastuzumab
- B-Raf and Mek testing and inhibitors
- ALK testing and ALK-inhibitors
- BCR-ABL testing and BCR ABL inhibitors
- Checkpoint inhibition using PD1/PD1L AB's-PD 1 expression, mutational burden, neoantigenicity
- FLT-3 mutation testing

Common features:

- Identify patients who have a chance to respond rather than those who do not
- Degree of certainty for identified patients varies and depends on biology of the disease and reliability of the marker and test

This slide contains a non-exhaustive list of medicines, it is a random selection and is for illustrative purposes only

Stratified medicine in Development-Today

- Studies either randomize all patients with the Dx test result specified for inclusion across one or more arm(s) or have strata of patients with none and various degrees of expression of the target marker
- Potentially smaller sample sizes and hence putting less patients at risk
  - If not tested for, its unclear what the effect in the WT or otherwise Dx not positive group would have been
- Neither defining responses no ADR's is clear cut
  - Drop in values, difference from baseline etc
  - Phenotypic difference in ADR's
- Who develops the test?

Lonergan, M. et al, Drug Discovery Today. Vol 22(1). 2017
Shaw, EC and Johnson, PWM Drug Discovery Today (17(5/6) 2012

Stratified medicines in development- The future

- Move from sporadic testing to Real Time Oncology
  - Use novel Biopsy (Bx)methods-Liquid Bx
  - Artificially supported Intelligence
- Integrate continuous assessment of key genomic, epigenetic and proteomic analysis describing
  - The disease
  - The micro-environment
  - The interaction
- Modify treatment
  - Measure real time impact

Source of variability of a medicines' benefit risk profile

- Subject phenotype
- Subject genotype
- Disease/Environment phenotype and heterogeneity
- Disease/Environment genotype and heterogeneity
- Interaction between disease and environment
- Drug formulation, dose route
- Diet and lifestyle

Uncertainty or variability?

Regulators and stratified medicine

- Differences in EMA and US with regards to companion Dx approval (to be aligned)
- By how much has the response to be enriched in the stratified group (if all comers have been included)
- Could drive platform and protocol development
- Continue and enhance breakthrough/temporary approval solutions with real life data for confirmation

What is happening

- I-SPY2 breast cancer trial USA [69I-SPY 2 trial: Neoadjuvant and personlized adaptive novel agents to treat breast cancer: http://ispy2.org/]
- NCI cancer genome project (since 2006)
- Approval of medicines and associated Dx in defined tumors
- Approval of checkpoint inhibitor across tumors with a specific characteristic (MSI)

Stratified medicine and Patient access-The payer

- Potentially desirable to any healthcare system, possibly leading to more rapid access:
  - Clear identification of patients who do benefit (or clear which patients the medicine can be denied)
  - Predictable patient population as long as epidemiology the marker is stable
- Stratified medicines may pass the regulatory hurdle with little outcome data
  - Payer must show same flexibility as regulator and have interim funding mechanism
  - How long is interim ?

Stratified medicine and patient access- The test

- Costs of tests- especially if the number needed to test is high
  - Cheap homebrews vs. commercial tests with higher acquisition costs
- Differences in patient population between tests for the same marker/event may result in different populations treated in the real world versus the clinical trial setting
  - Cell source of origin
  - FISH vs IHC
  - Flow vs NGS
- Availability of test
  - CCR5 testing initially was only available in one global centre

Summary

- The age of stratified medicine is well underway- we need to move from one off assessment to Real Time Oncology fully deploying
  - Liquid Bx
  - Artificially supported intelligence
  - Novel omics test
- Several, but certainly not all diseases are likely to be suitable
  - Unmet need
  - Cancer heterogeneity
- The outcomes for the patient so far have been encouraging
  - Increased Efficiency
  - Increased Tolerability
  - At reduced cost to the Health system
- More data needs to be collected to allow backward and forward analysis of the success of this approach in the long term and in more diseases
- More needs to be done to promote stratified medicine to all stakeholders
- “We invariably overestimate the short-term impacts of new technologies and underestimate their longer-term effects”

Collins , F. Nature. 2010 Apr 1; 464(7289): 674–675.
doi: 10.1038/464674a

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A more cheerful end- never forget the "macro environment"

"It is so much more important to know what sort of a patient has a disease than what sort of a disease a patient has"

William Osler