What is Personalized Medicine?

**Personalized Medicine:**
- Use of genetic or other molecular biomarker information to improve the safety, effectiveness, and health outcomes of patients via more efficiently targeted risk stratification, prevention and tailored treatment management approaches

**Pharmacogenomics:**
- Use of genomic tests to inform patient treatment selection and dosing by predicting drug response

Several examples thus far...
- HER2/neu
- KRAS/PTEN/BRAF: Vectibix/Erbitux
- EGFR: Tarceva/Iressa
- Oncotype DX: breast cancer chemo

Source: Scientific American 2000 and 2006

Are Diagnostics & Personalized Medicine in Flux?

- What is different versus current requirements for drug development? Should diagnostics be handled any differently than drugs?
- How have decision makers handled early cases of co-development and what problems have they encountered?
- What system incentives & disincentives effect HEOR, HTA and reimbursement? What solutions are practical and relevant?

Are Existing Evidence & HTA Standards Sufficient for Dx & Personalized Medicine?

- What is unique? Are we reinventing the wheel or are new approaches applicable?
- Initial evidence requirements emerging; little harmonization to date
  - Canada: CADTH developing HTA criteria & base case models for Dx value assessment (e.g., EGFR testing)
  - UK: NICE Diagnostics Assessment Programme methods and process statements - building from a similar base as drug assessment, but taking some unique attributes into account
  - US: CMS taking more active interest; no guidance yet; BCBS TEC has evaluated multiple tests; focus is clinical
- How to address codevelopment scenarios vs. stand alone diagnostics?
  - How to handle from a policy perspective?
  - What ripple effect on other Dx applications?
How do we recognize value? Lack of value

UK House of Lords Report on Genomic Medicine

How based

Alliances involving personalized medicine industry

Evidence Standards & Reimbursement Decision Criteria

- Most frequently cited challenges from recent oncology HTAs in Canada, UK & US:
  - Variable sensitivity, specificity, and predictive value in published studies
  - Insufficient integration of positive and negative predictive value (i.e., extent to which test identifies or misses responders)
  - Inappropriate stratification or comparison designs using the biomarker
  - Insufficient power: to correlate marker with treatment & outcomes (i.e., to characterize clinical utility)
  - Cross-over design/approach causes ethical & interpretational issues
  - Relationship between size of responder population and cost-effectiveness
  - Concerns regarding infrastructure to support testing

- Despite challenges, examples have achieved reimbursement in global markets...though denials have occurred as well

Do Existing Processes Need to Change to Support Personalized Medicine?

- Do regulator & payer activities need to change to support personalized medicines? What implications for HEOR?
  - EMA Pharmacogenomics Working Party
  - Proposed FDA/CMS parallel review process for drugs, biologics and devices
  - Initial activities may not address issues specific to drug-diagnostic combinations

- Do HTA bodies and payer decisions need to be better coordinated? What implications for HEOR?
  - HTA & reimbursement for diagnostics and drugs often flow through different decision channels with different evidence requirements
  - How do we reconcile evidence requirements & communications with/selling market access?
  - Australia: PBAC/MSAC parallel review of codependent technologies;

- Even if reimbursement is achieved, can we accommodate testing in the existing clinical delivery infrastructure?
  - What are the implications for patient access?

- Infrastructure concerns have been cited in multiple HTAs of personalized medicines
  - UK: 2009 House of Lords report on Genomic Medicine
  - Centralization of testing approaches
  - Evaluation of infrastructure requirements & capacity
  - Consideration of who is responsible for testing

- What educational considerations relevant to appropriate physician adoption?

Can We Accommodate Emerging Dx & Personalized Medicine Scenarios?

Cross-cutting Policies & Increasing Emphasis

Emerging Initiatives Suggest Unique Considerations…

- US Proposed Legislation:
  - H.R.1321/S.244 (Medicare Advanced Laboratory Diagnostics Act)
  - S.736 (Laboratory Test Improvement Act)
  - S.976 (Genomics and Personalized Medicine Act)

- UK House of Lords Report on Genomic Medicine

- Alliances involving personalized medicine industry stakeholders
  - Personalized Medicine Coalition (PMC)
  - European Device Manufacturers Association (EDMA)
  - British In Vitro Diagnostics Association (BIVDA)
  - Association of the British Pharmaceutical Industry (ABPI)
  - European Personalized Medicine Diagnostics Association (EPEMED)

Tying It Back to ISPOR and HEOR

- What new HEOR approaches are necessary AND acceptable?
  - Diagnostics
  - Drug/diagnostic combinations

- Is a different standard for value demonstration a lower standard?
  - Where we go from the traditional pharmaceutical model?
  - What is reasonable in the absence of value-based payment for diagnostics?
  - Should the approach vary depending on budget impact and unit cost?

- What are the challenges and implications for economic modeling and assessment?
  - How do we address uncertainty? How much will decision makers accept?
  - What is the right “yardstick” or threshold?

- How do we address comparative effectiveness requirements for diagnostics & drug/diagnostic combinations?
Ex ante and Ex poste Scenarios: Implications for Regulatory, Reimbursement and Licensing of Dx and Codeveloped Personalized Medicines

Adrian Towse, MD, MPH
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Requirements for societal gain

- Regulation, pricing and reimbursement, IP
  - Three public policy determinants as to whether the scientific advance and competition can realise health gain from PGx
- Focus on the companion diagnostic component
  - Ex ante companion diagnostic
  - Ex post companion diagnostic

Ex ante: Herceptin and HER2 testing

- Prior to approval of trastuzumab (Herceptin) in 1998, Genentech, partnered with DAKO to develop a diagnostic kit to detect over expression of HER2/neu (HercepTest) and identify responders to therapies that target HER2/neu
- The test and drug were appraised together in RCTs for licensing purposes which showed clear health gains for patients receiving the drug vs. nonresponders
- The test was approved under a different process vs. the drug, and did not require an RCT
- There are now several competing tests and HER2 testing is now used for Tyverb/Tykerb
- There has been inter-laboratory variability in HER2 testing. In one trial only 6 out of every 9 specimens submitted by local laboratories as FISH+ were confirmed by central laboratories

Ex post: Iressa

- Use of EGFR mutation testing in lung cancer
  - Identification of EGFR mutations and association with outcomes for patients treated with gefitinib is a rare example of a drug that was rescued because of a predictive, ex post companion diagnostic
  - Erlotinib (Tarceva) and gefitinib (Iressa) are two EGFR-TKIs used to treat patients with advanced non-small cell lung cancer (NSCLC)
  - Gefitinib was approved for use in refractory NSCLC in May 2003 in U.S. on phase II trial results but the phase III trial failed to demonstrate a survival benefit
  - Erlotinib was approved in November, 2004 in the U.S. after a phase III trial showed a survival benefit over BSC with improvement in median survival of approximately 2 months. However only a small subset of patients (approximately 10%-20%) showed a measurable response according to the response evaluation criteria in solid tumors (RECIST1) guidelines
  - More recently, two phase III clinical trials have provided evidence to support the use of EGFR mutation testing to select advanced NSCLC patients for first line treatment with EGFR-TKIs

Ex post: Cetuximab/panitumumab, and KRAS mutations in colorectal cancer

- The for the KRAS mutation is a predictive companion diagnostic, albeit the original pivotal trial for cetuximab collected specimens to test for a different EGFR marker
- A strong association with KRAS was discovered in an ex post sub group analysis
- This example illustrates that given a convincing body of evidence—even if generated ex post (not being a pre-specified primary analysis of trial data)—both regulatory authorities and clinical guideline preparers are willing to consider such evidence as sufficient to change recommended treatment protocols

Agenda

- Requirements for societal gain from stratified medicine (PGx) to be achieved
- Case studies
- Regulation of drug / companion diagnostics combinations
- Conclusions
**NICE Recommendations in these three areas**

- HER2 tests plus trastuzumab (Herceptin) and lapatinib (Tyverb). Herceptin approved for: adjuvant treatment of early stage (TA197); advanced breast cancer (TA34). Tyverb review in process (FAD)
- Erlotinib (Tarceva) and gefitinib (Iressa) two EGFR-TKIs used to treat patients with (NSCLC). Tarceva only accepted 2nd line at equal overall treatment cost to docetaxel, no EGFR-TK testing (TA162). Iressa recommended 1st line option if test +ve for EGFR-TK mutation plus fixed price PAS (TA192)
- Cetuximab/panitumumab, and KRAS mutations in colorectal cancer. Cetuximab not recommended for metastatic colorectal cancer. "the improvement in median PFS of 1.2 and 0.5 months respectively, as demonstrated by the two trials, is considered to be limited. And concerns were raised that the KRAS wild type subgroup analysis was based on a small sample and carried out post hoc, at the request of EMEA." (TA118)

**EU consultation regarding revision to the IVD Regulation Directive In June 2010**

- Is movement to a risk based classification better? This would be in line with GHTF/501/04/5:2008. Currently there is an Annex II list
- Should the exemptions for "in-house tests" (home brews) be limited?
- Should higher standards of clinical evidence be required? In particular:
  - Should demonstration of **clinical validity** include NOT ONLY sensitivity and specificity, BUT ALSO negative and positive predictive values based on the prevalence of the disease?
  - Should demonstration of **clinical utility** be required (i.e., evidence linking test use to outcomes)? If so, how should it be demonstrated?
- Should conditional CE marking be allowed for a limited period subject to obligations to confirm the safety and performance of the tests?
- Do we need to move beyond self-certification for companion diagnostics to guarantee a high quality?

**Conclusions**

- Ex ante and ex post stratification using MDx are acceptable to regulators and payers – depending on the quality of evidence
- Separate institutions undertaking drug and device/test/lab regulation may not make sense anymore
- Low regulatory threshold for MDx means payers may not get evidence of clinical utility
  - In all of our cases the drug manufacturer paid for the trial and data analysis
  - Limited evidence base presents HEOR challenges
  - But raising the threshold for evidence will mean less MDx R&D unless reimbursement and IP is realistic

**Reimbursement of Diagnostics as a Key Factor for the Delivery of Innovative Treatments for the Right Patients, at the Right Time and Right Dose**

Diego Ossa, MD, MPH
Head, HE&OR, Novartis Molecular Diagnostics

**Demonstrating the Added Value of Diagnostics Would Improve Reimbursement of Innovative Technologies**

- Trastuzumab efficacy: For the 2nd line treatment of TRAM review, increased sensitivity in the HER2 group weld be superior to trastuzumab efficacy in HER2 group.
- Tyverb efficacy: Same discussion applying potential matching or super-selective treatments.
- Cetuximab efficacy: In the setting of WTK/TKR, demonstration of clinical utility in the docetaxel group needs to be compared with other treatments outside the EMA.

**Summary**

- Clinical impact & cost savings for health care systems
  - Clinical utility – patient outcomes
  - Demonstrate cost effectiveness
  - Treatment
  - Monitoring

**Reimbursement Framework for CDx & Innovative Technologies**
We need to prepare for:

- Establishment of new codes/procedures to adequately define the test
- Development of more robust clinical & economic evidence and their communication to payers
- Exploration of novel payment approaches and risk sharing agreements

**Dx Hurdles can be Higher vs. Drug Development Due to Limited Payer and Agency Familiarity**

**Innovative Reimbursement Frameworks can be Better Suited to Recognize & Reward Value of CDx**

**Traditional**
- Reimbursement for Rx and Dx sought independently
- Perceived value is not related to the test
- Clinical evidence required to demonstrate added value

**Value based on Dx**
- Value is based on the test
- Clinical evidence required to demonstrate added value
- Value is based on the test

**Combined**
- Value is based on the test
- Clinical evidence required to demonstrate added value

**Performance-based/Risk sharing**
- Value is based on the test
- Clinical evidence required to demonstrate added value

**Reimbursement Framework is Pivotal in the Innovation & Evidence Generation Process of Dx**

**Today**
- Reimbursement
  - Focus on basic regulatory approval (e.g. CE marking)
  - Overseeing specific quality and clinical aspects
  - Perception of (simple) molecular tests as "costly" relative to historical diagnostics

**Future**
- Reimbursement
  - Focus on basic regulatory approval (e.g. CE marking)
  - Overseeing specific quality and clinical aspects
  - Perception of (simple) molecular tests as "costly" relative to historical diagnostics

**Innovation Reimbursement Frameworks can be Better Suited to Recognize & Reward Value of CDx**

- Reimbursement for Rx and Dx sought independently with recognition of double-charging
- Reimbursement accounting to steps of test rather than its added value
- Translational use for HER-2 breast cancer

**Points for Discussion**

- Is there a reimbursement alternative that prevails when considering the added value of the diagnostics and delivering winning solutions to both payers and manufacturers?
- Is there a case for a ‘traditional’ reimbursement framework?
- How can industry, payers and other key stakeholders work together in defining the appropriate reimbursement framework(s) for molecular diagnostic technologies?

**Economic evaluation in PM – How is it different? How should it be used? Which role should modeling have in the evaluation of PM?**

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www.oncotyrol.at
PM strategies have specific features in HTA and cost-effectiveness analysis (CEA):

- Defining the test strategies & care pathway
- Defining patient-relevant outcomes
- Using the evidence
  - Evidence levels (e.g., diagnostic studies for test performance, RCTs for clinical endpoints)
  - Combining the evidence, linking test results to clinical outcomes
- Subgroup analysis
- Assessing the uncertainty
- Decision criteria (e.g., threshold)

Basic strategies:
- Treat all / Treat None / Test
- Combination of tests for risk/prognosis (natural hx of disease) and predictive tests (treatment effect, dosing)
  - Example: Warfarin pharmacogenomic testing
    - Meckley et al., PCE 2009; Eckman et al., Ann Int Med 2009
  - CYP2C9 (> 50 SNPs) + VKORC1 (AA, AB, BB) + further patient characteristics (age, height, body weight, diet)
- Need to collapse categories for trials and modeling
- Multiple comparators (test combinations and parallel/sequential test strategies)
  - Optimal cut-off on ROC curve or diagnostic scores
  - Diagnostic work-up and care path

Linking test results with patient-relevant outcomes
- Assess dominant situations (e.g., test strategy has better accuracy and is less costly)
- Semi-quantitative approaches
- Decision-analytic modeling

"Duration of the model should be sufficient to cover outcomes significant enough, after discounting, to affect the results."

Subgroup Analysis: Identifying the “Sweet Spots”

- Identification of subgroups in which PM strategies are effective and cost-effective
  - Benefit and ICER often function of a priori risk
- Stratification on prognostic and predictive test results
  - Warfarin example: CYP2C9 & VKORC1
- Stratification on individual patient preferences
  - Warfarin example: disutilities for AF, TIA, stroke, MI, bleeds

CEA: Value Beyond the QALY

- Seeing the whole diagnostic picture
- Prognostic information for life planning
- Unknown benefits for future treatments
- Changes in procedure time
- Cost savings from the value of prognostic information on Tx of other conditions
  - not included by e.g. NICE, IQWiG, Washington Panel
- Value for further research & innovation
- “Ethical risks”
- Other measures for PM test value?
  - WTP (e.g., safety vs. diagnostic knowledge)
  - €/correctly diagnosed
  - €/AUC

ICER often a function of individual factors
- Vol analysis to inform further research
- One PM strategy may trigger the next one
Points for Discussion

- Should economic evaluation in PM be performed differently (compared to standard HTA guidelines)?
- Which role should modeling have in the evaluation of PM technologies?
- Are there important outcomes beyond cost per QALYs?
- What is the decision criterion for cost-effectiveness of PM?

Tying it Back to ISPOR and HEOR

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ISPOR Personalized Medicine Special Interest Group

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Goal:
To develop good research practices in personalized medicine and inform appropriate health care decision and policy making using personalized medicine information

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