Meeting the Biotech Challenge

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The Challenge

Biotech drugs consume a larger portion of health plan budgets each year. To survive, a health plan must:

- Quickly assess biotechnology products
- Position them appropriately in the benefit structure
- Manage appropriate utilization at the appropriate cost
- Align incentives for providers, patients and health plan
This involves:

Complex system changes, detailed planning and execution:

- Benefit designs
- Specialty pharmacy contracting
- Provider contracting
- Claims processing
- Provider and member education
What is a “Biotechnology Product?”

- Complex molecules (usually proteins)
- Sophisticated manufacturing
- Major cost driver for health plans
  - very high R&D costs
  - usually > $2000 per patient-month
- Cost-effectiveness requires targeting:
  - specific indications
  - appropriate patient populations
Biotechnology Drugs vs Specialty Pharmacy

Not all biologics are specialty pharmacy drugs
Not all specialty pharmacy drugs are biologics

Biotechnology Drugs
- Humulin
- Lantus
- Byetta
- Glucagon
- Enbrel
- Avastin
- Cerezyme
- Interferons

Specialty Pharmacy Drugs
- Tarceva
- Gleevec
- Sutent
- Revlimid
Biotechnology products

- **Already available:**
  - Monoclonal antibodies (Remicade, Avastin)
  - Interferons (PEGIntron, Betaseron)
  - Enzyme replacement drugs (Cerezyme, Prolastin, Myozyme)
  - Genetic tests (Oncotype DX)

- **In development:**
  - Nanotechnology
  - Proteomics
  - Gene therapy
  - And more…
Demographic Trends

An aging population with

- Active lifestyles
- Wellness focus
- Health entitlement mentality
Disease Trends

Chronic diseases:

- Cancer
- Diseases of aging (Osteoarthritis)
- Lifestyle-related diseases (Diabetes)
- Genetic diseases (Gaucher, Pompe, etc.)
- New viral diseases (HIV, HCV, HSV, HPV)
Specialties that will Use Biotechs

- Oncology
- Rheumatology
- Gastroenterology
- Cardiology
- Neurology/Psychiatry
- Endocrinology/Diabetology
- Nephrology
- HIV/Infectious Disease
The systems challenge

Health Plan

Pharmacy Benefit
- Mail order
- Retail

Medical Benefit
- Retail
- Home Health
- Physicians
- SpecialtyRx

Biotech Med Claims $
Example: Xolair

- **Omalizumab**
  - Humanized monoclonal IgE ab
  - Unique asthma treatment
  - SC clinic injection, q 2-4 wks
  - Cost $10-15,000 per patient-year

- Pre-launch concerns (2003)
  - Off-label use (allergic rhinitis)
  - **Meaningful benefit to only 10-15% of patients**
  - Only 25% of asthma exacerbations IgE mediated
  - Claritin moving to OTC left a vacuum
Concern: Xolair and Allergic Rhinitis

- AR and asthma overlap by 30-50%
- AR trials showed improved symptoms & QOL
- **This is very expensive symptom relief!**
- Allergists may prescribe Xolair for patients with mild asthma and severe rhinitis
- Replace $80/month Claritin with $1000/month Xolair in a large population!
Retrospective assessment (2005)

- Xolair still very expensive
- Volume of patients significantly less than predicted
- Off-label use *not* being requested
- Allergists’ anecdotal feedback
  - Using Xolair in a select few patients
  - Results in those patients are quite good
- Severity & recent multiple exacerbations best available predictor of response (no biomarkers)
What industry says:

"By any standards, Xolair would be considered a blockbuster drug. This is one of those things that will, hopefully, change people's lives."

- Jacqueline Northcut Waugh, President
  BioHouston
What the press says:

“This will put Houston [where the molecule was discovered] on the biotech map.”

- Financial Times
What FDA advisory committee says:

“We already have less efficacy than we’d like to see for the magic bullet. So if we extended [Xolair] to a patient population where there was no testing done, **there are potentially a lot of patients who you would not expect to respond**... The actual efficacy of the general [asthma] population would be lower than what we’ve seen.”

- Polly Parsons, MD, Acting Chair
  FDA Pulmonary-Allergy Drugs Advisory Committee
Off-label use: rituximab*

*Kocs D and Fendrick M. AJMC 2003;9:393.
Formulary decisions in the biotech world

- Choices among “comparable alternatives:
  - TNFIs
  - Growth hormones
  - Interferons

- How to choose non-comparable therapies
  - Pharmacoeconomic evaluation (CEA/CUA)
  - Address complex ethical issues

- How to deal with the high cost
  - Improve pricing
    - Specialty pharmacy contracts
    - Negotiate with manufacturers
  - Convince employers of value of therapy
Patient Management Strategies

- Select appropriate patients using PA criteria
- Higher tier (cost share) for Specialty Drugs
- Manage diagnostics along with drugs
- Merge claims data:
  - Utilization management
  - Disease management
  - Case management
Patient selection for cost-effectiveness

Target the Right People

- More responsive patients
- Sicker patients
- Lower Number Needed to Treat or Test (NNT)

For Example:

- Treatment X costs $10,000 per pt-year
- If 100 people receive X and one gets cured, X costs $1,000,000 per cure
- If 10 people receive it and one gets cured, X costs $100,000 per cure
- Targeting has improved ICER by an order of magnitude

*If genetic screening can help us do this more effectively, it will add value!*
Cost-Effectiveness Research and Biologics
Age-related Macular Degeneration

- Degeneration of macula with central vision loss
- Neovascularization
- “Wet” AMD is worst type
  - 2 million in U.S.
  - 90% become legally blind
- Phototherapy
  - Laser photocoagulation
  - PDT (Visudyne) $3000/tx
VEGF Inhibitor Therapy for AMD

- Choroid neovascularization (CNV)
- VEGF inhibitors slow vessel growth

- Available products:
  - Macugen (pegaptanib)
  - Lucentis® (ranibizumab)
    - FDA approved for all Wet AMD patients
    - First to actually IMPROVE vision in 40% of pts
  - Avastin® (bevacizumab)
    - Same pharmacology as ranibizumab
    - FDA approved for cancer
    - Ophthalmic use NOT FDA approved
Avastin and Lucentis are similar drugs from the same company; while Avastin is far cheaper for treating macular degeneration, only Lucentis is FDA-approved for this. (www.allaboutvision.com)
Early pilot studies

- Ophthalmologists took the initiative
  - Concern about high cost to patients
  - No obvious reason bevacizumab shouldn’t work, assuming safety could be demonstrated

- Small trials, accumulating evidence
  - Safety
  - Patient response
  - Paired data possible (pts have 2 eyes)

- Expert opinion tipped in 2006
Summary of Current Evidence

- **Bevacizumab (Avastin)**
  - Five uncontrolled OL studies, total n > 1500
  - Significant improvement in visual acuity (VA) (mean 20/180 -> to 20/125 @ 3 months), Some with complete symptom resolution
  - Adequate demonstration of safety??

- **Ranibizumab (Lucentis)**
  - Two 24 month Phase 3 RCTs, total n > 1100
  - One vs verteporfin, one vs sham injection
  - > 90% had < 15 letter loss in VA @ 2 yrs, and 25-40% improved VA on ranibizumab
Premera Reviewer’s Conclusion

- Ranibizumab RCTs provide normal evidence of safety/efficacy for a new product (2 yrs)
- Bevacizumab has lower grade evidence
  - Effect size & % responders similar to ranibizumab
  - Used in > 1500 pts, no safety issues noted
  - Dosage form must be compounded
- Intravitreal bevacizumab should be covered
  - Majority of ophthalmologist expert opinion supports its safe & effective use
  - Incremental cost is negative; therefore, it is reasonable to apply a lower evidence standard
What’s missing here?
Comparison of Age-Related Macular Degeneration Treatments Trials (CATT)

- Federally Funded
  - National Eye Institutes of Health/NIH
- Head-to-head
  - Intravitreal bevacizumab vs ranibizumab
- The well-designed trial *we were waiting for*
  - 3 bevacizumab arms (different doses)
  - Adequate size: 1200 patients, 24 months
  - Started 1/2008, completing in 2011
  - Meaningful endpoint: mean change in VA

Source: www.clinicaltrials.gov/ct2/show/NCT00593450?term=CATT&rank=2
Questions CATT Will Answer

- Is intravitreal bevacizumab safe?
- Is it comparably effective vs ranibizumab?
- What is the optimal dose of bevacizumab?
- Is the effect durable up to 24 months?
Drugs and diagnostics: The new power pair
Personalized medicine: the next wave?

- Big promises:
  - Predict effect of individual genotypes on drug response
  - Compensate for genetic differences
  - Improve safety and effectiveness

- But will it be cost-effective?
  - Depends on wise use of companion diagnostics
What is Personalized Medicine?

- **Pharmacodiagnosics** – specific use of genetic diagnostic testing to design a personalized medication treatment regimen for a patient.

- **Companion diagnostic** – a test designed to predict patient response (safety, efficacy or both) to a specific drug or drug class.
Personalized Medicine: Potential Problems

- “Cannibalizing” existing mass markets
- Mostly unproven theory
- High level of investor risk
  - Requires massive venture capital
  - Long delays before ROI
  - High failure rate of startup companies
- Payer resistance to new pricing paradigms
  - Savings from waste avoidance offset by higher cost
  - Manufacturers will want same or higher profit levels
  - Will U.S. accept pharmacoeconomic pricing models?
Clinical benefit is uncertain

- Benefits of pharmacodiagnostic testing:
  - Possible cost avoidance
  - Dose optimization
  - Adverse event avoidance

- Risks:
  - May cost more than it saves
  - Correct interpretation of results critical
  - Information may not be actionable
Pharmacogenomic Test Limitations

- Several factors will slow rate of adoption:
  - Complex interactions involving multiple genes
  - Lack of large epidemiological databases for research
  - Lack of understanding of underlying biological mechanisms and implications for interpreting tests

- Projections (U W study):
  - 2010: 5-10 tests with established clinical utility
  - 2015: Many more tests, only 10-15 in routine use
  - 2025: Highly advanced testing technology, but limited understanding to drive applicability

Garrison, et al. (2007)
Three New Types of Genetic Tests

- **Pharmacogenomic tests**
  Predict individual response to one or more drugs

- Tests for **genetic markers of disease**
  Identify future disease risk in asymptomatic individual

- **Gene expression panels**
  Predict disease course and response to drugs

- **Difference from older genetic tests**
  - Wider distribution, potential cost impact
  - Use by primary care and other generalists
  - Focus on preventing/delaying disease
    - Potential for positive overall impact on population health
    - Potential for increased cost and utilization
Evaluation Criteria for Diagnostics

- **Analytic validity**
  Measures technical performance (Does the test accurately and reproducibly detect gene markers of interest?)

- **Clinical validity**
  Measures the strength of association between selected genetic markers and dose, therapeutic efficacy, and/or adverse events (How well does the test predict clinical events of interest?)

- **Clinical utility**
  Determines whether genotyping to guide treatment improves patient outcomes (therapeutic effect, adverse event rate) and has positive impact on the overall health of populations of interest

- **Incremental value**
  Calculates the incremental cost-effectiveness ratio (Is use of the test cost-effective? Does it add sufficient value to justify the price?)
DNA Microarray Chip

Example of an approximately **37,500** probe spotted oligo-microarray with enlarged inset showing detail.
Value: Historical Examples

- **Gleevec (imatinib)**
  - *Identifiable* mutations
    - Bcr-Abl1 kinase (Leukemia)
    - C-Kit (GIST)
  - **364** Premera patients in 2006

- **Iressa (gefitinib)**
  - Target EGFR tyrosine kinase
  - Launched without a genetic marker for resistance
  - No survival benefit in large clinical trial
  - Unidentifiable subset of patients gets good benefit
  - **11** Premera patients in 2006
Mechanism of Imatinib (Gleevec)

Missense mutations in 50% of imatinib-resistant patients are thought to prevent binding of imatinib to the Bcr-Abl protein. Dasatinib (Sprycel) can be used in resistant patients.
The ErbB Family of Tyrosine Kinases

- Cell surface receptors for extracellular proteins
- EGF receptor is common example (illustration)
- Four ErbB receptors:
  - ErbB-1 (EGFR, HER1)
  - ErbB-2 (HER 2/c-neu)
  - ErbB-3 (HER 3)
  - ErbB-4 (HER 4)
- Drugs:
  - MAbs: Erbitux, Vectibix
  - Small molecules: Iressa, Tarceva, Nexavar, Sutent, Tykerb
The EGFR System

**EGFR agonists & pathways, click**

- Panitumumab
- Zalutumumab, nimotuzumab, matuzumab, Cetuximab
- Trastuzumab

**Pertuzumab**
- Inhibits Her2/Her3 dimerization
- Anti EGFR or anti Her2 monoclonals prevent these receptors from being activated
  - *If they are IgG1s, they can also increase ADCC (antibody dependent cell cytotoxicity):*
    - trastuzumab, cetuximab

**Oral anti-EGFR-TKs**
- Inhibit enzyme cascades that are activated by stimulation of Her 1, 2, 3 & 4 membrane receptors
- *Inhibitors of tyrosine kinases triggered by EGFR stimulation
- **XL 647 also inhibits VEGFR2 & EphB4**
The EGF Receptor

EGFR_{III} is often found in glioblastoma, and has a deletion of exons 2 to 7 (a.a. 6 to 273)

KRAS^* a.a. 644

KRAS mutations can induce non-response to anti EGFR monoclonals (panitumumab, cetuximab) or EGFR-TK inhibitors. Such mutations trigger the RAS pathway.

Mutations of the intracellular portion of EGFR involving exons 17 to 21 (a.a. 712 to 979), and especially exon 19, in Non small Cell Lung Cancer, can facilitate efficacy of oral TK inhibitors (gefitinib and erlotinib)

The other escape route from the TK inhibitors is the c-MET pathway.

Most anti EGFR monoclonals target the extracellular portion of the EGFR.

These activating mutations of KRAS are met with in:
- 90% of pancreatic cancers
- 40% of colorectal cancers
- 10 to 20% of Non Small Cell Lung Cancers

They seem to have no influence on the activity of Avastin

^ KRAS Kirsten rat sarcoma viral oncogen homolog
a.a. = amino acid, followed by its number
Issues Involving Companion Diagnostics
Problems with Targeted Therapies

- Ineffective if don’t hit target
- Complex interacting pathways
  - Potential to develop resistance
  - Do we know all pathways?
- Blocking pathways may adversely affect normal cells
  - Potentially serious adverse effects
  - Cancer patients already vulnerable
  - May be difficult to differentiate from effects of underlying disease
Case Examples

- **Successful companion diagnostics:**
  - Bcr-Abl mutation and imatinib (Gleevec)
  - HER2 overexpression and trastuzumab (Herceptin)
  - Diagnosis, treatment, and monitoring protocols intimately linked
  - Target a selected, clinically appropriate patient population.

- **Industry observers predict early success in oncology**
  - Logical pairing of biomarkers and companion diagnostics tests
  - FDA fast track drug approval process for novel cancer drugs
  - Oncologists, patients and payers eager for targeted therapies with survival, cost-benefit and QOL breakthroughs

Safety of Genetic Tests Is a Complex Issue

- On the surface, genetic tests are not harmful
  - Minimally invasive sampling procedures
  - In most cases, sample is already taken for other tests

- Issues around interpretation of test results
  - Incorrect conclusions can lead to wrong treatment
  - Patient harm may result

- Issues around privacy of information
  - Appropriate content of informed consent for testing
  - Ownership of the resulting information
  - Safeguarding patients from future “genetic discrimination”
The Genetic Information Nondiscrimination Act of 2008 (GINA)

Need to update this slide with GINA 2

- A new federal law
- Protects Americans from being treated unfairly because of differences in their DNA that may affect their health
- Prevents discrimination from
  - Health insurers
  - Employers
- Health insurance provisions effective May 2009,
- Employer provisions effective November 2009.

National Human Genome Research Institute, www.genome.gov
What is Genetic Information?

Genetic information means information about:

- A person’s genetic tests
- Genetic tests of a person’s family members (up to and including fourth-degree relatives)
- Any manifestation of a disease or disorder in a family member
- Participation of a person or family in research that includes genetic testing, counseling, or education
How GINA affects health plans

**GINA strictly prohibits:**
- Requiring individuals to provide genetic info for eligibility or coverage
- Using genetic information to make enrollment or coverage decisions
- Requiring a genetic test as a condition for coverage
- Considering a gene for a future disease as a preexisting condition

**GINA does allow:**
- Use of genetic information to document medical necessity

Research exception:
- In collaboration with external researchers, a plan may ask that an individual undergo a genetic test—however such testing is *voluntary*
- Not being tested will not affect premium or enrollment status
- Test results may only be used for research and not for underwriting