

# Personalized Medicine Impact on specialty drugs

NAMCP – Fall Managed Care Forum

Lon Castle, MD  
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## Objectives

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- 1 Review specialty pharmacy growth rates
- 2 Discuss the principles of personalized medicine
- 3 Identify opportunities for PGx testing of specialty drugs
- 4 Provide examples of how PGx can impact specialty drug

## Legal disclaimer

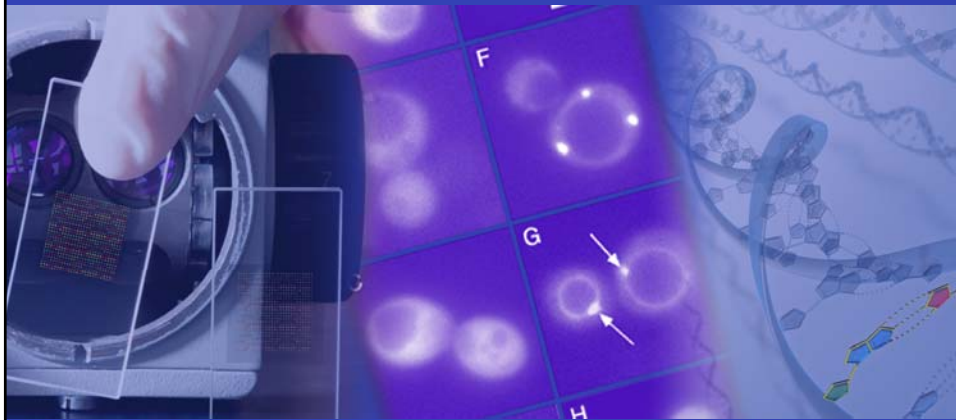
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**"Change is inevitable, except  
from vending machines."  
–Woody Allen**

Source: Peter Pitts. [www.pacificresearch.org](http://www.pacificresearch.org), April 13, 2005.

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## Specialty overview



## What are specialty drugs?

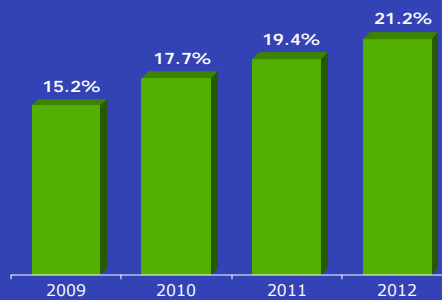
### The category generally includes:

- High cost, recombinant proteins – Biotech drugs
- High cost, non-recombinant proteins derived from human animal or bacterial sources (such as IVIG) – Biologics
- High cost small molecule drugs that are developed through advances in molecular biology/biotechnology (such as oral multi-kinase inhibitors)
- Other high cost small molecule drugs used for certain complex & orphan conditions (such as PAH, inborn errors of metabolism, & multiple sclerosis)

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## Specialty drug spending growth

- Specialty trend increased 15.8% in 2008
- Between 40% and 70% of specialty spend is billed through medical
- Expected industry-wide trend shows increasing spend rate through 2012
- By 2015, almost 1 in 4 dollars in drug spend will be for specialty drugs



**35–40% of new pipeline drugs are specialty**  
**40% of specialty drugs approved 2004 - 2008 were for cancer**

Source: PBM industry reports.

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## Specialty expands beyond rare diseases

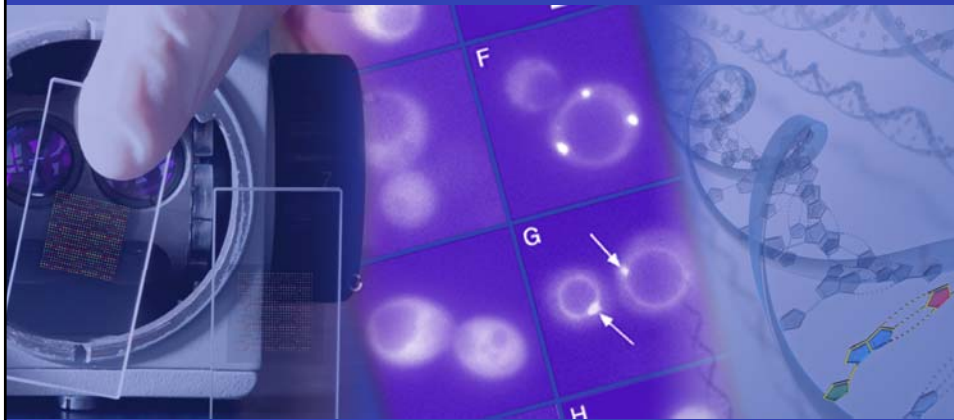
- Osteoporosis & Bone metastasis  $\approx$  45 million
- Osteoarthritis pain & neuropathic pain  $\approx$  26 million
- Asthma  $\approx$  16 million
- Cancer  $\approx$  12 million
- Alzheimer's disease  $\approx$  4 mm
- Chronic fatigue syndrome  $\approx$  1 - 4 million
- Gout  $\approx$  2 million
- Systemic Lupus Erythematosus (SLE)  $\approx$  1.5 million
- Eye diseases - Diabetic retinopathy affects 50-80% of type 2 diabetics

**Sources:**

Cancer Facts & Figures, 2009. American Cancer Society; [www.niams.nih.gov/healthinfo/bone/osteoporosis/osteoporosis](http://www.niams.nih.gov/healthinfo/bone/osteoporosis/osteoporosis); Arthritis Rheum 2008;58(1):15-25; [www.fda.gov/ohrtms/dockets/ac/08/briefing/2008-4355B2-](http://www.fda.gov/ohrtms/dockets/ac/08/briefing/2008-4355B2-); [www.cdc.gov/arthritis/arthritis/osteoarthritis.htm](http://www.cdc.gov/arthritis/arthritis/osteoarthritis.htm); [www.nih.gov/alzheimers/publications/adfacts.html](http://www.nih.gov/alzheimers/publications/adfacts.html); [www.cdc.gov/cfs/](http://www.cdc.gov/cfs/); [www.cdc.gov/arthritis/arthritis/gout.htm](http://www.cdc.gov/arthritis/arthritis/gout.htm); [www.nihbi.nih.gov/health/dci/diseases/asthma/asthma.html](http://www.nihbi.nih.gov/health/dci/diseases/asthma/asthma.html); [www.cdc.gov/arthritis/arthritis/osteoarthritis.html](http://www.cdc.gov/arthritis/arthritis/osteoarthritis.html).

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## Personalized medicine overview



# Definitions

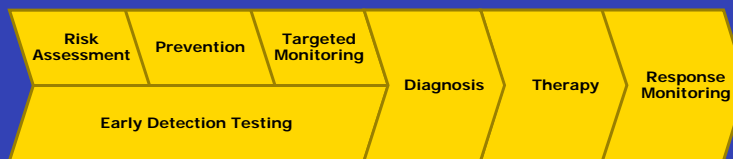
## Terms commonly used when discussing Personalized Medicine

<b>Pharmacogenomics</b>  phar·ma·co· ge·no·mics  <i>noun</i>	<b>Definition:</b>  <b>Science of predicting drug response:</b> the general study of all of the many different genes that determine drug behavior.
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Source: [http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4263s1\\_02\\_Harper-FDA.pdf](http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4263s1_02_Harper-FDA.pdf)

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# Pharmacogenomics (PGx)



### What it is not...

- Using an individual's genetic information to identify diseases or predict their future risk of developing other medical conditions

### What it is...

- A science that examines the inherited variations in genes that dictate drug response (whether a drug will be effective or safe)
- Personalizing drug therapy based on each patient's genetic variability

Source: Personalized Medicine Coalition: Personalized Medicine 101. Available at [http://www.personalizedmedicinecoalition.org/sciencepolicy/personalmed-101\\_overview.php](http://www.personalizedmedicinecoalition.org/sciencepolicy/personalmed-101_overview.php).

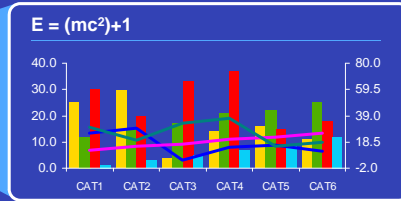
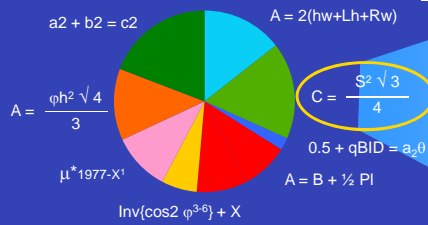
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# Pharmacogenomics: The concept

- The U.S. Pharmacogenomic diagnostic market is expected to grow to approximately \$3.0B by 2012
- The Origin of Species: It introduced the theory that populations evolve over the course of generations through a process of natural selection

Field of Study	Incremental Value	Additional benefit
Pharmacogenetics	$\theta * 12\lambda + /-\varphi^{17}$	55.0%
Metabolomics	$129 + A^4 / 73_n H_2O$	20.0%
Proteomics	$\mu^* 1977 - X^1$	35.6%
Translational medicine	$AB^2 - Y^*5/qBID$	38.4%
Nostradamusomics	$\Sigma \beta(?) [\sin 2 \varphi^{3-6}]$	61.9%

**Molecular Diagnostic Market Future Forecast based on Inverse Rationale**



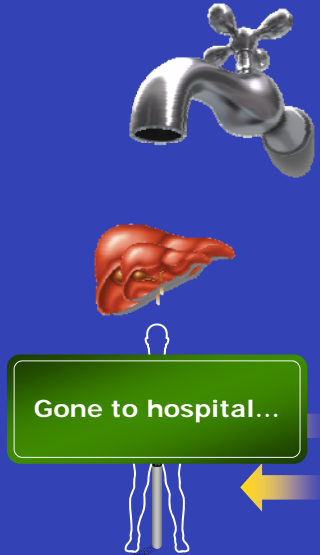
# Pharmacogenomics: The reality

Genetic or biomarker response

Drug metabolism

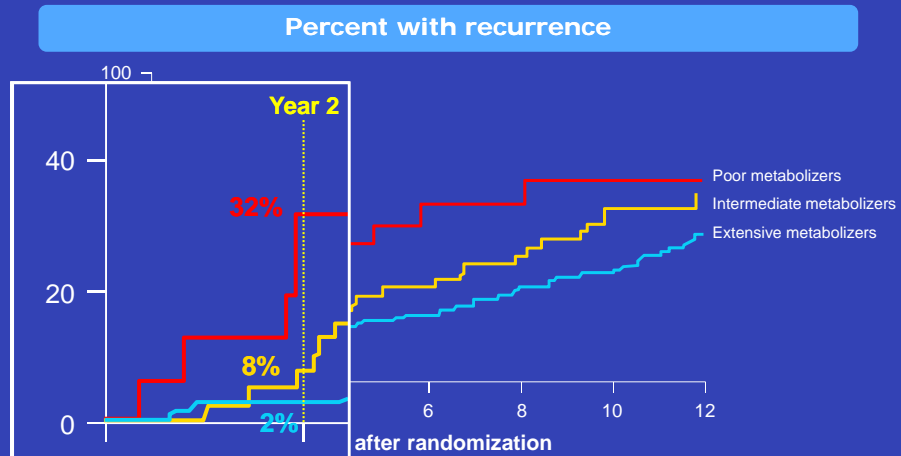


## How metabolizing enzymes work



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## Tamoxifen effectiveness - 2D6 phenotype

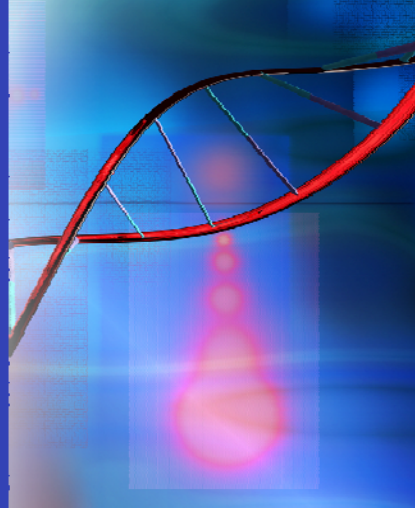


Source: Goetz, et al. *Breast Cancer Res Treat.* 2007;101:113-121.

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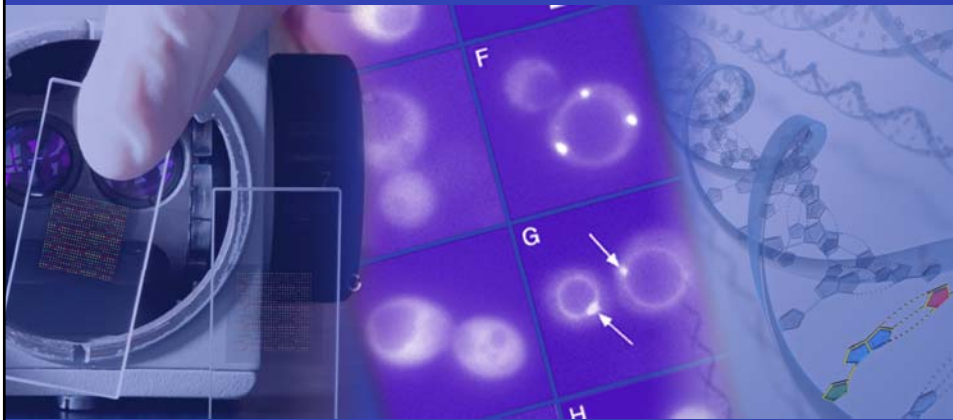
## Benefits of Pharmacogenomics

- Encourage the use of the right drug for patients
- Identify potential for adverse drug events based on genetic or biomarker information
- Reduce unnecessary drug expenditures and avoid potential health care costs
- Improve clinical care and health outcomes for patients

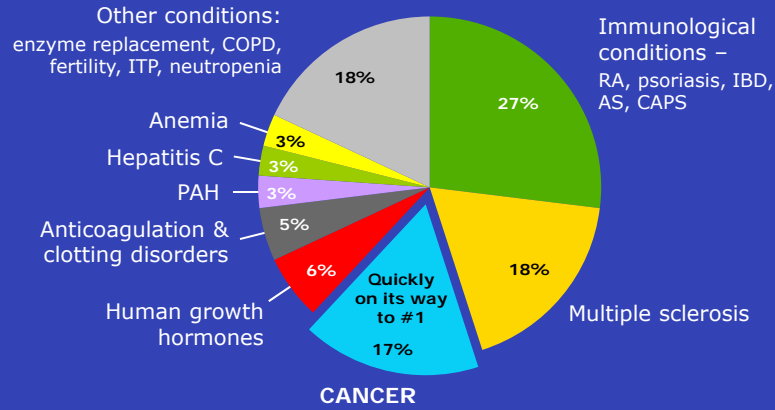


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## PGx opportunities in specialty



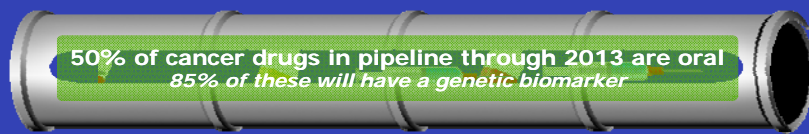
# Distribution of specialty spending



**40% of new specialty drugs are for the treatment of cancer**

Source: Medco Drug Trend Report, 2009.

# PGx opportunities for specialty



Year	Drug	Target / Biomarker
2009	Pazopanib	VEGF2 Inhibitor
	Ofatumumab	CD20 antigen
2010	Vandetanib	VEGF2 Inhibitor
	Omacetaxine	T3151 mutation
2011	Tafamidis	V30M TTR mutation
	BIBW 2992	EGFR mutations
	Bosutinib	BCR-ABL
	Mipomersen	APO B-100
	Constugene	P53 gene mutations
	Neratinib	HER2
	Ridaforolimus	HER2 / EGFR
2012	Bapineuzumab	ApoE4
	Midostaurin	FLT3 receptor
2013 & Beyond	VX 770	CFTR mutations
	Pertuzumab	HER2
	Motesanib	HER2
	BSI-201	Triple negative breast cancer (ER-/PR-/HER2-)

Sources: FDC Reports: NDA Pipeline, www.ndapipeline.com; FDC Reports: "The Pink Sheet", www.thepinksheet.com; R&D Insight, http://bi.adisinsight.com; DataMonitor: Pipeline Insight, www.datamonitor.com; Pharmacogenomics Reporter, www.genomeweb.com; OncologySTAT: 13<sup>th</sup> annual NCCN Conference, March 5, 2008.

## Example: Cancer



## Cancer treatment

### Cancer care & drug costs

- Cancer drugs are now the largest single therapeutic category<sup>1</sup>
- Growing at 12–15%/year reaching \$80 billion worldwide by 2012<sup>2</sup>
- In 2008, about 20 of the top 200 Rx drugs were for cancer, with 3 cancer-related drugs in the top 10<sup>3</sup>
- >90% of cancer drugs approved by FDA in the last 4 years have cost > \$20,000 for a 12 week course of therapy<sup>4</sup>
- There are 800 drugs in development for treatment of cancer; 35% are oral drugs<sup>5</sup>

**Sources:**

<sup>1</sup>Time to consider cost in evaluating cancer drugs. [www.medscape.com/viewarticle/705689](http://www.medscape.com/viewarticle/705689).

<sup>2</sup>The Oncology Pipeline: maturing, competitive & growing. *Oncology Business Review*. Sept, 2008.

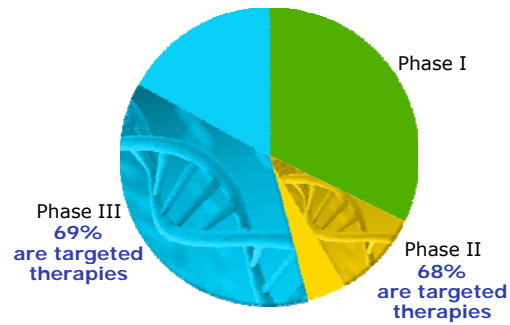
<sup>3</sup>Taking risk for profit, Industry seeks cancer drugs. *NY Times*. September 2, 2009.

<sup>4</sup>J Natl Cancer Institute 2009;101:1044-1048.

<sup>5</sup>Oral oncology drugs are a new frontier in specialty pharmacy, [www.aishhealth.com/drugcosts/specialty/SPN\\_Oncology.html](http://www.aishhealth.com/drugcosts/specialty/SPN_Oncology.html).

## Cancer biomarkers

### Drugs in the pipeline with potential biomarkers



**Targeted therapies predicted to show 30% CAGR**

Source: SG Cowen Equity Research.

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## BCR-ABL overview – CML

### What is it?

- A fusion protein created by a genetic translocation
- Responsible for the development of chronic myelogenous leukemia (CML)

### What is it used for?

- To identify patients who will respond to kinase inhibitors (imatinib, nilotinib, and dasatinib)
- To monitor treatment response

### How many people are affected?

- 21,749 people are living with CML
- 4,830 new cases of CML will be diagnosed in 2008

### What are the benefits of testing?

- Monitor disease at the molecular level
- Early identification of drug resistance

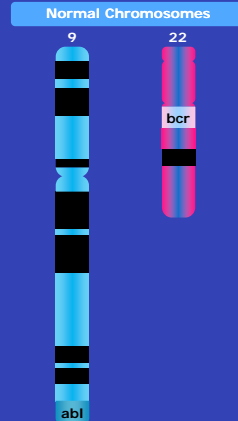
Source: SEER, National Cancer Institute, 2008.

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## What is BCR-ABL?

### Translocation of Chromosomes 9 and 22 form the BCR-ABL fusion protein

- Also known as the "Philadelphia Chromosome"



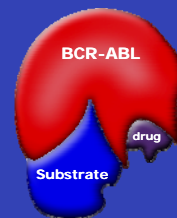
Source: [http://en.wikipedia.org/wiki/Philadelphia\\_chromosome](http://en.wikipedia.org/wiki/Philadelphia_chromosome).

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## Guidelines support BCR-ABL testing

National Comprehensive Cancer Network (NCCN) guidelines recommend patients on therapy have BCR-ABL transcript levels measured at least every 3 - 6 months.

If transcript levels begin rising, indicating treatment failure or poor adherence, retesting should be done within 1 - 3 months.



*Kinase inhibitors bind with the activated BCR-ABL protein to prevent tumor growth.*

Source: NCCN Clinical Practice Guidelines in Oncology - Chronic Myelogenous Leukemia, V.2.2010.

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What does the future hold?

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What does the future hold?

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What does the future hold?

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What does the future hold?

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What does the future hold?

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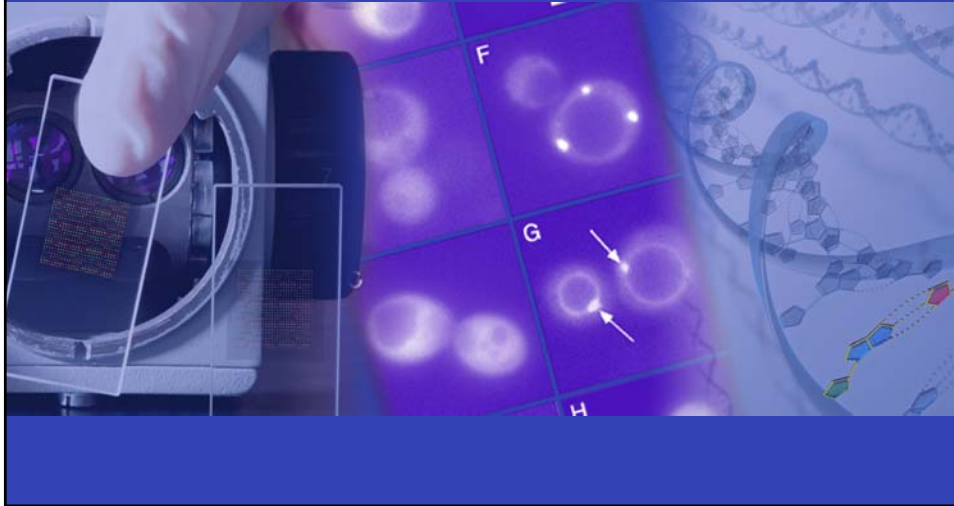
What does the future hold?

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## Example: Rheumatoid arthritis



## Immunologic conditions

- Broad therapeutic category encompassing:
  - Rheumatoid arthritis (RA)
  - Juvenile rheumatoid arthritis
  - Psoriatic arthritis
  - Plaque psoriasis
  - Crohn's disease
  - Ankylosing spondylitis
- In the United States, approximately 10 million people suffer from RA, Crohn's disease, and plaque psoriasis<sup>1</sup>
- Immunologic conditions rank as the top specialty therapeutic class<sup>2</sup>
  - 27.1% of total specialty drug spend in 2008
  - 30.2% of total specialty drug trend in 2008

**Sources:**

<sup>1</sup>DATAMONITOR, Commercial Insight: Autoimmune Overview, Publication Date: 12/2007.

<sup>2</sup>Medco Drug Trend Report, 2009.

## Top 10 Drug Categories (net cost PEPM)

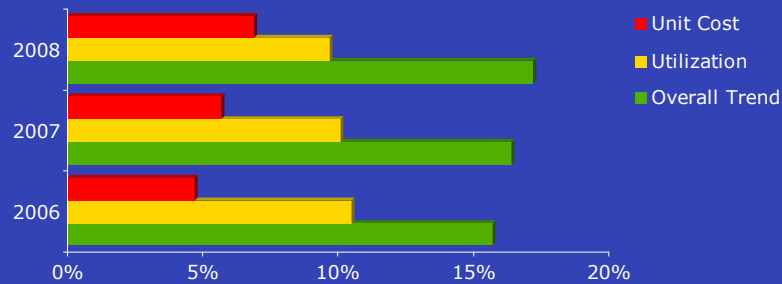
1. Lipid/Cholesterol Lowering Agents
2. Proton Pump Inhibitors
3. Miscellaneous Pulmonary Agents
4. Non-Insulin Hypoglycemic Agents
5. Anticonvulsants
6. Antidepressants
7. Immunologic Agents
8. Angiotensin II Receptor Blockers & Renin Inhibitors
9. Antipsychotics
10. Insulin Therapy

Source: Medco Drug Trend Report, 2009.

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## Spending on RA is increasing

### RA drug trend

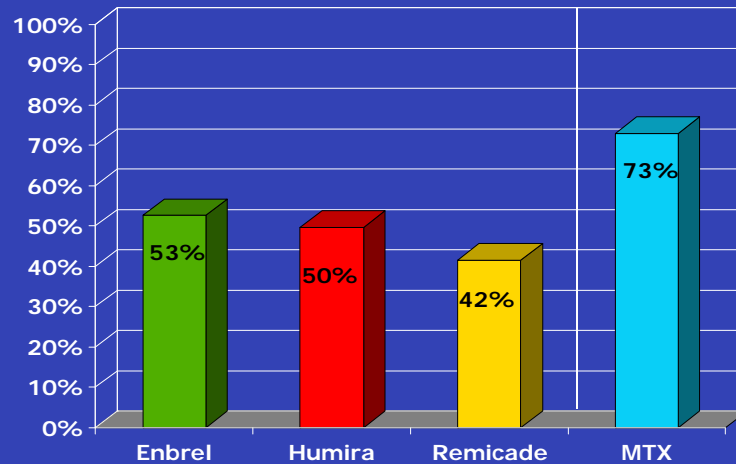


The annual cost of drug per member is between \$15,000–\$40,000\*\*\*

Sources: DATAMONITOR, Commercial Insight: Autoimmune Overview, Publication Date: 12/2007; Medco Drug Trend Report, 2009; AWP pricing.

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## Anti-TNF Blockers: Rheumatoid Arthritis



Source: 2008 IMS data

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## ACR Guideline recommendations

### Methotrexate

Recommended for all patients with all disease durations and all degrees of disease activity, irrespective of poor prognostic features

Can be combined with other DMARDs

- Hydroxychloroquine
- Leflunomide
- Sulfasalazine

### Anti-TNF Agents

#### Early RA

- Recommended if high disease activity
- Combine with MTX if high disease activity < 3 months with a poor prognosis

#### Intermediate or longer duration

- Recommended if response to MTX inadequate

#### Efficacious when used:

- Alone
- Combined with MTX
- In patients with inadequate non-MTX DMARD response

Source: Saag KG, et al. *Arthritis & Rheumatism*. 2008;59:762-784.

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## Opportunity: MTX

The clinical effect is mediated through intracellular accumulation of MTX<sup>1</sup>

- Biomarker has been identified for MTX dose monitoring

Early genetic research indicates gene-gene interactions may predict efficacy<sup>2</sup>

Gene-association studies have suggested that a 3-gene panel may be able to predict those more likely develop side effects<sup>3</sup>

- Neurologic
- Gastrointestinal

**Sources:**

<sup>1</sup>Hornung N, et al. *J Rheumatol*. 2008;35(9):1709-15.

<sup>2</sup>Dervieux T, et al. High-Order Epistatic Interactions Between Folate and Adenosine Biological Systems Affect Methotrexate Efficacy in Rheumatoid Arthritis. Abstract presentation at ACR Annual Conference, October 2009.

<sup>3</sup>Dervieux T, et al. Gene-Gene Interactions Among Folate, Purine and Pyrimidine Gene Pathways Impact Methotrexate Tolerability in Rheumatoid Arthritis. Abstract presentation at ACR Annual Conference, October 2009.

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## Opportunity: Anti-TNF blockers

A pilot study identified an 8-gene set that may predict response to TNF-blockers<sup>1</sup>

- Nearly 40% of patients do not respond to their initial TNF-blocker<sup>2</sup>
- If can select drugs based on genetic testing, could select the most appropriate initial therapy
  - Patient avoids months of ineffective therapy
  - Payor avoids cost of ineffective therapy

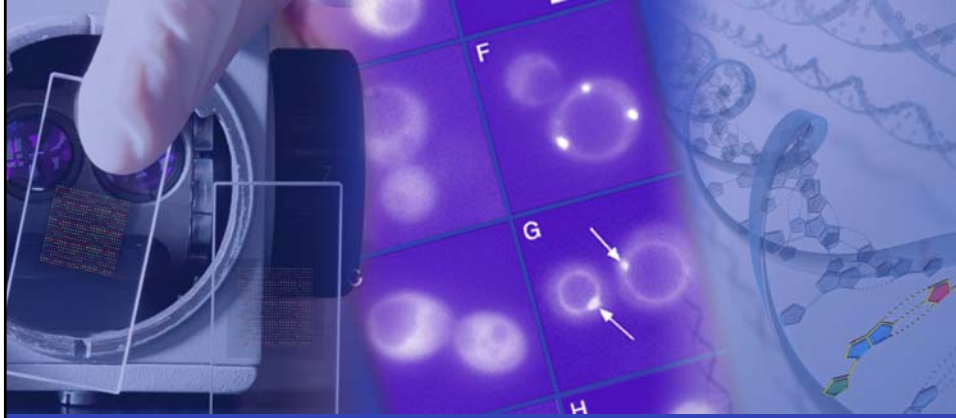
**Sources:**

<sup>1</sup>Battliwalla F, et al. Differential Peripheral Blood Gene Expression Profile of Rheumatoid Arthritis in Response to Anti-TNF Treatment. Abstract presentation at ACR Annual Conference, October 2007.

<sup>2</sup>Hyrich KL, et al. *Rheumatology*. 2008;47(7):1000-1005.

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## Summary



## Summary

- 1 Many specialty drugs could be developed with a PGx test
- 2 PGx testing programs can help select appropriate patients
- 3 Cancer therapy provides the biggest short-term opportunity
- 4 Rheumatoid arthritis therapies are potential PGx targets

# What you learned in a single slide

What can genetic testing for specialty medications provide?

In a word...

**Precision**

To improve...

**Efficacy and Clinical care**

**Pharmacogenomics will eventually become an integral component of a multidisciplinary approach to disease management, treatment, and monitoring**

FDA U.S. Food and Drug Administration  
 CENTER FOR DRUG EVALUATION AND RESEARCH  
[http://www.fda.gov/cder/genomics/genomic\\_biomarkers\\_table.htm](http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm)

Biomarker	Label Context	Test	Drug	Examples of other Drugs Associated with this Biomarker	Reference
<b>C-KIT expression</b>	Gastrointestinal stromal tumor <i>c-Kit</i> expression "In vitro, imatinib inhibits proliferation and induces apoptosis in gastrointestinal stromal tumor (GIST) cells, which express an activating mutation." "Gleevec is also indicated for the treatment of CD117 (KIT) positive unresectable or metastatic gastrointestinal stromal tumor."		Imatinib		12851888 16226710 16294026
<b>CCR5 -Chemokine C-C motif receptor</b>	CCR5 is a chemokine receptor that HIV uses to bind to and enter target cells for viral replication. "The efficacy of maraviroc in combination with other antiretroviral agents, is significantly reduced in HIV-1 strains resistant to multiple antiretroviral agents." "SELENTRY blocks a specific receptor called CCR5 that CCR5-tropic HIV-1 uses to enter CD4 or T-cells in your blood. Your doctor will do a blood test to see if you have been infected with CCR5-tropic HIV-1 before prescribing SELENTRY for you." "Pharmacogenomics: The impact of CCR5 promoter and coding sequence polymorphisms on the efficacy of maraviroc is being evaluated."	1	Maraviroc		17933726 17933725 17933724 17933723 17933722
<b>CYP2C19 Variants</b>	CYP2C19 Variants (Poor Metabolizers-PM and Extensive Metabolizers-EM) with genetic defect leads to change in drug exposure. "In vivo studies indicated that CYP2C19 is significantly involved in the metabolism of voriconazole. This enzyme exhibits genetic polymorphism. For example, 15-20% of Asian populations may be expected to be poor metabolizers. For Caucasians and Blacks, the prevalence of poor metabolizers is 3-5%. Studies conducted in Caucasian and Japanese healthy subjects have shown	3	Voriconazole	Omeprazole [m1] Pantoprazole [m2] Esomeprazole [m3] Dlanoprazole [m4] Nefopam [m5] Rabeprazole [m6]	12867215 11866669

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## Additional resources

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**PGx for cancer therapies:**

<http://caonline.amcancersoc.org/cgi/content/abstract/59/1/42>

**KRAS testing:**

[http://www.cpdgateway.com/ce-bin/owa/pkg\\_disclaimer\\_html.display?ip\\_mode=secure&ip\\_company\\_code=CPD&ip\\_test\\_id=14509&ip\\_cookie=32881979](http://www.cpdgateway.com/ce-bin/owa/pkg_disclaimer_html.display?ip_mode=secure&ip_company_code=CPD&ip_test_id=14509&ip_cookie=32881979)

**American College of Clinical Pharmacology:**

[www.accp1.org/~user/index\\_new.html](http://www.accp1.org/~user/index_new.html)