Blockbusters
Blockbuster business model

- Pharmaceutical industry is dominated by the blockbuster model, in which companies built their operations around a few products. For example (data for 2002):
  * AstraZeneca - 3 drugs - $7.7 bln.
  * Johnson & Johnson - 3 drugs - $4.9 bln.
* Lipitor (Atorvastatin, Pfizer) - $13.7 (2007) - mega blockbuster (more than $10 billion)
* Plavix (Clopidogrel, Sanofi-Aventis) - $8.1 (2007)
* Enbrel (Etanercept, Amgen) - $5.5 (2007)

- The blockbuster drug is defined as one with peak annual global sales exceeding $1 billion (market definition):

- From medical point of view blockbuster drug is:
  * single compound effective in most or all patients, who have particular condition
  * labeled for use by the general population
  * prescribed for a chronic condition (thus, providing long-term sale)
STATINS – inhibitors of HMG-CoA reductase – 3-hydroxy-3-methylglutarylcoenzyme A reductase

- converts HMG-CoA to mevalonate
- one of the enzyme in cholesterol synthesis pathway
Orphan diseases: Atryn
Pharmacogenetics – the study of how our genes influence the way in which we respond to the drug

1959 – term introduced by Friedrich Vogel,

Two main ways in which genes can alter the response to the drug:

1. **Variations in the drug target** - such as variant form of the receptor

2. **Variations in pharmacokinetics** – the processes of absorption, distribution, metabolism and excretion by which the drug enters into the body
Orphan medicines

- Medicines that are developed for the treatment of very uncommon diseases.

- The EU defines an orphan medicine as one that could treat a disease with a prevalence of less than 5 per 10,000 of the population (250,000 cases across the European Union).

- As the number of patients who would benefit is too small to be profitable for the pharmaceutical industry, regulatory incentives such as a period of market exclusivity and research grants, currently exist for orphan medicines in the EU, along with tax incentives developed by individual member states.

Neglected diseases

- Diseases that primarily affect the developing world.

1999: There have only been 13 new neglected disease drugs since 1975. Multinational companies had very little neglected disease activity.

2005: Four of the top 12 companies now have neglected disease R&D units employing over 200 scientists; three others work on a smaller scale. This activity is driven by ‘non-commercial’ motives and is conducted under a new ‘no profit-no loss’ model that provides drugs to developing country patients at cost price.
Pharmacogenetics was born during the period of intense interest in clinical genetics in the 1950s, after three discoveries:

* It was found that individuals who received the drug isoniazid for the treatment of tuberculosis could be clearly divided into slow and rapid metabolisers of the drug, and that this rate was genetically determined.

* Patients who had prolonged effects of the anaesthetic agent succinylcholine (suxomethonium), had an atypical enzyme, in this case a cholinesterase that was inherited. Several alleles of the butyryl cholinesterase (BCHE)

* Studies of the red blood cells of African-American soldiers who had developed severe anaemia after taking the anti-malarial drug primaquine were found to be deficient in the enzyme glucose-6-phosphate dehydrogenase. This inherited error of metabolism was later found to affect 200-400 million people worldwide.
Glucose-6-phosphate dehydrogenase (G6PD) is a key enzyme in the pathway which generates reducing power in the form of NADPH, maintaining an adequate level of reduced glutathione (GSH).

- G6PD is present in all cells but is particularly important to red blood cells, where it protects the -SH groups of hemoglobin and the cell membrane from oxidation by the reactive oxygen species. Defects in this pathway due to defective G6PD can lead to inadequate protection against oxidation, resulting in oxidation of sulfhydryl groups, precipitation of hemoglobin, and hemolysis.

- Multiple hemolysis episodes in a short time span lead to a condition known as hemolytic anemia (jaundice, dark urine, abdominal and back pain, lowered red blood cell count, and elevated bilirubin).

- Primaquine induces strong oxidative stress.

- The gene for G6PD is located on the X-chromosome.
Enormous number of different polymorphisms

Four kind of deficiencies:
1. Type 1 - chronic hemolyric anemia, even in the absence of precipitating drugs or infection
2. Type 2 - less than 10% normal enzyme activity - hemolytic reactions to various drugs and/or infections
3. Type 3 - 10-60% of normal enzyme activity - less severe hemolytic reactions
4. Type 4 - more than 60% of normal activity, no apparent clinical problem

Complete absence of G6PD - lethal

Mutations in G6PD gene - more than 100 mutations or combined mutations associated with more than 200 variants

Over 400 million people in the world have G6PD deficiency

Some variants confer protection against malaria
N-acetyl transferase polymorphism: slow and fast acetylators

Isoniazid – an anti-tubercular drug
Hydralazine – a vasodilator
Procainamide – an anti-arrythmic

1. Slow acetylators - high plasma concentrations of isoniazid and the other drugs are achieved =- those individuals are at a much greater risk of an adverse reaction to these drugs; have also increase susceptibility to some diseases, such as bladder cancer

2. Rapid acetylators – only low plasma acetylators are achieved - therapeutic effectiveness of these drug is reduced

A number of allelic variants have been identified
Gene-based medication

Individuals vary in their reaction to anti-leukemia drugs.

- Fast metabolism:
  - No mutation
  - Normal dose

- Slow metabolism:
  - Mutation in the gene coding for the enzyme TPMT
  - Reduced dose

- Weak metabolism:
  - Drug can be lethal
  - Dose (one single tablet) for an extremely slow metabolism (TPMT deficiency)

After a blood test, patients are given the dose that suits their genetic profile.
Molecular diagnostic-based therapies

Proportion of Drugs Metabolized by P450 Enzymes

- CYP2D6: 19%
- CYP1A/2: 11%
- CYP2C19: 8%
- CYP2C8/9: 16%
- CYP2B6: 3%
- CYP2E1: 4%
- CYP2A6: 3%
- CYP3A4/5: 36%

25% of prescribed drugs

- **Codeine**, a commonly used analgesic, must be converted from an inactive form to the active form (morphine) by the CYP2D6 enzyme for a therapeutic effect to occur.

* Patients with a polymorphism leading to increased production of CYP2D6 are ultra-rapid metabolizers of codeine and are more likely to develop adverse effects and toxicity when taking a standard dose of codeine, including impaired breathing and sedation.

- Patients with decreased CYP2D6 production are poor metabolisers and will show little or no conversion of codeine to morphine; they will not experience any pain relief, but will become nauseated due to the higher amounts of codeine in their body.

- Frequency of CYP2D6 alleles varies in different ethnic groups:
  * 7% of Caucasians may have a defective CYP2D6 gene, resulting in reduced pain relief due to poor metabolism of the drug.
Genotyping tests:

* **AmpliChip CYP450 Genotyping Test** (Roche and Affymetrix’s), the first DNA microarray test approved by the FDA (2004), is a blood test that allows to select medications and doses of medications for a wide variety of common conditions such as cardiac disease, psychiatric disease, and cancer.

* It analyzes **cytochrome P450 Cyp2D6**, which are active in the liver to break down certain drugs. Variations in this gene can cause a patient to metabolize certain drugs more quickly or more slowly than average, or, in some cases, not at all.

* Cytochrome P450 CYP2D6, plays an important role in metabolism of some commonly prescribed antidepressants, anti-psychotics, beta-blockers, and some chemotherapy drugs.
# Population Differences for CYP2D6

<table>
<thead>
<tr>
<th>Allele</th>
<th>Predicted Enzymatic Activity</th>
<th>Japan</th>
<th>China</th>
<th>Caucasian EU</th>
<th>Caucasian US</th>
<th>Black American</th>
<th>Black African</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1</td>
<td>Normal</td>
<td>42-43%</td>
<td>23%</td>
<td>33-37%</td>
<td>37-40%</td>
<td>29-34%</td>
<td>28-56%</td>
</tr>
<tr>
<td>*2</td>
<td>Normal</td>
<td>9-13%</td>
<td>20%</td>
<td>22-33%</td>
<td>26-34%</td>
<td>20-27%</td>
<td>11-45%</td>
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<tr>
<td>*4</td>
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<td>12-23%</td>
<td>18-23%</td>
<td>7-9%</td>
<td>1-7%</td>
</tr>
<tr>
<td>*5</td>
<td>None</td>
<td>5-6%</td>
<td>6%</td>
<td>2-7%</td>
<td>2-4%</td>
<td>6-7%</td>
<td>1-6%</td>
</tr>
<tr>
<td>*10</td>
<td>Reduced</td>
<td>39-41%</td>
<td>50-70%</td>
<td>1-2%</td>
<td>4-8%</td>
<td>3-8%</td>
<td>3-9%</td>
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<tr>
<td>*17</td>
<td>Reduced</td>
<td>*</td>
<td>*</td>
<td>&lt;1%</td>
<td>*</td>
<td>*</td>
<td>15-26%</td>
</tr>
<tr>
<td>*41</td>
<td>Reduced</td>
<td>*</td>
<td>*</td>
<td>20%</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

Percentages represent ranges of allelic frequencies reported in published studies.

- **Warfarin** (inhibitor of vitamin K regeneration) was first synthesized in 1948 in as part of a program to develop more potent rodenticides.

- Warfarin is a routinely used oral anticoagulant (750,000 patients in the UK, increase by 10% yearly), given to prevent blood clot formation in people who have coronary artery disease, or venous thrombosis, particularly after surgery and periods of immobility.

- Warfarin is metabolized in the liver by a CYP2C9, but a variant *CYP2C9* gene alters the rate of its metabolism.

- People with the "slower" variant of gene break the drug down more slowly than usual, so require lower doses to achieve the same anticoagulant effect (1-5 mg a week instead of 5 mg a day). High doses of anticoagulant can lead to potentially dangerous bleeding (side effect rate: 8-26% in the patients treated for one year).

- This variant genes occur at a higher frequency in Caucasians than Afro-Caribbeans or Asians.
Vitamin K in its reduced form (vitamin K1 dihydroquinone, KH2) is the essential cofactor for post translational activation of the vitamin K dependent clotting factors, the procoagulants – factors II, VII, IX, X, and the anticoagulant proteins C and S.

In the reaction, glutamic acid is converted to γ-carboxy-glutamic acid by γ-glutamyl-carboxylase, and vitamin K1 is converted to vitamin K epoxide which is rapidly reduced back to vitamin K quinone by the Vitamin K Epoxide Reductase Complex 1 (VKORC1) and then to vitamin K hydroquinone (KH2).

VKORC1 is the molecular target inhibited by warfarin, which exerts its anticoagulant activity by interrupting the regeneration of KH2, the active (reduced) form of vitamin K, leading to decreased carboxylation of the vitamin K dependent clotting factors with loss of activity.
Mutations in the VKORC1 gene can lead to coding a protein that is either sensitive or resistant to warfarin inhibition.

VKORC1 - vitamin K epoxide reductase complex 1

Warfarin
Modulation of warfarin effect

1. Metabolism - CYP2C9 polymorphism

2. Target – VKORC1 – a functional variant in a promoter region

3. Vitamin K availability:
   a) diet - change in diet can affect the level of vit K
   b) synthesis by gut bacteria - antibiotics can affect

4. Plasma protein-binding - competition with aspirin, which bins to the same protein

5. Age - elderly people are more sensitive

6. Diseases – eg. fever increases the effect of warfarin & thus the risk of excessive bleeding;
   hyperthyroidism - decreases the effect of warfarin and increases the risk of thrombosis

7. Compliance – how the patients are taking the drugs…
Warfarin

bleeding after warfarin

No. of patients

Warfarin dose (mg/day)

0 2 4 6 8 10 12 14 16

Rettie and Tai 2006
Personalized medicine - warfarin

- In 2007 the FDA changed the labelling of the drug to recommend the use of genetic testing in clinical practice to adjust the dosing according to genotype.

- The recent discovered polymorphism of the warfarin target gene, VKORC1 (vitamin K epoxide reductase complex 1) indicates the likely complexity of studies needed to obtain such data.

- Although a gene test would be useful in determining drug dose, many other factors can have an effect on the response to different drugs, but probably the most important are:
  * Environmental influences such as diet, alcohol consumption and cigarette smoking.
  * Diseases, especially liver and kidney disorders, which affect the metabolism of drugs.
  * Interactions with other drugs, which can influence rates of drug metabolism.

„Personalized, predictive medicine offers great promise, but we need to carefully examine benefits and understand the cost-effectiveness of such strategies before we spend a lot of money for very expensive tests”

Eckman et al. Pharmacogenomics 2009.
- Physicians routinely start patients on low doses of warfarin, monitor their blood clotting, and increase the dose gradually until the appropriate level is reached. A 20- to 30-fold variation is commonly seen in the response to drugs.

- Possibly, pharmacogenetic testing for CYP2C9 alleles may identify people at risk of warfarin-associated bleeding. Potentially such tests are close to clinical application although rigorous data showing clinical use and cost effectiveness are not yet available. The recent discovery of the warfarin target gene, VKORC1 indicates the likely complexity of studies needed to obtain such data.
Clopidogrel

• an oral, thienopyridine class of antiplatelet agents, used to inhibit blood clots in coronary artery disease, peripheral vascular disease and cerebrovascular disease.

• It is marketed by Bristol-Myers Squibb and Sanofi under the trade name Plavix.

• The drug works by irreversibly inhibiting a receptor called P2Y12, an adenosine diphosphate (ADP) chemoreceptor on platelet cell membranes. The blockade of this receptor inhibits platelet aggregation by blocking activation of the glycoprotein IIb/III pathway. The IIb/IIIa complex functions as a receptor mainly for fibrinogen and vitronectin but also for fibronectin and von Willebrand factor. Activation of this receptor complex is the "final common pathway" for platelet aggregation and is important in the cross-linking of platelets by fibrin.
Clopidogrel

- there is a wide interindividual variability in response

- clopidogrel is a prodrug – highly dependent on cytochrome P4502C19 for activation
  - normally functioning allele is *1
  - *2 – loss of function allele – homozygotes for this allele represent 2-3% of whites & black population but up to 15-20% of East Asian
    - heterozygotes: 30-35% & 40-45, respectively

- About 30% of individuals carrying a variant of CYP2C19 gene are unable to generate active form

- alternative, more costly anti-P2Y12 drug does not require activation

Adverse effects include hemorrhage, severe neutropenia, and thrombotic thrombocytopenic purpura (TTP).
Plavix is marketed worldwide in nearly 110 countries, with sales of US$6.6 billion in 2009. It had been the 2nd top selling drug in the world for a few years as of 2007 and was still growing by over 20% in 2007. U.S. sales were US$ billion in 2008.

In 2006, generic clopidogrel was briefly marketed by Apotex, a Canadian generic pharmaceutical company, before a court order halted further production until resolution of a patent infringement case brought by Bristol-Meyers Squibb. The court ruled that Bristol-Myers Squibb's patent was valid and provided protection until November 2011. More recently, the FDA extended the patent protection of clopidogrel by six months, giving exclusivity that would expire on May 17, 2012.

Generic clopidogrel is also produced by several pharmaceutical companies in India and elsewhere, and often sold under its INN (International nonproprietary name) clopidogrel.
Ethnic- and gender-based medicine

- Some drugs, including common blood-pressure medicines and antidepressants, exhibit significant ethnically correlated safety and efficacy differences.

* BiDil - first drug for use in a specific ethnic group, approved by FDA in 2005. BiDil, a life-saving medication for heart failure in had failed to beat placebo in a broad population but showed promise in African Americans.
Nitric oxide generation

Isosorbide dinitrate
Stimulation
L-Arginine

Physiologic pathway
Formation of cyclic guanosine monophosphate
S-nitrosylation: post-translational modification of effector molecules

Oxidase
Hydralazine
Inhibition

Pathologic pathway
Peroxynitrite (ONOO−)
DNA damage
Cell damage
Oxidized proteins

NO
O2−

Citrulline

Inhibition

Ethnic- and gender-based medicine

Non-African Americans

African Americans

Risk Ratio = 0.53
P = 0.04

Survival by 47%
Ethnic- and gender-based medicine

* **Interferon** - appears to be less effective in blacks with hepatitis than white patients (19 percent vs. 52 percent response rate).

* **Cozaar** (Losartan) - one of the most common blood pressure drugs has a reduced effect in black patients.

* **Iressa** - it seems that Japanese cancer patients are three times more likely to respond to Iressa, apparently because of a mutation in a gene for the drug’s target, epidermal growth factor receptor.

* **Aspirin** - prevents heart infarction rather in men but not in women.

---

**Aspirin**

<table>
<thead>
<tr>
<th></th>
<th>Men - MI</th>
<th>Women - MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>P&lt;0.001</td>
<td>P=0.98</td>
</tr>
<tr>
<td>Placebo</td>
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<td></td>
</tr>
</tbody>
</table>

*after Berger et al. JAMA 2006*
BiDiL – critics

The short life of a race drug - *Lancet, commentary, 14th January 2012*

Let us suppose reliable evidence indicates that a drug is particularly effective for treating a medical condition among patients with $MC1R$ recessive genes on chromosome 16. The alleles of these recessive genes are known for producing red hair.

Perhaps initially persuasive, the analogy between a “redhead drug” and a “race drug” breaks down. First, there are specific genes associated with red hair so there is a clearly identifiable genetic marker that can be used to develop a mechanistic model for why the drug works for this population group. In the case of BiDiL, no genetic markers were used to obtain a population sample in the clinical trial. Second, there are no racial genes, no clear genomic divide between any of society’s socially constructed racial categories, and no stable cluster of medically relevant genes that is necessarily linked with ancestry or skin colour. BiDiL’s success with self-identified black people could have been a statistical accident or there could be, as yet, some unknown factor that accounted for it.

The idea behind BiDiL has not been disputed—namely, that for some people with congestive heart failure who do not produce enough nitric oxide, vasodilators can be an effective adjunct therapy in reducing heart attacks. But who can benefit? Neither socially constructed nor self-identified concepts of “race” can serve as a proxy for an unknown or ill-defined biological marker that provides a causal connection to or strong association with a drug’s effectiveness. Personalised medicine requires nothing less. If a drug works it is because of the genetics and physiology of the patient. Nothing I have
Decrease in mortality from cardiovascular diseases

Figure 1. Decline in Deaths from Cardiovascular Disease in Relation to Scientific Advances.

E. Nabel & E. Braunwald, NEJM, 2012
Hematopoietic stem cells

- Myeloid Stem Cell
  - Myeloblast
  - N. Promyelocyte
  - N. Myelocyte
  - Immature Monocyte
  - N. Metamyelocyte
  - N. Band
  - Megakaryocyte
  - Platelets

- Lymphoid Stem Cell
  - Pronormoblast
  - Basophilic Normoblast
  - Polychromatric Normoblast
  - Orthochromatric Normoblast
  - Polychromatric Erythrocyte
  - Erythrocyte
  - Lymphocyte
Chronic myeloid leukemia (CML)
sustains about 3% of cancers in humans (15-20% all leukemias in adults),
approximately 1-2 cases per 100 000 people

- average age of diagnosed patients: 53 years (30% patients is older than
  60 years, less than 10% under 20 years of age)

- in about half of patients the disease is asymptomatic and is detected
during routine blood control

- untreated is fatal
Chronic myeloid leukemia

First cancer for which the genetical mutation causing the disease has been identified (1960, Philadelphia)

- Mutated chromosome Philadelphia forms after translocation fragment of long arm of chromosome 9 (coding for Abl kinase) to long arm of chromosome 22 (coding for Bcr protein) (9 → 22)

- This mutation is present in 95% patients with CML; it can also be found in patients with other leukemias (e.g. in 15-30% cases of acute lymphoid leukemia)

- Translocation leads to formation of hybrid gene Bcr/Abl and fusion protein of constitutive, unregulated kinase activity
Chronic myeloid leukemia

Translocation
BCR-Abl
Chronic myeloid leukemia

In a vast majority of patients Philadelphia chromosome can be detected using the standard cytogenetic methods.

- other good tools are FISH or RT-PCR
Gleevec® Targets the Cause of CML

- Gleevec—a specific inhibitor of a small family of tyrosine kinases, including Bcr-Abl, Kit, and PDGF receptor
Chronic myeloid leukemia

- 2-phenylaminopyrimidine derivative
- first commercially available inhibitor of tyrosine kinase accepted for a clinical use
- specifically inhibits kinases Bcr-Abl, c-Kit (CD117) and PDGF-R
- this way it inhibits proliferation and increases apoptosis of cells expressing those kinases
- causes relatively mild side-effect
Acute promyelocytic leukaemia can affect adults of all ages.

It represents 10% of all acute myelocytic leukaemias in adults (~3,000 cases yearly in USA - M3 type).

It is a rapidly progressing type of leukaemia that affects promyelocyte, which continue to divide, but do not mature.

These immature dividing cells fill up the bone marrow and prevent it from making blood cells properly.

As the leukaemia cells do not mature, they cannot do the work of normal white cells, leading to an increased risk of infection and haemorrhages. And as the bone marrow cannot make the right numbers and quality of red blood cells and platelets, symptoms such as anaemia and bruises also occur.
Acute promielocytic leukemia

- In 99% of patients there is an exchange of fragment of chromosome 15 and 17, which is a marker of this disease. Chronologically there was a second example (after Philadelphia chromosome) of understanding the genetical background of cancerogenesis.

- Translocation involves RAR\(\alpha\) on chromosome 17 and PML (promyelocytic leukemia gene) on chromosome 15 creating a chimeric protein PML-RAR.

- Therapeutical benefits:
  - in 1960s time from diagnosis APL to death of patients ranged from 1 to 2 weeks, depending on the quality of care (!).
  - currently ~80% of cases are fully curable.
Acute promielocytic leukemia

PML locus
RARα locus

chromosome 15
chromosome 17

PML/RARα fusion gene
RARα/PML fusion gene

chromosome 15/17
chromosome 17/15

Acute promielocytic leukemia
- Normal protein PML is present in nucleus (Kremer bodies, 10-30/nucleus), where colocalized with SUMO-1, Sp-100, Sp140, CBP, DAXX, RB and p53 proteins.

- PML-RARα interacts with PML, leading to destabilization of Kremer bodies. Proteins normally included into the bodies are located in different places of nucleus. Thus, PML cannot function normally.

- PML is crucial for maintaining the correct structure of Kremer bodies, so PML-RARα acting through PML disturbs activity of all proteins located in the Kremer bodies.
Dual leukemic function of PML-RARα

- **PML**
  - Control of genome stability
  - Proapoptotic factor
  - Cell cycle regulatory factor

- **RARα**

- **RXRa**

- **RARα**

- **Dr5**

- **Differentiation**

  - **Acute Promielocytic Leukemia (APL)**

- **Growth survival advantage**
Trastuzumab (Herceptin)

Extracellular effects of trastuzumab
- Inhibition of cleavage of HER2 extracellular domain
- Interference with homodimer and heterodimer formation between HER-family receptors
- Antibody-dependent immune mechanisms

Intracellular effects of trastuzumab
- Induction of apoptosis
- Decreased cell proliferation
- HER2 downregulation, dephosphorylation, or both
- Decreased VEGF production
- Potentiation of chemotherapy
- Modulation of downstream signal paths
- Altered cross-talk with other signal paths

Amplified number of HER2 genes on chromosome 17
- Antibody-based drug invented by Genentech:
  * IND - 1991
  * Phase III completed - 1997.

- **Herceptin** is used in the treatment of metastatic breast cancer. Administered either in combination with chemotherapy or alone may significantly reduce tumor size, increase median time to disease progression, and increase one-year survival rates. (Results of III phase clinical trial: median survival rate **25.1 months** for herceptin and chemotherapy over **20.3 months** for chemotherapy only)

- Herceptin is used for a sub-group of breast cancer patients who have a genetic mutation resulting in overexpression of HER2. Herceptin blocks the receptor and selectively kills cancer cells that overexpress HER2. Around 25-30% of breast tumors have high levels of HER2 and these may respond to treatment with Herceptin.

- Her2 positive patients have:
  * more aggressive disease
  * faster progression of disease
  * poorer prognosis - shorter (by half) live-expectance
- Herceptin can only be prescribed in conjunction with the relevant genetic test to ensure the optimum outcome for the patient. HercepTest was the first combination of drug product and diagnostic test approved by FDA (in 1998).

- The frequently used testing methods to determine HER2 status are immunohistochemistry (IHC) and fluorescence in-situ hybridization (FISH). Both methods are reliable, robust and highly specific when performed using standardized and validated testing protocols, and both are globally accepted as the established standard for HER2 testing.

- Patients with either a positive IHC or FISH test result should respond well to Herceptin.

- The FISH test uses fluorescent probes to the HER2 genes in a tumor cell, to see the number of gene copies. If a FISH test detects more than two copies of the HER2 gene, it means that the cell is HER2-positive.
- The IHC test is used to measure HER2 receptor overexpression in the tumor sample.

- Results of the test are graded from 0 to 3+.

- Herceptin is only prescribed if the result is 3+, when the cancer is considered HER2-positive.
IRESSA (gefitinib) - medication that targets and blocks the activity of the EGFR-TK, an enzyme that regulates intracellular signalling pathways implicated in cancer cell proliferation and survival.

Tumours with an EGFR mutation are particularly sensitive to IRESSA. A mutation in the EGFR is a characteristic occurring in about 10-15% of non-small cell lung cancers (NSCLC) in Europe and around 30-40% in Asia.¹,²,³

EGFR mutations are more common in:

- never-smokers
- patients with adenocarcinoma histology
- females
- Asian patients
IRESSA (gefitinib)

EGFR Pathway and EGFR Mutation

- Ligand
- EGFR
- EGFR-TK
- EGFR-TKI
- Mutation

- Proliferation
- Inhibition of Apoptosis
- Invasion
- Metastasis
- Angiogenesis

from Astra Zeneca web site
Iressa: inhibitor of HER2
Ono and Kuwano, Clin Cancer Res 2006

A, B: comparison of the inhibitory effects of gefitinib on activation of EGFR, Akt, and ERK1/2 between gefitinib-sensitive NSCLC lines (PC9 and H3255) and gefitinib-resistant NSCLC lines (QG56 and H1781): PC9m and H3255m harbor EGFR mutations del E746-A750 and L858R, respectively, whereas QG56WT and H1781WT carryWT EGFR.

C: In gefitinib-sensitive cell lines, only EGFR-driven signaling dominates following Akt and ERK1/2 activation for survival and growth. In gefitinib-resistant lines, EGFR is not a survival factor and other receptors or signals could dominate.
Personalized medicine - Iressa (gefitinib)

10 studies, 2568 resected NSCLC

9.5 v. 5.1 months
5.6 v. 5.1 months
Pharmacogenomics is the study of the role of inherited and acquired genetic variation in drug response.

Evolution from pharmacogenetics, which focused on individual candidate genes, to pharmacogenomics – drug response viewed through genomewide association studies (GAS).

Less than half of the patients who are prescribed extremely expensive drugs benefit from them. More than 90% of all pharmaceutical products are effective in only 30-50% of patients – A. Roses

<table>
<thead>
<tr>
<th>Condition</th>
<th>Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s disease</td>
<td>30%</td>
</tr>
<tr>
<td>Analgesics</td>
<td>80%</td>
</tr>
<tr>
<td>Asthma</td>
<td>60%</td>
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<tr>
<td>Cardiac arythmia</td>
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<td>Diabetes</td>
<td>57%</td>
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<tr>
<td>Hepatitis C</td>
<td>47%</td>
</tr>
<tr>
<td>Incontinence</td>
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<tr>
<td>Acute migraine</td>
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<tr>
<td>Oncology</td>
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<tr>
<td>Arthritis</td>
<td>50%</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>60%</td>
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</table>
Some of the factors that may influence the way in which an individual responds to a drug.
Currently, genetic testing is available for approximately 2000 clinical conditions, and the number of available diagnostic tests is increasing exponentially.

Are they all valid?