UNMET MEDICAL NEEDS

For many common diseases (cancer, diabetes, dementia, multiple sclerosis, emphysema, etc.) there are only partially effective and no curing therapies.

Even with well established drug therapies, there are many patients that do not respond.

All drug therapies lead to unwanted or adverse effects in some patients.
UNMET MEDICAL NEEDS

*Why do we have no effective treatments for these diseases?*

*Why is drug response so variable?*

*How can we improve?*

---

THE PROBLEMS WITH THERAPY

- A *dearth of new drugs*
- *Existing treatments inadequate* (90% of drugs work in only 30 to 60% of patients, 300 billion $/year spent on ineffective treatments)
- *Too many drugs recalled because of ADRs*
- *Too many drugs fail in late stages of development*
- *Enormous complexity of disease mechanisms*

The present R & D model needs rethinking
Identify responders to drug therapy
Identify patients at risk for ADRs*

VARIABLES AFFECTING DISEASE RISK AND DRUG RESPONSE

**Clinical factors**
- Age
- Gender
- Family history
- BMI
- Diseases
- Circadian rhythms
- Placebo effect
- Compliance

**Personal omics**
- Genome
- Transcriptome
- Proteome
- Metabolome
- Epigenome

**Environment**
- Ethnic background
- Nutrition
- Drugs (DDIs)
- Chemical exposure
- Lifestyle
- Life events
- Microbiome

Personal genome + Clinical parameters + Environment = Phenotype
THE STRATEGY

New & more efficient approaches to go from scientific innovation to clinical utility

• **Personalized Medicine (treat the individual)**
• **Genomic Medicine (use genome information)**
• **Precision Medicine (new taxonomy)**
• **Stratified Medicine (groups with shared findings)**
• **Translational Medicine (bench to bedside)**

Tools: Biomarkers – Molecular Diagnostics

PERSONALIZED MEDICINE

A strategy to predict and improve clinical outcomes

*Not a new paradigm*

*Doctors have practiced PM since time immemorial*

*Nobody is practicing «impersonal medicine» by purpose*

**BUT**

*Technological breakthroughs with explosion of data on:*
  • human genetic diversity
  • molecular/environmental/behavioural causes of disease
PERSONALIZED MEDICINE
A strategy to predict and improve clinical outcomes

• Prediction of individual disease risk
  family history, early assessment, prevention

• Precise diagnosis
  subphenotypes of disease, biomarkers for prognosis & choice of therapy

• Individualized therapy
  including pharmacogenomics, biomarkers for efficacy and safety, prediction of individual dose

• Evaluation of personal clinical outcome


The emerging treatment profile of non-small-cell lung cancer NSCLC

Modified, from William Pao & Katherine E Hutchinson
1. More precise diagnosis

2. Treatment more effective, less adverse events

3. Force changes in regulatory and reimbursement rules

The Promise

“Science is about making predictions“
Questions

• What determines the individual risk of a certain disease?

• What determines the individual course of the disease?

• What determines the individual response to (drug) treatment?

THE STRATEGY

New & more efficient approaches to go from scientific innovation to clinical utility

• Personalized Medicine (treat the individual)
• Genomic Medicine (use genome information)
• Precision Medicine (new taxonomy)
• Stratified Medicine (groups with shared findings)
• Translational Medicine (bench to bedside)

Tools: Biomarkers – Molecular Diagnostics
The Human Genome
Recent developments to explain diversity in disease risk and drug response


The Blueprint

Next steps:

NGS, sequencing faster, cheaper, deeper, more
Genome-wide association studies with SNPs (GWAS)
Encode (how cells interpret the genome information)
Parallel development of other «omics» technologies

NGS: next generation sequencing; SNPs, single nucleotide polymorphisms; GWAS: genome-wide association studies
Whole genome sequencing: Simpler, faster, cheaper, more

Pocket Money Sequencing

While Roche and Applied Biosystems launch price cutting sequencing systems, former 454 protagonist Jonathan Rothberg is announcing his own solution.

NGS: next generation:
- Illumina/Solexa
- Roche/454 Life Sciences
- Life Technologies/SOLiD

The Sequencing Explosion

Cost of sequencing vs. time

<table>
<thead>
<tr>
<th>Year</th>
<th>Human Genomes Sequenced</th>
<th>Cost of sequencing</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>1</td>
<td>$3 billion</td>
</tr>
<tr>
<td>2008</td>
<td>10</td>
<td>$2 million</td>
</tr>
<tr>
<td>2009</td>
<td>100</td>
<td>$1 million</td>
</tr>
</tbody>
</table>
| 2010 | 1,000 | $100,000 | (Moore’s Law)

<table>
<thead>
<tr>
<th>Cost of computing (Moore’s Law)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
</tr>
<tr>
<td>2010</td>
</tr>
</tbody>
</table>

Genomes by the Thousands

ARTICLE

An integrated map of genetic variation from 1,092 human genomes


- Genome sequence information of
- > 1000 individuals from 14 populations
- Haplotype map of 38 million SNPs
- 1.4 million short insertions & deletions
- > 14,000 large deletions

www.1000genomes.org

Genomes by the Millions

Beijing Genomics Institute in Shenzhen (Guandong)
Largest sequencing facility in the world
>4000 scientists & technicians

3-Million Genomes Project launched November 2011:
• Million Human Genomes Project
• Million Plant & Animal Genomes Project
• Million Microecosystem Genomes Project

www.genomics.cn

INTERINDIVIDUAL VARIABILITY OF THE HUMAN GENOME SEQUENCE

We are all „mutants“, there is no „normal“ genome sequence. Each individual, on average, has:

~ 3.6 million basepairs difference (SNPs), 24,000 SNPs in coding regions
~10'000 SNPs are nonsynonymous
~350,000 small indels (insertions, deletions)
~700 large deletions
~ 400'000 to 600'000 new or private SNPs in each individual genome
~ 1000 copy number variants (CNVs) exceeding 500bp & other structural changes
~ 100 loss of function (LoF) variants of «disease» genes

Total sequence variation ~ 1-2 % or ~ 30-60 million basepairs
INTERINDIVIDUAL VARIABILITY OF THE HUMAN GENOME SEQUENCE

GENOMIC MEDICINE
Recent developments to explain diversity in disease risk and drug response

Next steps:

NGS, sequencing faster, cheaper, deeper, more

*Genome-wide association studies with SNPs (GWAS)*

*Encode (how cells interpret the genome information)*

*Parallel development of other «omics» technologies*

**NGS**: next generation sequencing; **SNPs**: single nucleotide polymorphisms; **GWAS**: genome-wide association studies
Genome-wide association studies (GWAS) and Manhattan plots
Arrays and beads with 500'000 to 5 million SNPs

Affymetrix/Illumina

Manhattan plot

www.genome.gov/GWAStudies

Published Genome-Wide Associations through 07/2012
1536 published GWA at p ≤ 5X10⁻⁸ for 18 trait categories

SIMPLE MINDS – COMPLEX TRAITS
MISSING HERITABILITY

Modest effect sizes of associations small (ORs of 1.1 to 1.5). Genetic variants, even in combination, explain only a small fraction of known genetic variation or inheritability.

Table 1 | GWAS for common diseases and traits

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Number of GWAS loci</th>
<th>Proportion of heritability explained (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 diabetes</td>
<td>41</td>
<td>~60</td>
</tr>
<tr>
<td>Fetal haemoglobin levels</td>
<td>3</td>
<td>~50</td>
</tr>
<tr>
<td>Macular degeneration</td>
<td>3</td>
<td>~50</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>39</td>
<td>20–25</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>71</td>
<td>20–25</td>
</tr>
<tr>
<td>LDL and HDL levels</td>
<td>95</td>
<td>20–25</td>
</tr>
<tr>
<td>Height</td>
<td>180</td>
<td>~12</td>
</tr>
</tbody>
</table>

HDL: high-density lipoprotein; LDL: low-density lipoprotein.

At present, the primary value of most GWAS is not the prediction of individual disease risk, but the discovery of novel biological mechanisms explaining the pathophysiology of disease and thereby provide new strategies of treatment.

Examples: glaucoma, macular degeneration, Crohn’s, Alzheimer, Memory.

Genome-wide associations studies (GWAS) associate gene variants with drug response:

- **CYP2C19** & antiplatelet effect & efficacy of clopidogrel
- **CYP2C9, CYP4F2, VKORC1** & warfarin dose
- **CYP2C9, CYP4F2, VKORC1** & acenocoumarol dose
- **IL28B** & response of HCV infection to peginterferon-α
- **SLCO1B1** & clearance & GI toxicity of methotrexate in childhood ALL

18 GWAS with significant association, 7 GWAS with no association.
GWAS and serious ADRs

Using Genome-Wide Association Studies to Identify Genes Important in Serious Adverse Drug Reactions

Annu K. Daly
Institute of Clinical Medicine, Neurosciences, Neurogenetics, Type II Diabetes, United Kingdom; e-mail: ak.daly@ucl.ac.uk

<table>
<thead>
<tr>
<th>Type of toxicity</th>
<th>Number of published studies</th>
<th>Drugs involved</th>
<th>Genes implicated</th>
<th>Highest level of significance (lowest p value)</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>4</td>
<td>Ximelagran, Flucloxacillin, Luminarox, Anoxicillin- clorohexane</td>
<td>HLA classes I and II</td>
<td>$8.7 \times 10^{-13}$</td>
<td>37, 39, 40, 42</td>
</tr>
<tr>
<td>Skin and hypersensitivity</td>
<td>3</td>
<td>Carbamazeptine plus miscellaneous agents</td>
<td>HLA-A</td>
<td>$1.2 \times 10^{-13}$</td>
<td>48, 59, 62</td>
</tr>
<tr>
<td>Myotoxicity</td>
<td>1</td>
<td>Simvastatin</td>
<td>SLCO1B1</td>
<td>$4.0 \times 10^{-9}$</td>
<td>68</td>
</tr>
<tr>
<td>QT prolongation</td>
<td>1</td>
<td>Biperidone</td>
<td>CYP3A4</td>
<td>$2.8 \times 10^{-6}$</td>
<td>78</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>1</td>
<td>Pantolactone, zoledronic acid</td>
<td>CYP2C1</td>
<td>$6.2 \times 10^{-4}$</td>
<td>80</td>
</tr>
</tbody>
</table>

Next steps:

NGS, sequencing faster, cheaper, deeper, more

Genome-wide association studies with SNPs (GWAS)

Encode (how cells interpret the genome information)

Parallel development of other «omics» technologies

NGS: next generation sequencing; SNPs, single nucleotide polymorphisms; GWAS, genome-wide association studies
How will we integrate this data intensive biology or better understanding of disease into tangible benefits for patients?
Questions

- What determines the individual risk of a certain disease?
- What determines the individual course of the disease?
- What determines the individual response to (drug) treatment?

PARADIGM FOR THE FUTURE: 4 P MEDICINE

How will we make medicine more...

(Precise) Predictive Preventive Personalized Participatory

*Weston & Hood, 2004; Hood & Friend, 2011*
Questions

- **What determines the individual risk of a certain disease?**
- **What determines the individual course of the disease?**
- **What determines the individual response to (drug) treatment?**
PHARMACOGENETICS
PHARMACOGENOMICS

Linking information on the variation of human genomic and transcriptomic (or other omics) data to individual variation in clinical responses to drugs

>100 approved drugs include pharmacogenomic information in labels
~40 different biomarkers (gene variants, functional deficiencies, expression changes, chromosomal abnormalities) are linked to drug response
>50 drugs with safety/efficacy associated with gene variants

Pharmacogenomics Research Network and Knowledge Base: www.pharmgkb.org
**PHARMACOGENETICS**

**PHARMACOGENOMICS**

**PGx GERMLINE GENOME BIOMARKERS**

*Clinical relevance established – Standard of care* for ~13 drugs-gene variant pairs

**PGx TUMOR OMICS BIOMARKERS**

*Clinical utility established – Standard of care* for 18 drugs and 9 somatic gene variants

*depending on country*


---

**CASE REPORT:**

- Codeine prescribed after labour for pain (episiotomy)
- Active metabolite of codeine is morphine
- CYP2D6 catalyses O-demethylation of codeine to morphine
- The mother was ultrarapid metabolizer by genotype
- Morphine concentration in breast milk was increased
- Baby: difficulty in breast feeding, lethargic, found dead on day 13

Lancet 368:704, 2006

**Codeine toxicity and CYP2D6 Ultrarapid Metabolizer Genotype**

Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother

Gideon Krems, James Cairns, David Chlupatý, Andrea Garbík, Steven J. Leader
Codeine toxicity and CYP2D6 Metabolizer Genotype

- Avoid codeine when breastfeeding
- Avoid breastfeeding when taking codeine
- Inform and monitor mother and baby for signs of toxicity
- Genotype mother for CYP2D6

First DNA test to identify poor metabolizers of debrisoquine by allele-specific PCR amplification

Pre-prescription genotyping should help physicians decide

- **not to prescribe this drug**
- **start with a low dose of this drug**
- **start with a high dose of this drug**

or that

**this patient has to be monitored more closely**
**for ADRs, lack of response, drug levels**
Abacavir Hypersensitivity and HLA-B*5701 (Rx of HIV/AIDS)

- Idiosyncratic reaction, not predicted in animal models
- Appears within 6 weeks of therapy (fever, rash, GI-symptoms, eosinophilia)
- Discontinuation of therapy mandatory, serious (fatal) rechallenge reaction
- Affects 2-9% of treated patients

Courtesy Munir Pirmohamed
PGx TUMOR OMIC BIOMARKERS

*Clinical utility established – Standard of care*

Anastratol, Exemestan, Fulvestrant, Letrozol, Toremifen, Tamoxifen - *Hormone receptors (ER, PR)*

Trastuzumab, Lapatinib, Pertuzumab - *HER2 (ERBB2)*

Imatinib, Dasatinib, Nilotinib - *BCR-ABL*

Imatinib - *KIT (C-KIT)*

Panitumumab, Cetuximab - *KRAS*<sub>wt</sub>, *EGFR*

Erlotinib, Gefitinib - *EGFR*

Crizotinib - *EML4-ALK fusion*

Vemurafenib - *BRAF*<sub>V600E</sub>

~ 18 drugs, ~ 9 somatic gene variants

---

SIMPLE MINDS – COMPLEX TRAITS

*Could whole-genome or exome sequencing resolve the missing heritability issue of GWAS?*

*Will whole-genome or exome sequencing become a new standard of care?*
The personal genome - the future of personalized medicine?

Clinical assessment incorporating a personal genome

40 y.o. patient with family history of coronary artery disease and early sudden death
Analyzed 2.6 million SNPs and 752 CNVs
Increased risk for myocardial infarction, type 2 diabetes and some cancers

The personal genome - The personal pharmacogenomic profile?

The personal genome sequence allows to assess the totality of known pharmacogenomic associations:

Personal Drug Response Profile

Stephen Quake genome
650 annotations for potential drug-response phenotypes and 63 pharmacogenetic variants with known potential for clinical relevance evaluated

Lancet 375:1525-35, 2010
Personal Drug Response Profile

High Interest Drug-Related Variants.

<table>
<thead>
<tr>
<th>Gene</th>
<th>rHD</th>
<th>Genotype</th>
<th>Drug Response Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19</td>
<td>rs12248560</td>
<td>C/T</td>
<td>Clopidogrel (Increased Activation)</td>
</tr>
<tr>
<td>LPP1</td>
<td>rs10192866</td>
<td>G/G</td>
<td>Repaglinide (Increased Effect)</td>
</tr>
<tr>
<td>VKORC1</td>
<td>rs9923231</td>
<td>C/T</td>
<td>Warfarin (Lower Dose Required)</td>
</tr>
</tbody>
</table>

GENOMIC & PERSONALIZED MEDICINE Challenges

Clinical utility
Costs
Understanding probabilities
Managing expectations
Acceptance by stakeholders
GENOMIC & PERSONALIZED MEDICINE
Challenges

Stakeholders- Another 4 P

Patients
Prescribers
Payors
Pharma business

PERSONALIZED MEDICINE
Challenges

Academic research, physicians and patients, regulators, providers, government, civil society, pharma industry.

The patient: Connected, informed, engaged
The personal genome - the future of personalized medicine?

The challenge

At present: Genome sequence ~ 3000 $, analysis ~ 30'000 $

MUSINGS

The $1,000 genome, the $100,000 analysis?

Biological meaning and clinical relevance of data
Trained individuals to interpret and deliver results
Appropriate consent process for unintended findings
Clinical outcome data

GENERAL CONCLUSION

Interactions between the entire genome and non-genomic factors result in health and disease and drug response

An increased understanding of these interactions is the basis for Personalized Medicine with new diagnostic & therapeutic approaches to disease and drug development
Personalized Medicine:
The Promise and the Challenge

THANK YOU FOR YOUR ATTENTION