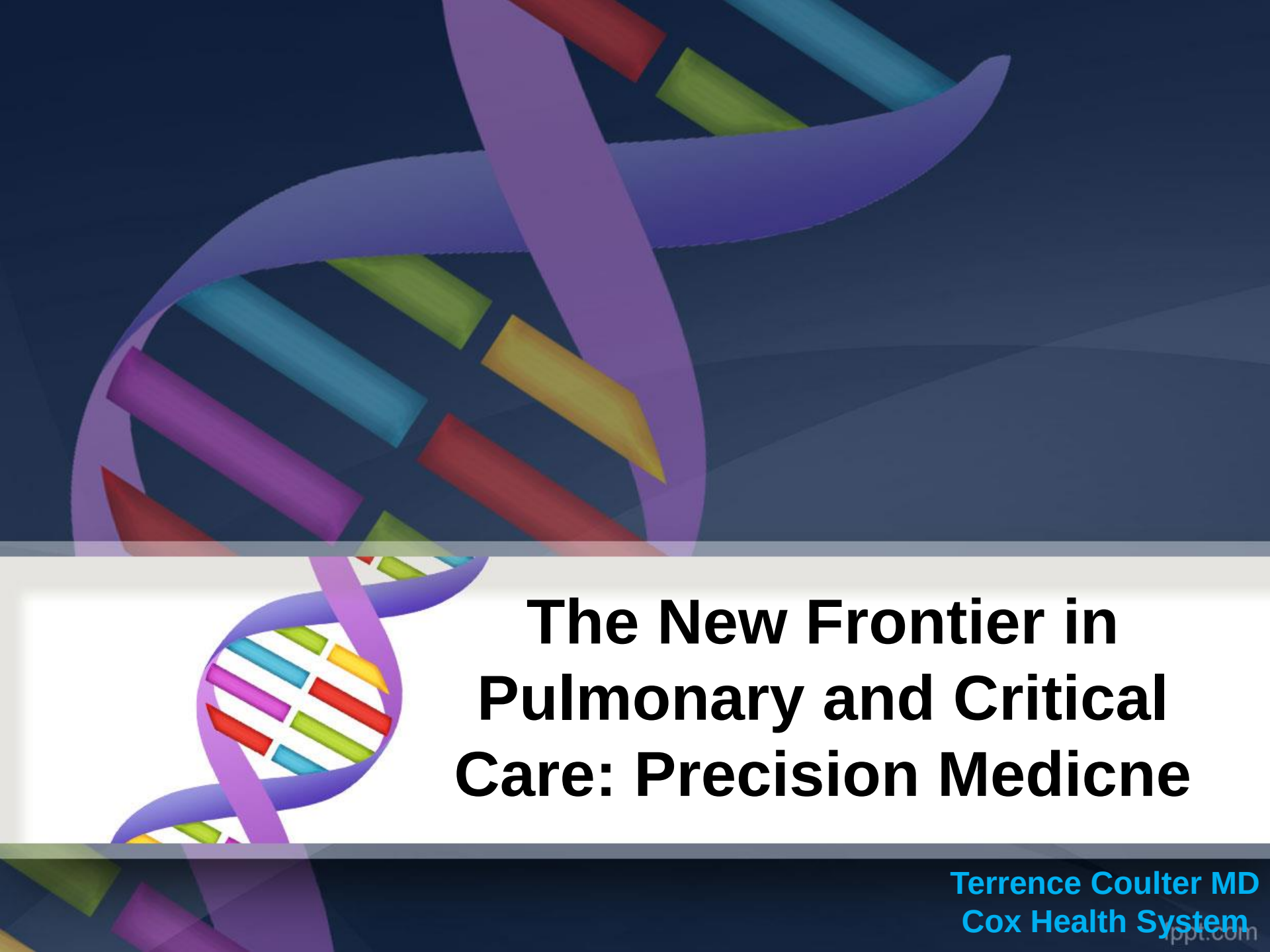
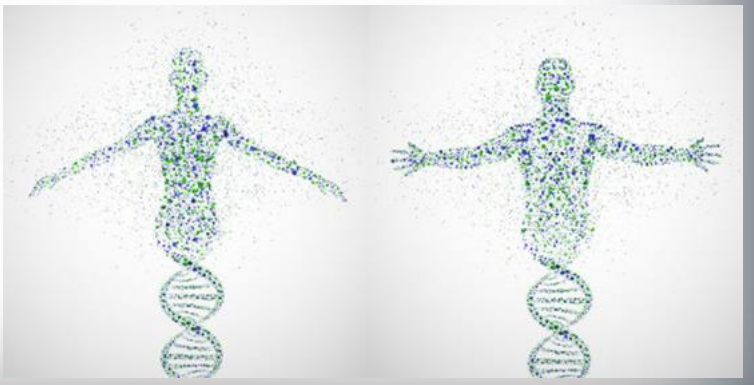


The New Frontier in Pulmonary and Critical Care: Precision Medicne

Terrence Coulter MD
Cox Health System

Objectives

- The state of affairs of precision medicine initiatives
- Define precision medicine vs personalized medicine
- Introduce the role of ‘Omics’ sciences in precision medicine
- Identify ways in which precision medicine may influence clinical practice through a case-based example, specifically focusing on:
  - Pharmacogenomics
  - Motivating behavioral changes
- To acknowledge the challenges and limitations of these initiatives



State of the Union, 2015

Obama's Precision Medicine Initiative

"Tonight, I'm launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes – and to give all of us access to the personalized information we need to keep ourselves and our families healthier."

-President Barak Obama

The promise: $215 million investment

https://www.whitehouse.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative

PMI Funding:

The President called for $215 million in fiscal year 2016 to support the Initiative

- $130 million allocated to NIH to build a national, large-scale research participant group (cohort)
- $70 million allocated to National Cancer Institute to lead efforts in cancer genomics
- $10 million to FDA to acquire additional expertise and advance the development of high quality, curated databases
- $5 million to Office of the National Coordinator for Health Information Technology (ONC) to support the development of interoperability standards and requirements that address privacy and enable secure exchange of data across systems

https://www.nih.gov/precision-medicine-initiative-cohort-program

2015 Precision Medicine Initiative

A consortium of NIH agencies, non-for-profits, and private sector partnerships

Francis Collins, *NEJM* 2015:

"2 main components: a near-term focus on cancers and a longer-term aim to generate knowledge applicable to the whole range of health and disease."

PMI Objectives:

- Develop ways to measure risk for a range of diseases based on environmental exposures, genetic factors, and interactions between the two
- Identify the causes of individual differences in response to commonly used drugs (pharmacogenomics)
- Discover biological markers that signal increased or decreased risk of developing common diseases
- Use mobile health technologies to correlate activity, physiological measures and environmental exposures with health outcomes
- Develop new disease classifications and relationships;
- Empower study participants with data and information to improve their own health
- Create a platform to enable trials of targeted therapies

https://www.nih.gov/precision-medicine-initiative-cohort-program

All of Us℠

THE FUTURE OF HEALTH BEGINS WITH YOU

The Precision Medicine Initiative®

-The Cancer Moonshot aims to make more therapies available to more patients, while also improving our ability to prevent cancer and detect it at an early stage by accelerating research.

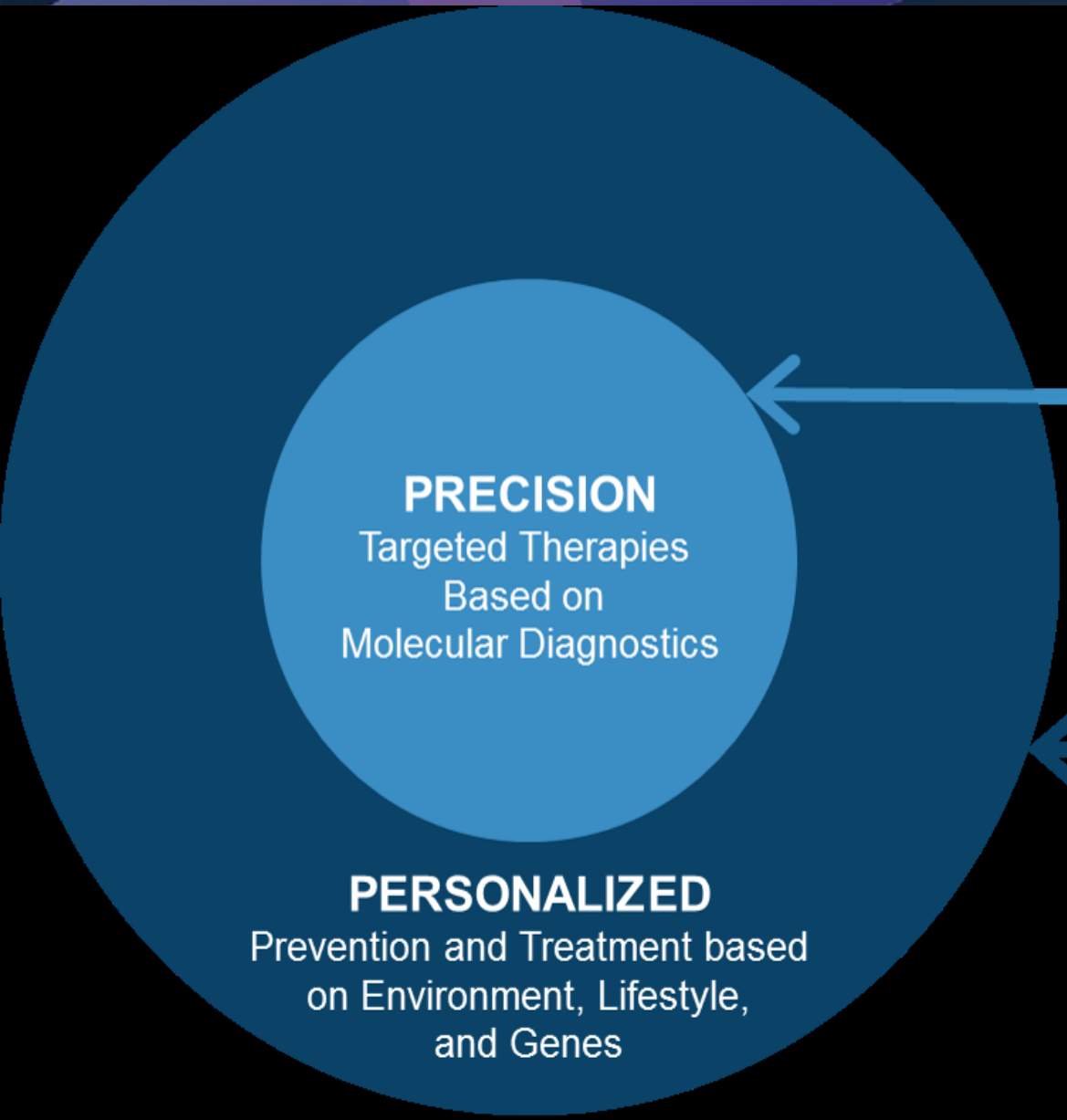
-Congress passed the 21st Century Cures Act in December 2016 authorizing $1.8 billion in funding for the Cancer Moonshot over 7 years. An initial $300 million has been appropriated in fiscal year (FY) 2017 to fund Moonshot initiatives.

https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative

Definitions

- **Precision medicine**: customization of medical decisions and courses of treatment based on the individual patient
- **Personalized medicine**: creation of new treatments in response to a particular patient's need
- **Pharmacogenomics**: the study of the role genetics plays in drug response

Precision Medicine vs Personalized Medicine

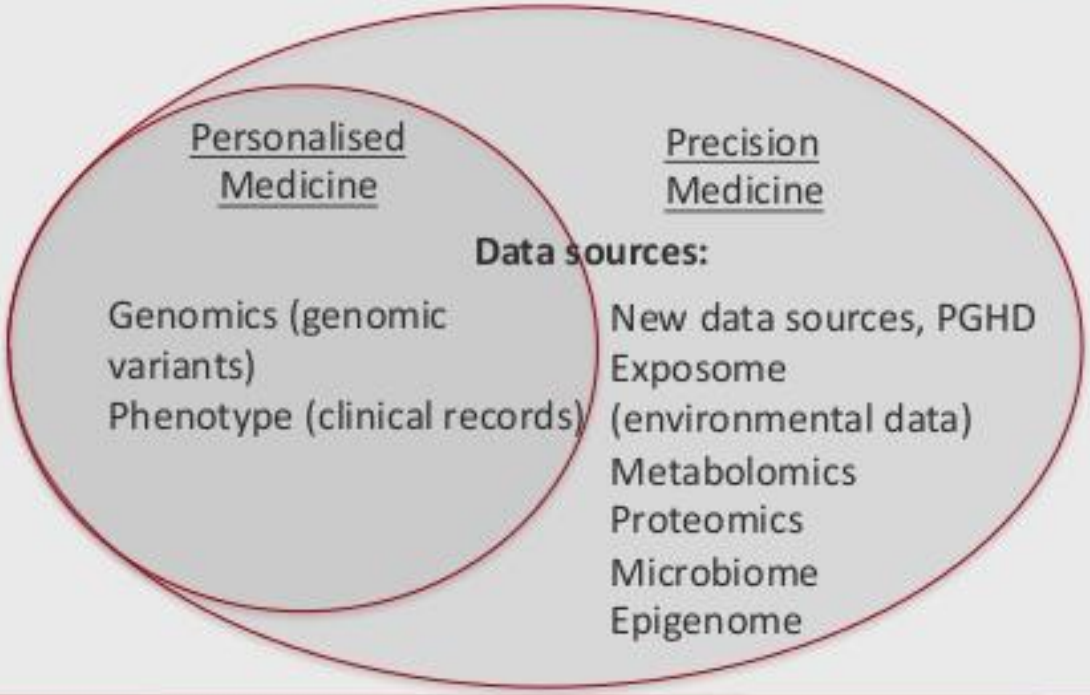


Precision Medicine
is science – a new wave of evidence-based medicine

Personalized Medicine
is a practice – managing a patient's care more holistically

Precision Medicine vs Personalized Medicine

Personalised vs Precision Medicine



PM combines the knowledge of the patient's characteristics with traditional medical records and environmental information to optimize health.

PM does not only rely on genomic medicine but also integrates any other relevant information such as non-genomic biological data, clinical data, environmental parameters and the patient's lifestyle.

Servant N et al. Front Genet. 2014; 5: 152.

Objectives

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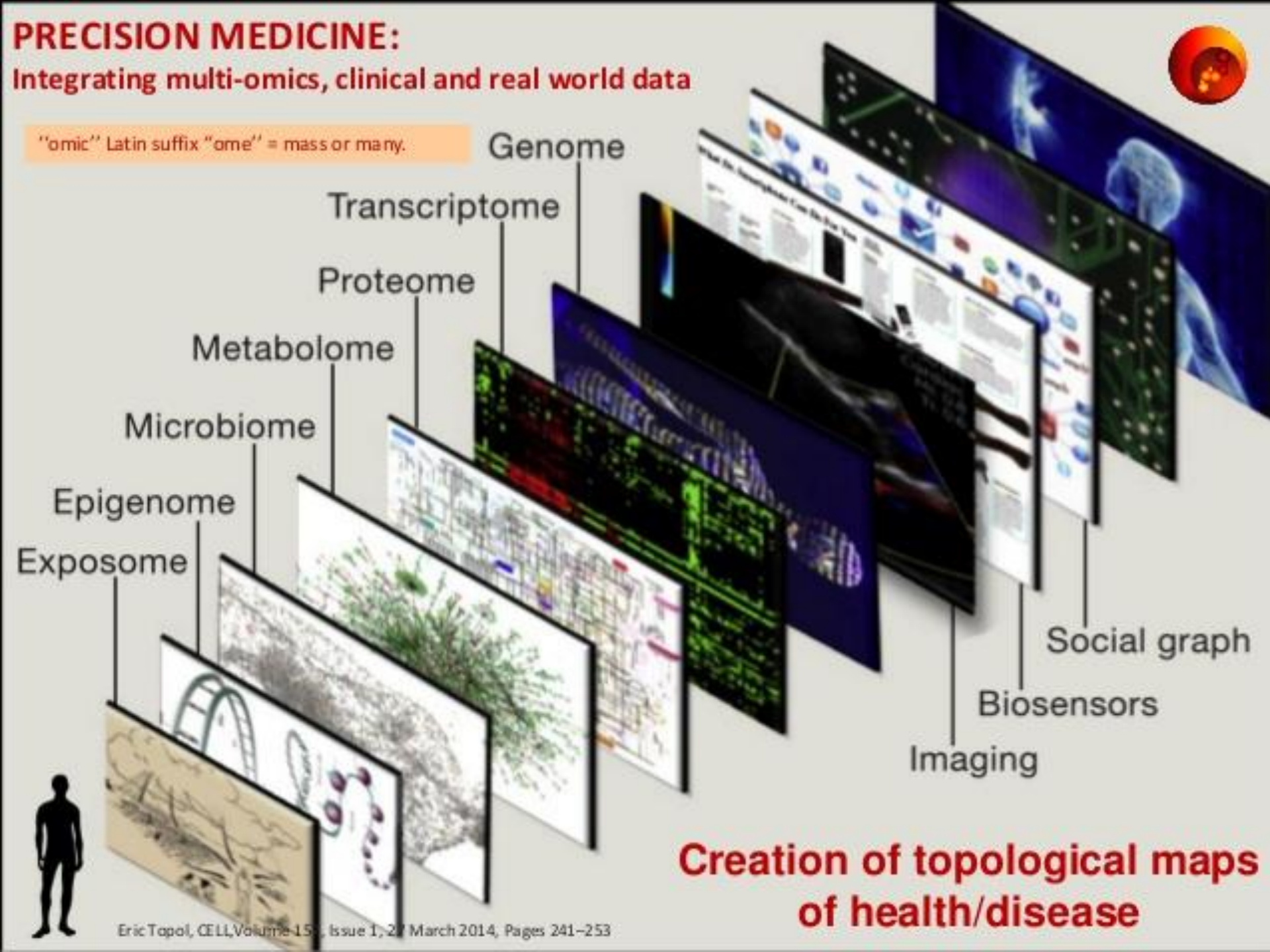
PRECISION MEDICINE:

Integrating multi-omics, clinical and real world data

"omic" Latin suffix "ome" = mass or many.



Creation of topological maps of health/disease

Eric Topol, CELL, Volume 157, Issue 1, 27 March 2014, Pages 241–253

‘Omics in Precision Medicine

- Exposome: the measure of all the exposures of an individual in a lifetime and how those exposures relate to health.
- Epigenome: the complement of chemical compounds that modify the expression and function of the genome
- Microbiome: the microorganisms in a particular environment (including the body or a part of the body).
- Metabolome: the unique chemical fingerprints that specific cellular processes leave behind, the study of their small-molecule metabolite profiles.
- Proteome: the entire complement of proteins that is or can be expressed by a cell, tissue, or organism.
- Transcriptome: the sum total of all the messenger RNA molecules expressed from the genes of an organism

Human Genome = “Our Library”

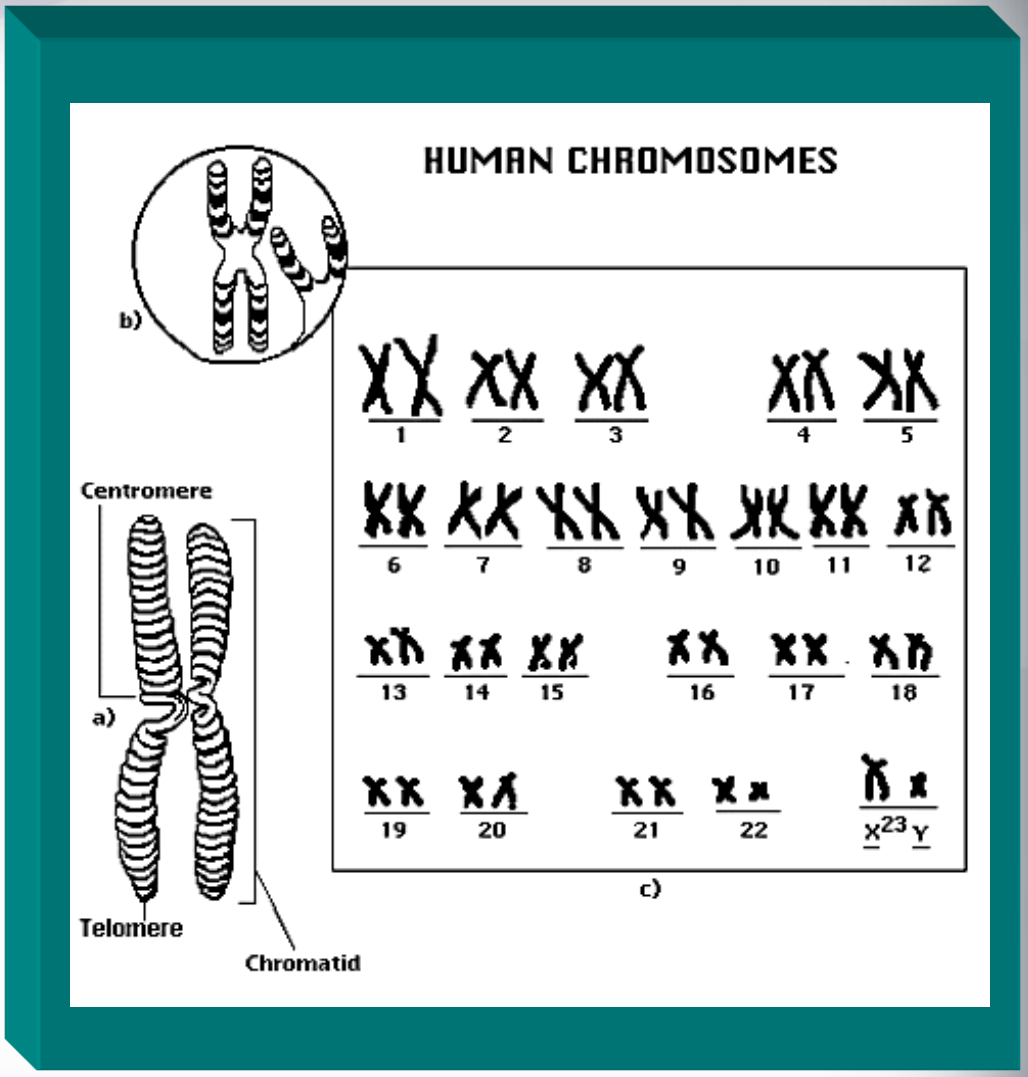
Human Genome

- Human DNA = approximately 3 billion DNA base pairs located on 23 pairs of chromosomes
- Human genome contains approximately 22,000 genes
  - Each encode average of 3 proteins

Chromosome = “Stacks”

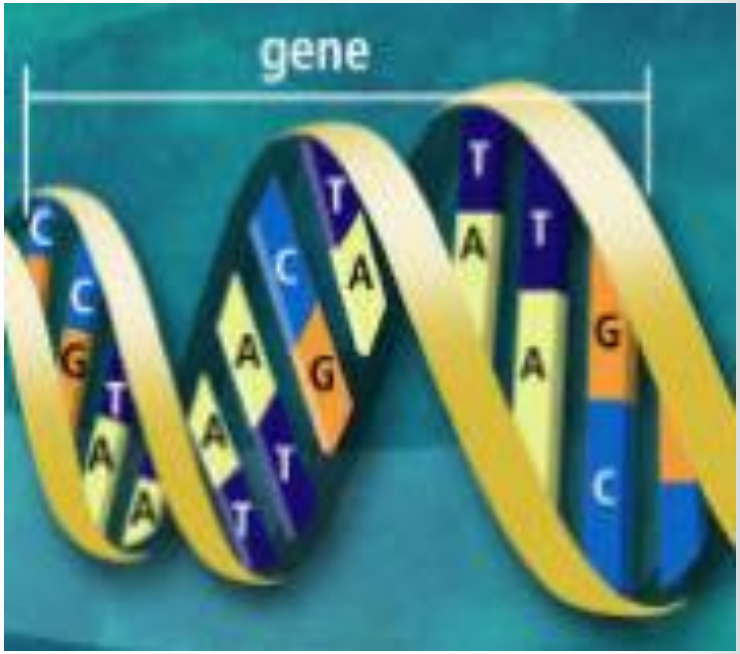
Most human cells contain 46 chromosomes:

- 22 pairs of chromosomes named autosomes.
- 2 **sex chromosomes** (X,Y):
  XY – in males.
  XX – in females.

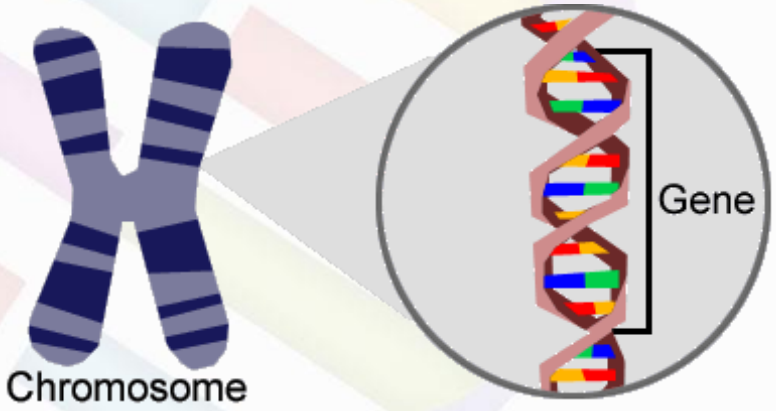


- Genes are located in chromosomes.
- There are thousands, of genes in one chromosome.
- A gene carries information that determines your traits.

Traits are characteristics you inherit from your parents.

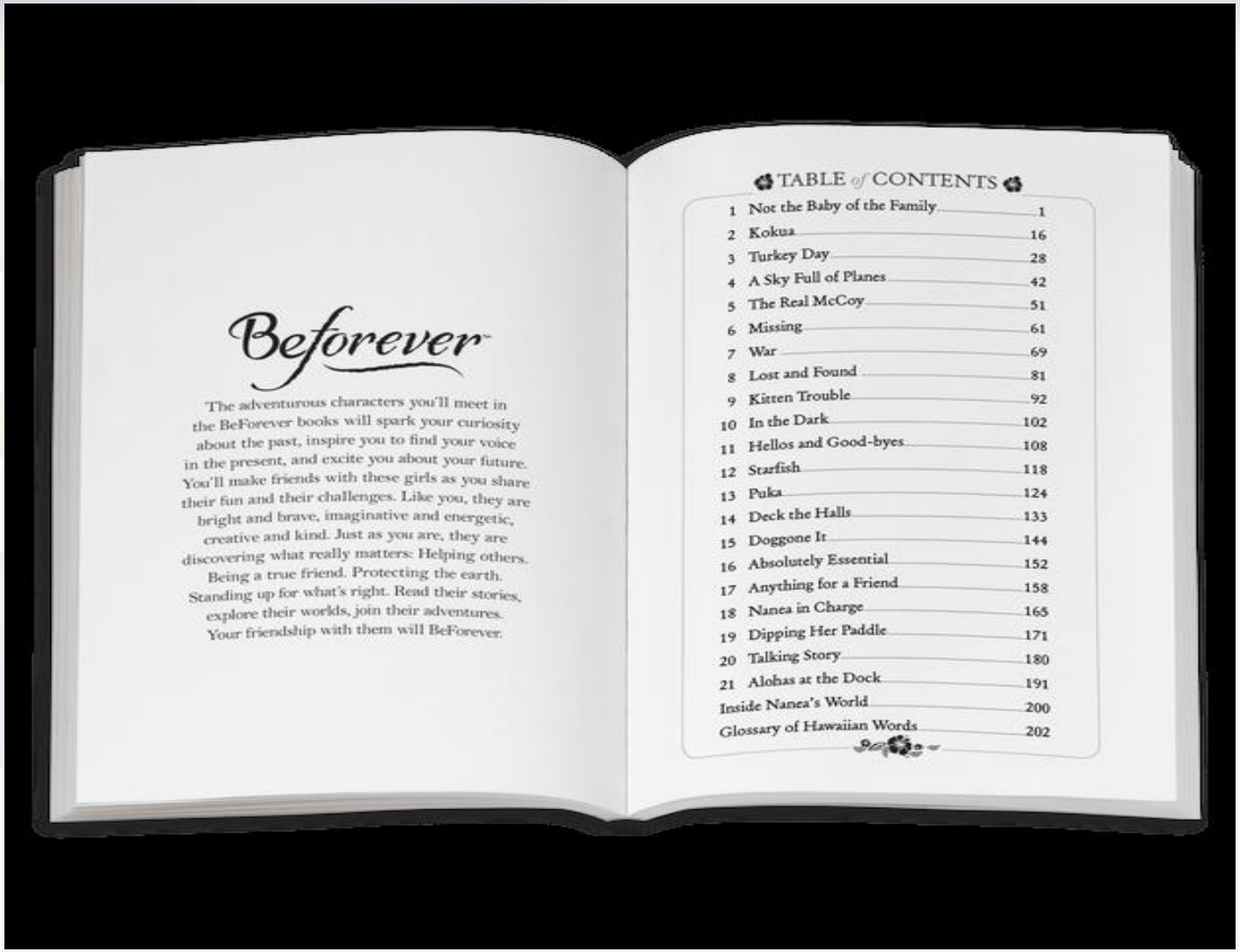


Genes = “Our Books”



- **Genes** constitute distinct regions on the chromosome
- Each gene codes for a protein product
- DNA -> RNA-> protein
- Differences in proteins brings about differences between individuals and species

Proteins = Chapters



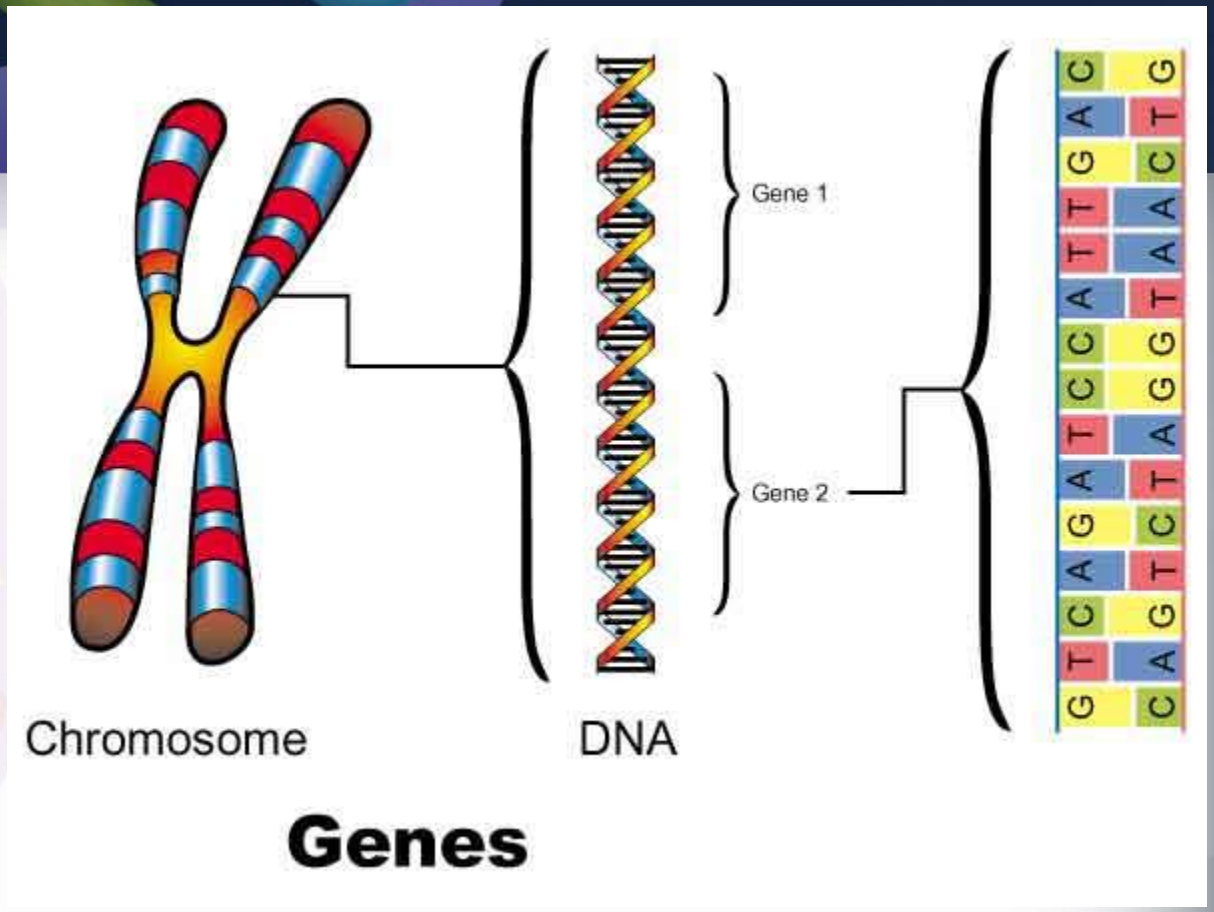
Beforever

The adventurous characters you'll meet in the BeForever books will spark your curiosity about the past, inspire you to find your voice in the present, and excite you about your future. You'll make friends with these girls as you share their fun and their challenges. Like you, they are bright and brave, imaginative and energetic, creative and kind. Just as you are, they are discovering what really matters: Helping others. Being a true friend. Protecting the earth. Standing up for what's right. Read their stories, explore their worlds, join their adventures. Your friendship with them will BeForever.

TABLE of CONTENTS

- DNA = “Our Words/Language”
- Nucleotides = “Our Letters”

- **Gene** – basic unit of genetic information. Genes determine the inherited characters.

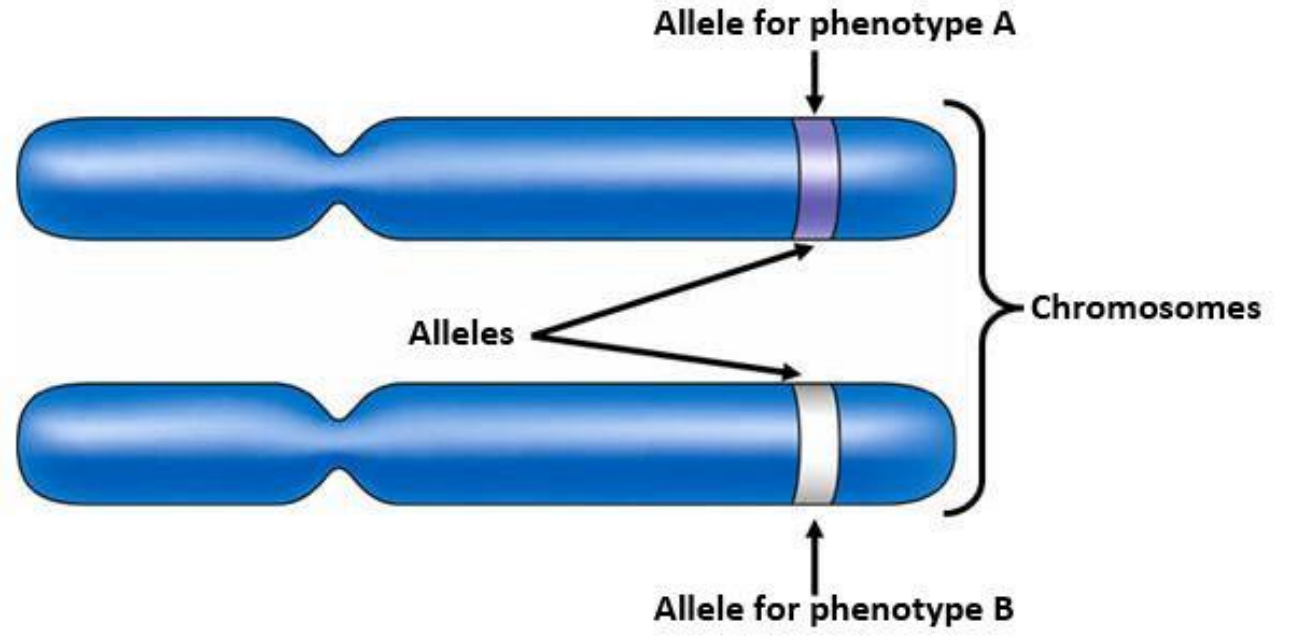


- **Chromosomes** – storage units of genes.

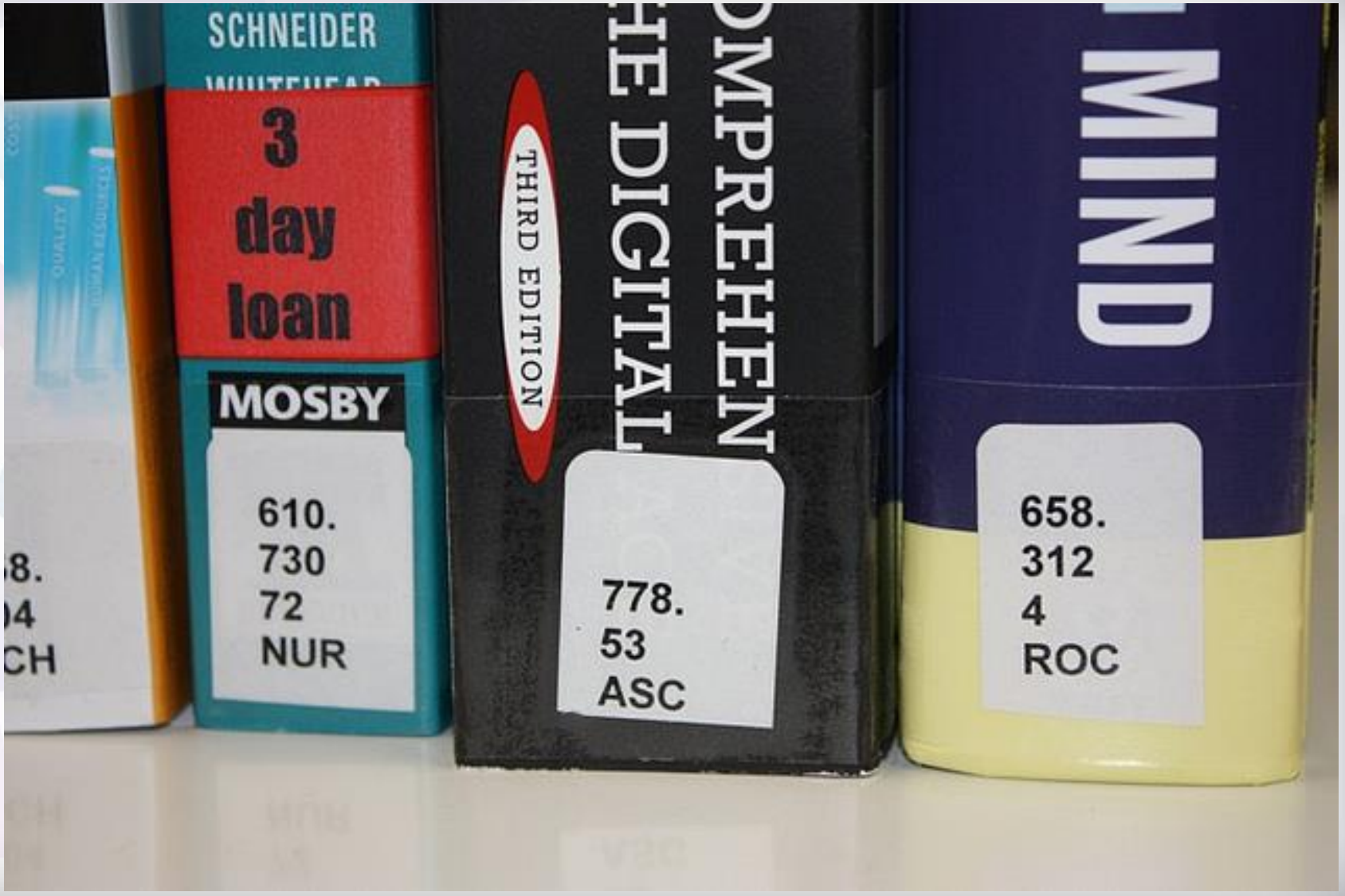
- **Genome** – the collection of genetic information.

Definitions

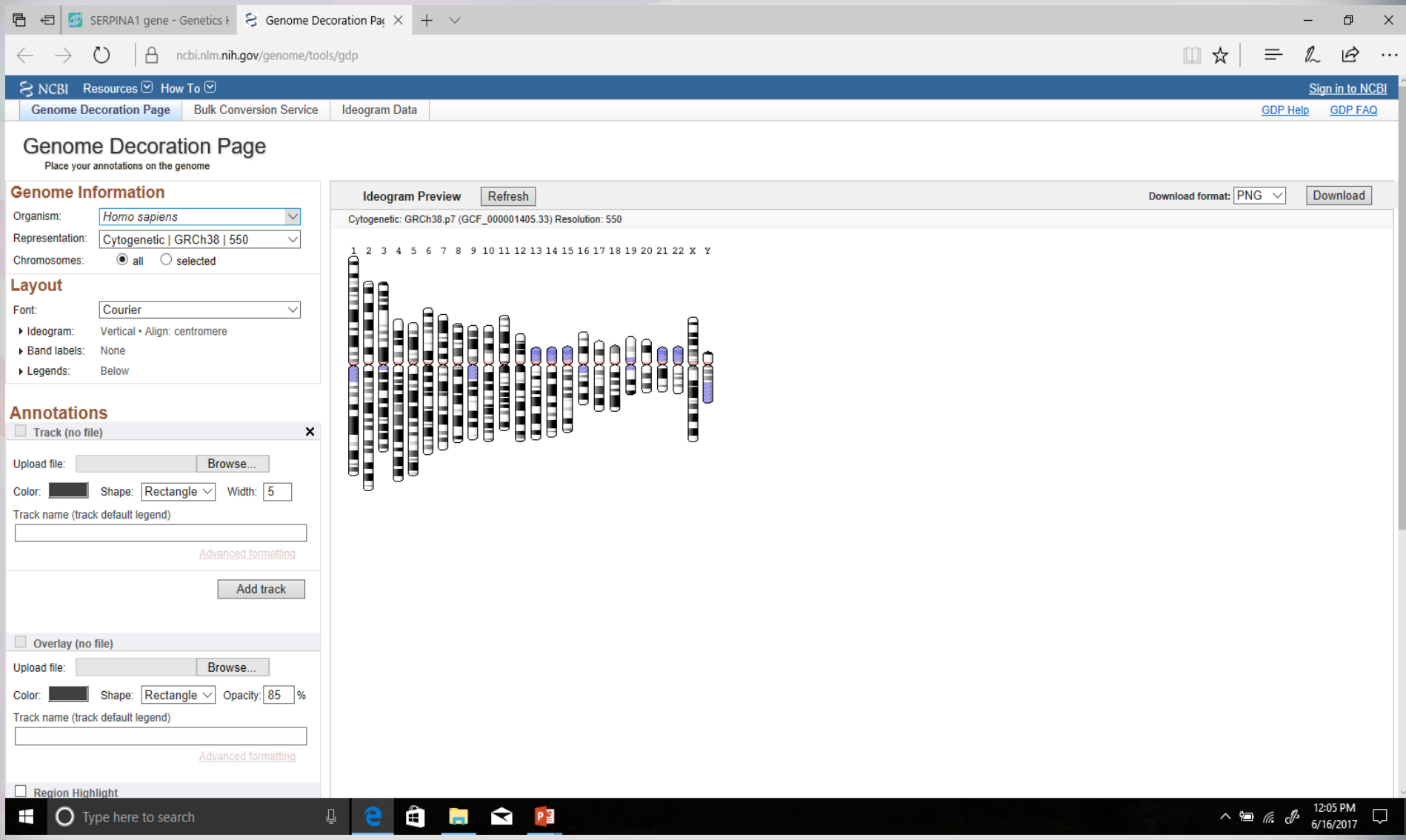
- Allele- discrete version of the same gene
- Genotype- the **g**enes of an organism for one specific trait
- Phenotype- the **p**hysical appearance of a trait in an organism



Dewey Decimal System



National Center for Biotechnology Information

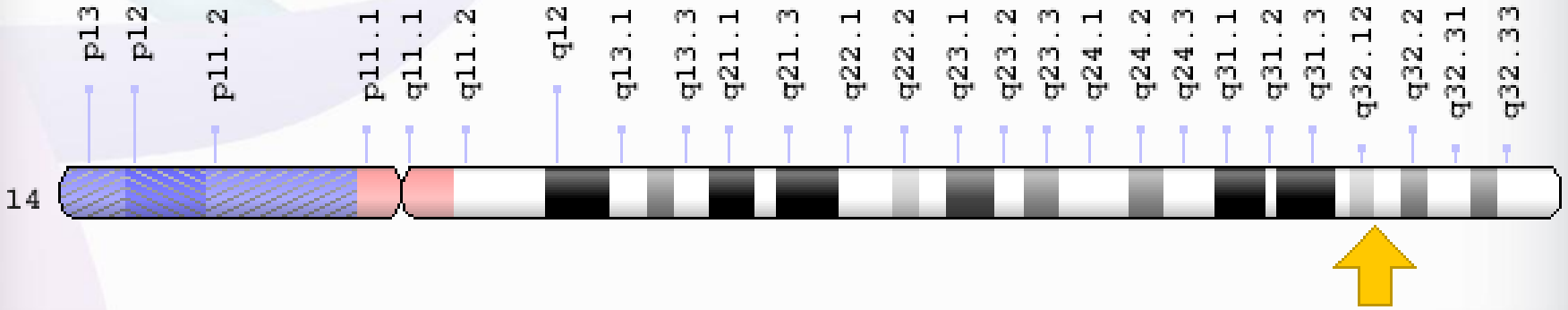


SERPINA1 gene → A1AT

-Cytogenetic Location: 14q32.13

-which is the long (q) arm of chromosome 14 at position 32.13

-Molecular Location: base pairs 94,376,747 to 94,390,692 on chromosome 14 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Genotypes  Phenotypes

- At each locus (except for sex chromosomes) there are 2 genes. These constitute the individual's ***genotype*** at the locus.

- The expression of a genotype is termed a ***phenotype***. For example, hair color, weight, or the presence or absence of a disease.

A1AT

PI Z Allele

aa342

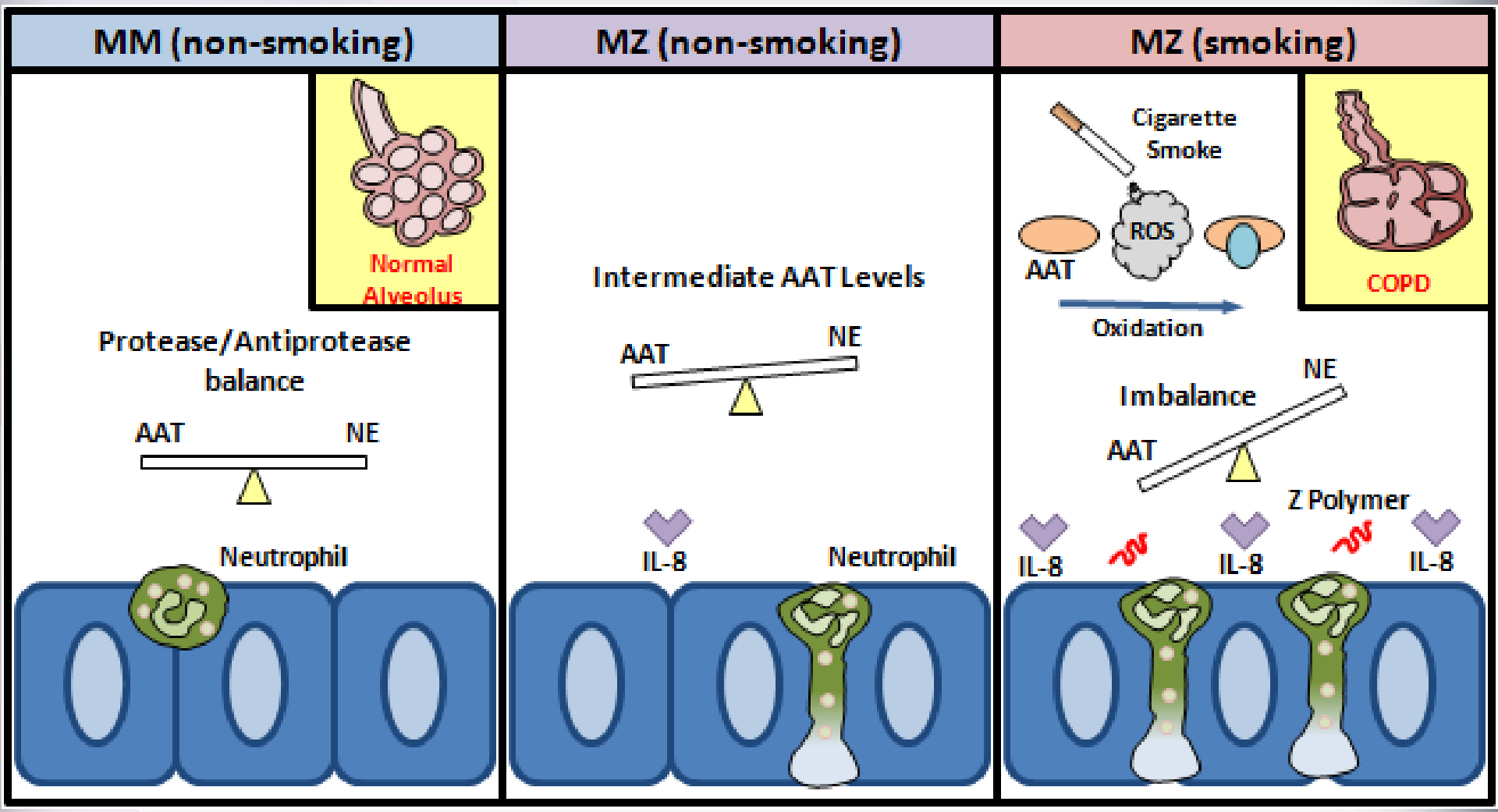
```
AAG GCT GTG CTG ACC ATC GAC AAG AAA GGG ACT GAA GCT GCT GGG GCC
 K   A   V   L   T   I   D   K   K   G   T   E   A   A   G   A

     TGCGCG-gac ugg uag cTG CTC uuu ccc tga cuu T
    T                                           T
    T                                           T
     TCGCGC CTG ACC ATC GAC GAG AAA GGG ACT GAA T
```

α1AT-Z

Normal Allele

```
AAG GCT GTG CTG ACC ATC GAC GAG AAA GGG ACT GAA GCT GCT GGG GCC
 K   A   V   L   T   I   D   D   K   G   T   E   A   A   G   A
```

A1AT



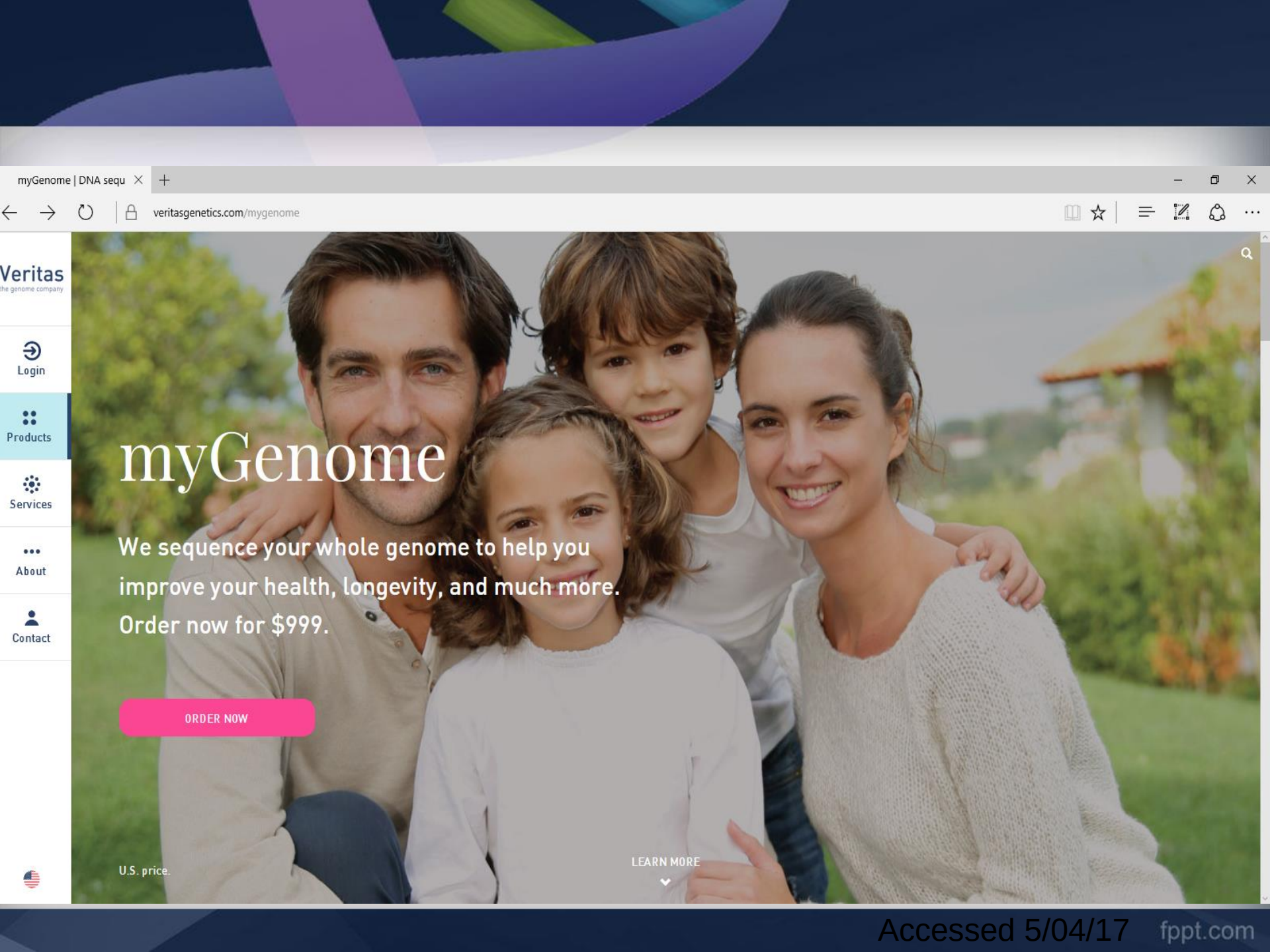
Human Genome Project

- The **Human Genome Project** (HGP) was an international scientific research project with the goal of determining the sequence of nucleotide base pairs that make up human DNA, and of identifying and mapping all of the genes of the human genome from both a physical and a functional standpoint.

Human Genome Project

- Launched in 1990
- Officially completed in 2003 (13 years)
- Cost $3 billion to sequence a single genome

- Cost insurmountable for this to have an impact clinically
- **Next-gen sequencing** now allows quicker and much less costly sequencing

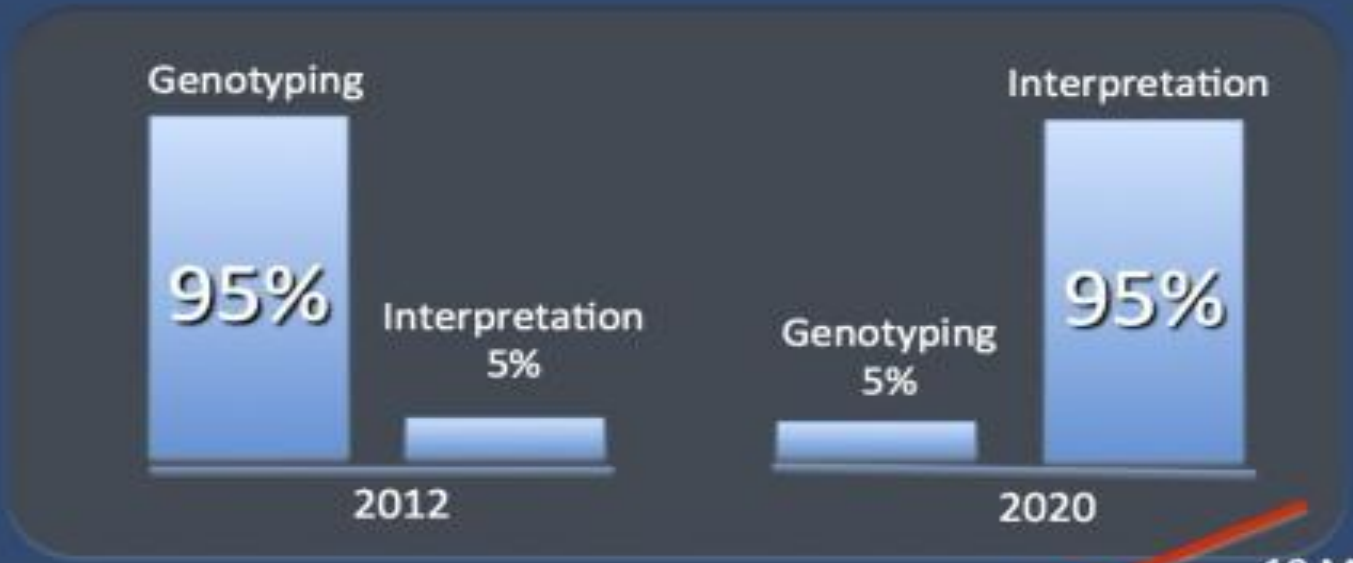


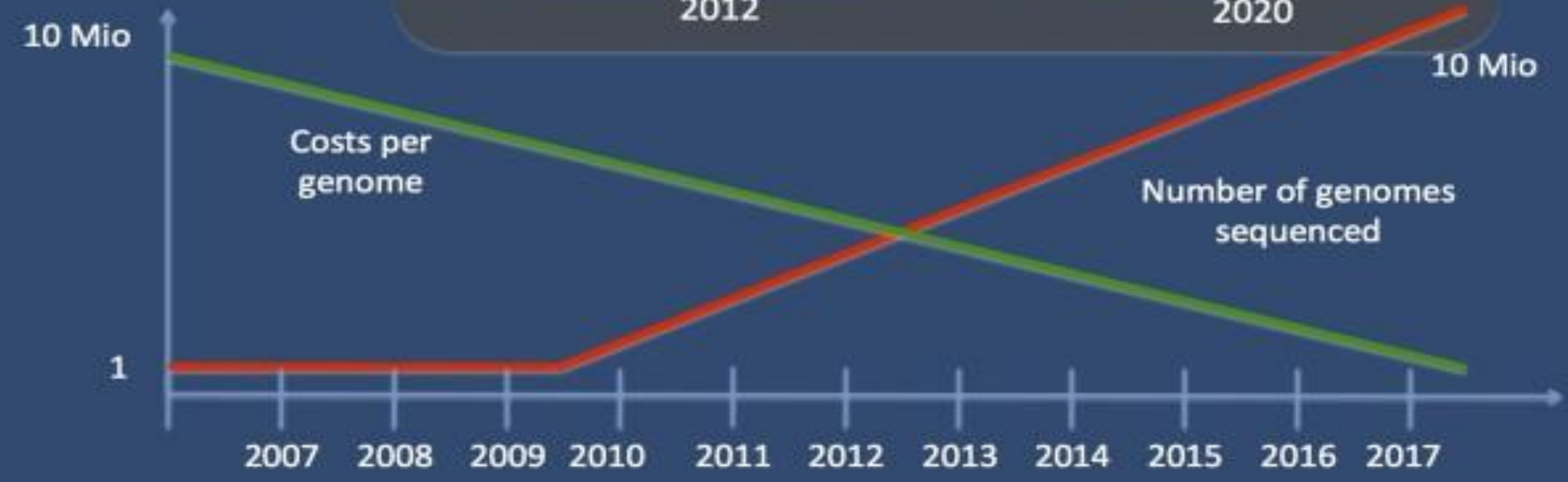
Accessed 5/04/17

- 1990 Ferrari **$400,000**

- Today buying it for **8 cents**

Genome vs. genome analysis





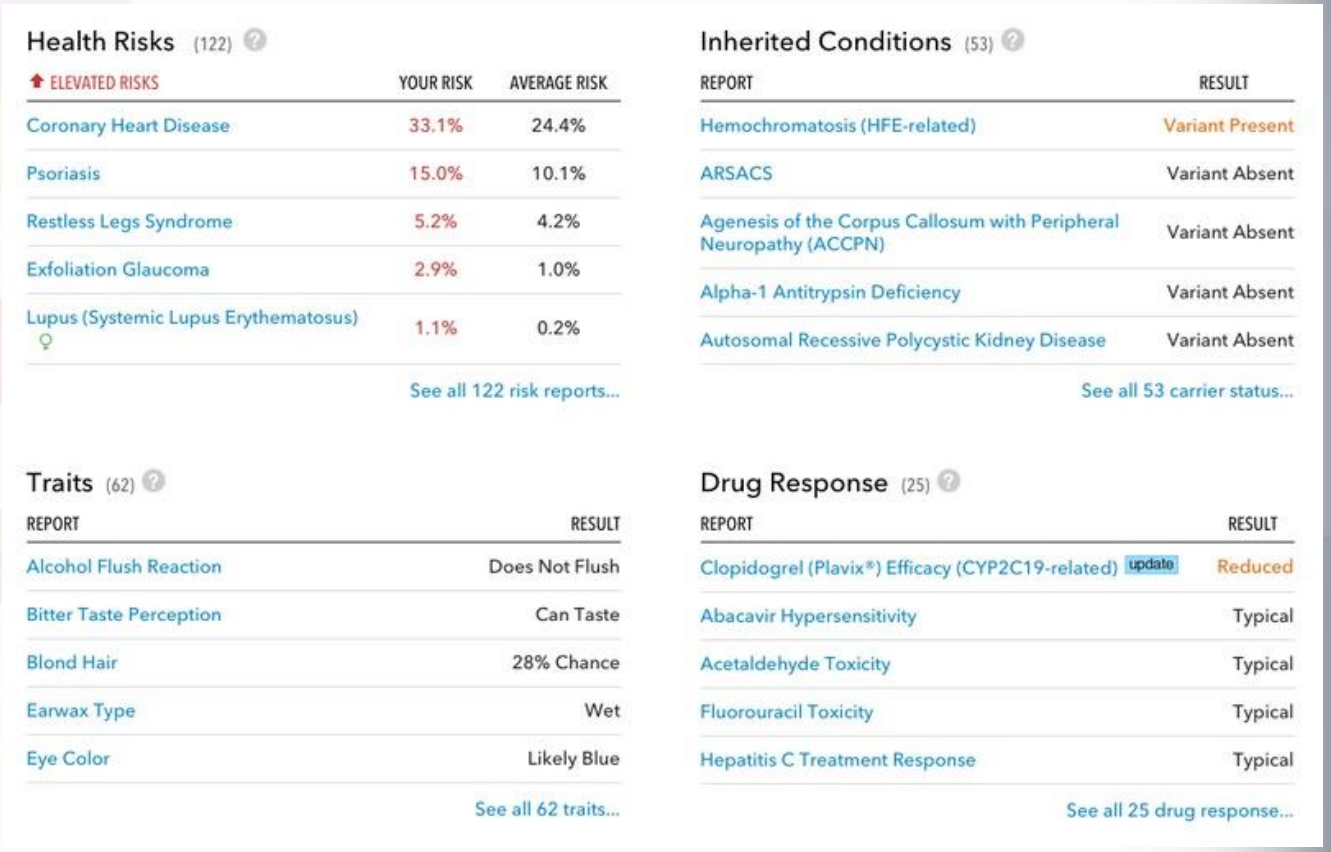
http://epilepsygenetics.net/2014/06/27/when-will-we-have-the-1000-epilepsy-genome/

Types of Genetic Testing

- Whole genome or exome sequencing
  - Whole genome sequencing – sequencing the coding and regulatory elements of our DNA (copy all 22,000 genes)
  - Exome sequencing – sequencing the coding regions of our DNA that actually encodes proteins (only 2% of the genome)
- Specific single gene tests
  - Usually for a focused evaluation of a heritable disease
  - Examples include *BRCA1* and *BRCA2* testing
- Specific gene panels
  - Panels testing for multiple mutations that cause the same phenotype (5 to 100 genes)
  - Examples include panels for autism, hereditary deafness, cardiomyopathies, inherited cancer syndromes, lung diseases

23 and Me Kits:

- $199 dollars
- Tests for:
  - >35 carrier traits
  - >19 appearance traits
  - 3 ancestry reports
  - 4 wellness reports



Health Risks (122)

ELEVATED RISKS	YOUR RISK	AVERAGE RISK
Coronary Heart Disease	33.1%	24.4%
Psoriasis	15.0%	10.1%
Restless Legs Syndrome	5.2%	4.2%
Exfoliation Glaucoma	2.9%	1.0%
Lupus (Systemic Lupus Erythematosus) ♀	1.1%	0.2%

See all 122 risk reports...

Inherited Conditions (53)

REPORT	RESULT
Hemochromatosis (HFE-related)	Variant Present
ARSACS	Variant Absent
Agenesis of the Corpus Callosum with Peripheral Neuropathy (ACCPN)	Variant Absent
Alpha-1 Antitrypsin Deficiency	Variant Absent
Autosomal Recessive Polycystic Kidney Disease	Variant Absent

See all 53 carrier status...

Traits (62)

REPORT	RESULT
Alcohol Flush Reaction	Does Not Flush
Bitter Taste Perception	Can Taste
Blond Hair	28% Chance
Earwax Type	Wet
Eye Color	Likely Blue

See all 62 traits...

Drug Response (25)

REPORT	RESULT
Clopidogrel (Plavix®) Efficacy (CYP2C19-related) update	Reduced
Abacavir Hypersensitivity	Typical
Acetaldehyde Toxicity	Typical
Fluorouracil Toxicity	Typical
Hepatitis C Treatment Response	Typical

See all 25 drug response...

www.23andme.com

Objectives

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  - Motivating behavioral changes
- To acknowledge the challenges and limitations of these initiatives

Clinical Case

31 year old Caucasian female who was recently diagnosed with a DVT in the ED. She presents to establish a primary care physician and for further management.

- PMHx:
  - Overweight (BMI 28)
- Social history:
  - Smokes 1 ppd x 14 years
  - Drinks 1-2 beers monthly
  - Denies illicit drug uses
  - Works at insurance company call center, highest level of education is some college
- Family history:
  - Maternal aunt diagnosed with pancreatic cancer at age 52
  - Maternal grandmother died of breast cancer, age of diagnosis unknown (died before patient was born)
  - Father has HTN, uses inhalers
- Current Medications:
  - OCPs

Vitals:

Ht 65 in. Wt. 168 lbs BMI 28
BP 122/78 P 76 R 16 Sats 99% RA

Exam:

Generally well-developed CF, in NAD

Right foot with trace pedal edema

Otherwise unremarkable

Given her diagnosis of DVT, the patient was discharged from the ED on Lovenox and will need to start bridging to Coumadin now that she has a PCP.

- What dose of Coumadin will you start the patient on?

- Is there a better way to “guess” the dose?

Pharmacogenomics

Trying to better tailor medications to patients to:

- Improve dosing
- Enhance effectiveness
- Decrease toxicity
- Develop new targeted therapies

Pharmacogenomics: Dosing

- Can genetic information help us with *dosing*?

- Polymorphisms of two genes and personal factors (age, body surface area) account for ~50% in warfarin dosing variability
  - *CYP2C9*2 AND CYP2C9*3* alleles; *VKORC1*

- Many hoped that this information would be helpful in developing a more efficient algorithm for dosing warfarin
  - Example algorithm:
    - http://www.warfarindosing.org/Source/Home.aspx

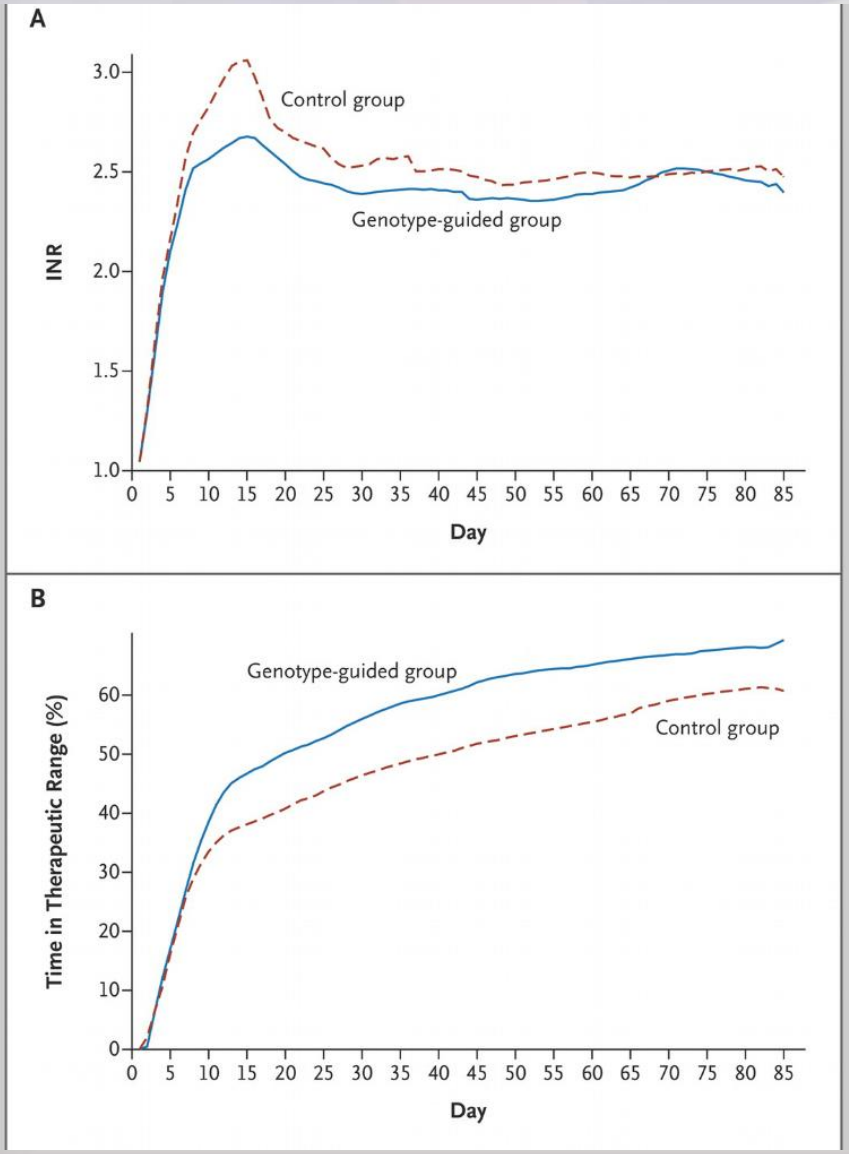


Figure 1. Mean International Normalized Ratio (INR) and Percentage of Time in the Therapeutic INR Range.

The differences between the genotype-guided dosing group and the standard dosing (control) group in the mean INR (Panel A) and the percentage of time in the therapeutic INR range of 2.0 to 3.0 (Panel B) are shown over a follow-up period of 3 months.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Genotype-Guided Dosing of Warfarin

Munir Pirmohamed, Ph.D., F.R.C.P., Girvan Burnside, Ph.D., Niclas Eriksson, Ph.D., Andrea L. Jorgensen, Ph.D., Cheng Hock Toh, M.D., Toby Nicholson, F.R.C.Path., Patrick Kesteven, M.D., Christina Christersson, M.D., Ph.D., Bengt Wahlström, M.D., Christina Stafberg, M.D., J. Eunice Zhang, Ph.D., Julian B. Leathart, M.Phil., Hugo Kohnke, M.Sc., Anke H. Maitland-van der Zee, Pharm.D., Ph.D., Paula R. Williamson, Ph.D., Ann K. Daly, Ph.D., Peter Avery, Ph.D., Farhad Kamali, Ph.D., and Mia Wadelius, M.D., Ph.D., for the EU-PACT Group*

N Engl J Med 2013; 369:2294-2303 | December 12, 2013 | DOI: 10.1056/NEJMoa1311386

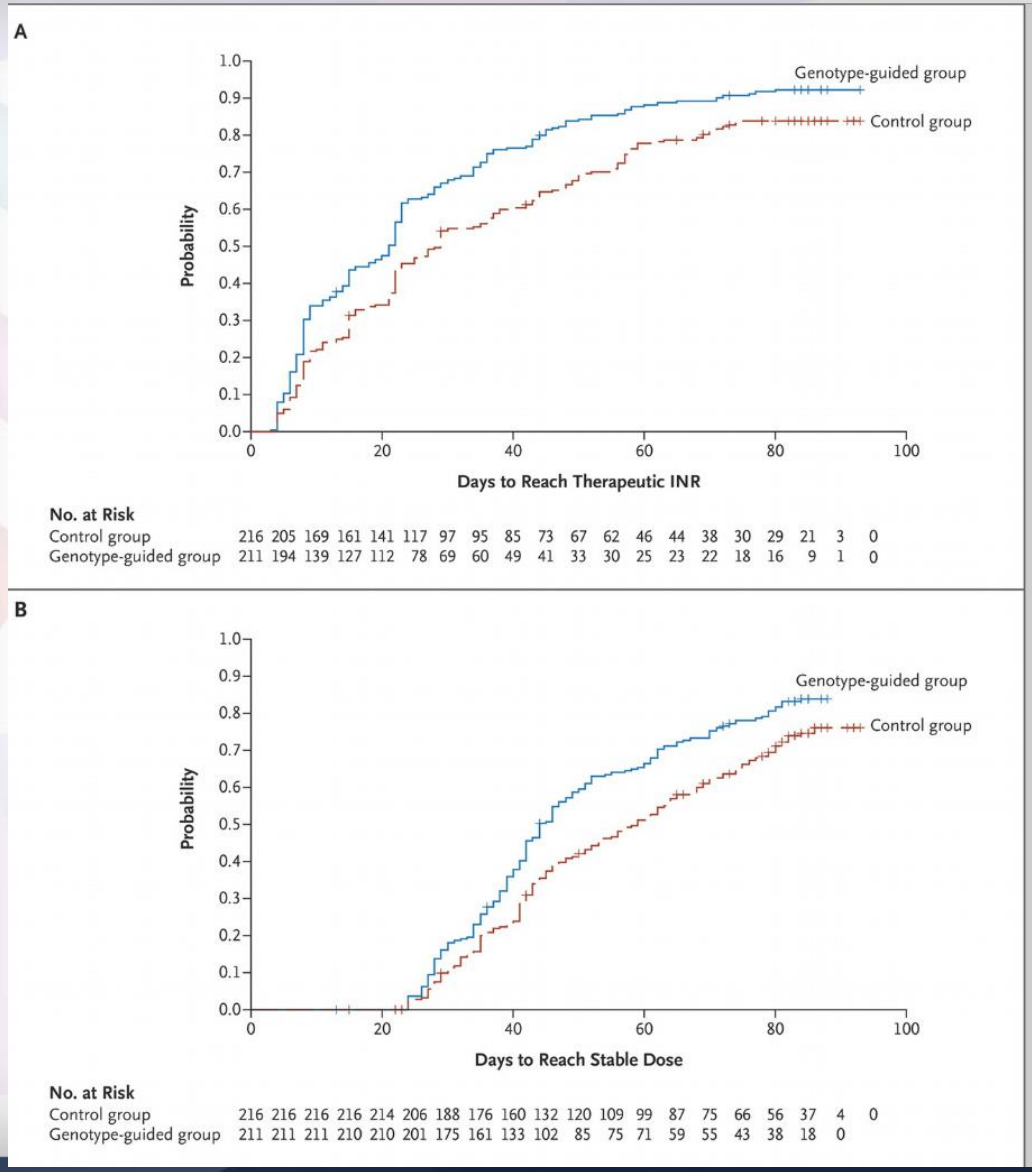


Figure 2. Kaplan–Meier Plots of the Time to Reach a Therapeutic INR and to Reach a Stable Warfarin Dose.

The plus signs indicate censored data.

Pirmohamed et al (2013)

- # Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Pharmacogenetics-Guided Warfarin Dosing: 2017 Update

- JA Johnson1,*, KE Caudle2, L Gong3, M Whirl-Carrillo3, CM Stein4, SA Scott5, MT Lee6, BF Gage7, SE Kimmel8,9, MA Perera10, JL Anderson11, M Pirmohamed12, TE Klein3, NA Limdi13, LH Cavallari1 andM Wadelius14

- Version of Record online: 4 APR 2017
- DOI: 10.1002/cpt.668

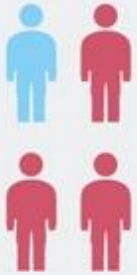
IMPRECISION MEDICINE

For every person they do help (blue), the ten highest-grossing drugs in the United States fail to improve the conditions of between 3 and 24 people (red).

1. ABILIFY (aripiprazole)
Schizophrenia

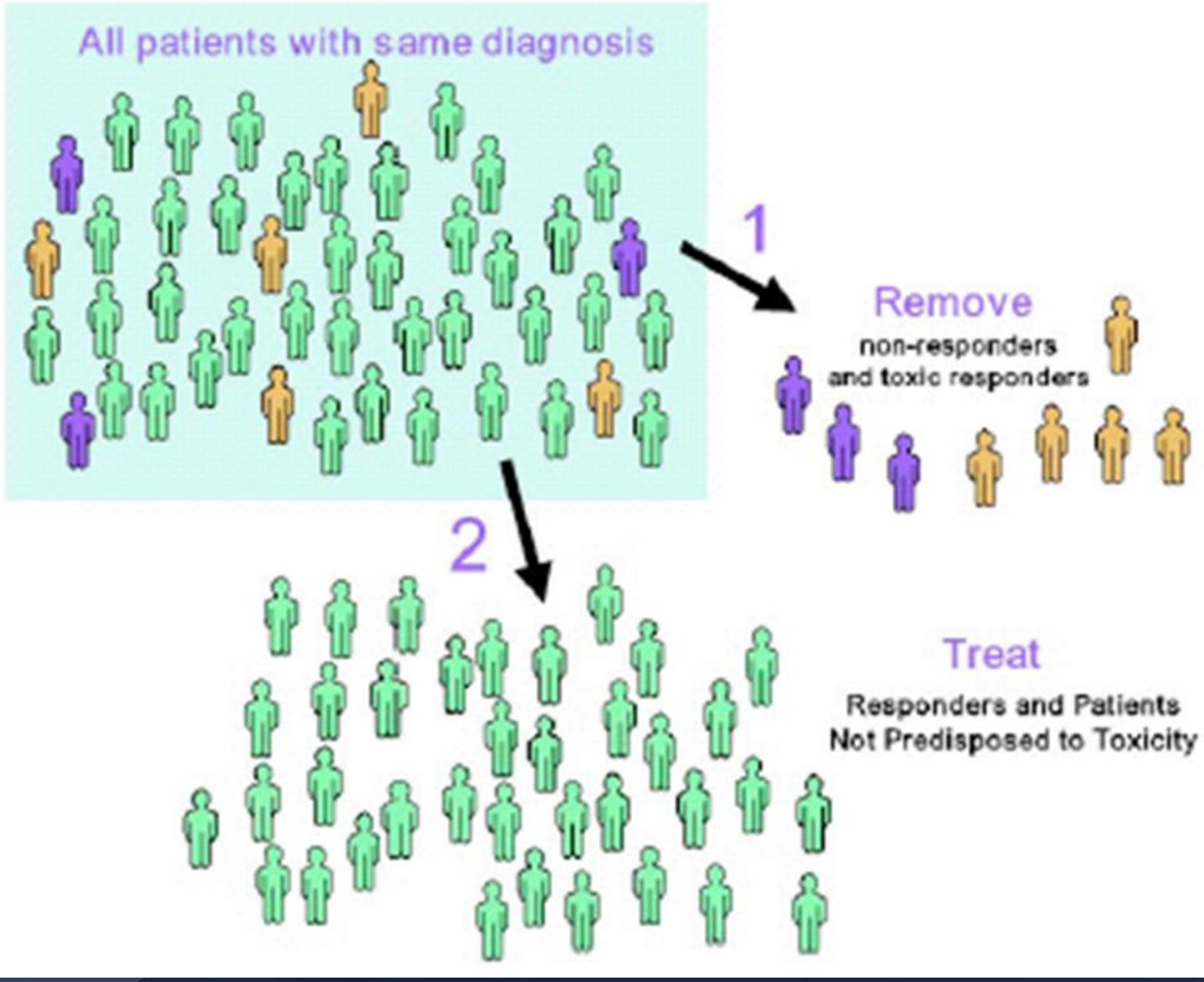
2. NEXIUM (esomeprazole)
Heartburn

3. HUMIRA (adalimumab)
Arthritis



4. CRESTOR (rosuvastatin)
High cholesterol

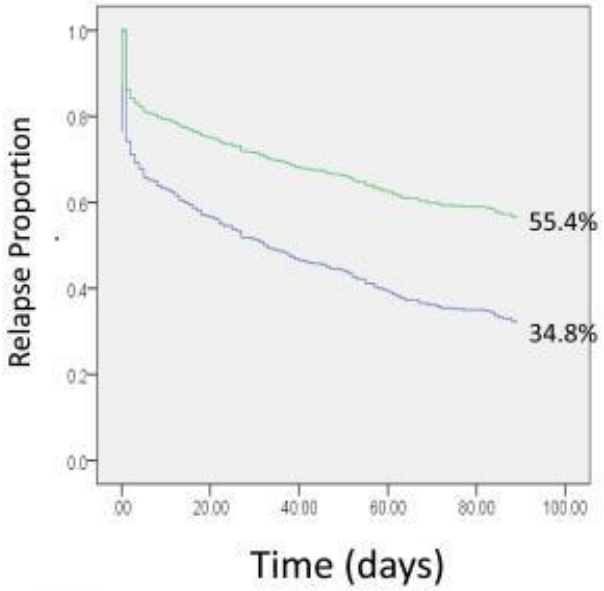
Schork 2015


All patients with same diagnosis
1
Remove
non-responders
and toxic responders
2
Treat
Responders and Patients
Not Predisposed to Toxicity

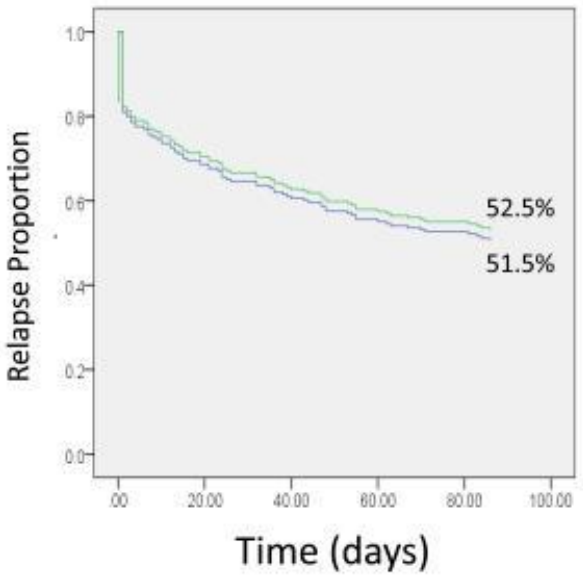
Pharmacogenomics: Drug effectiveness

- Smoking Cessation:
  - Why do nicotine patches work for some people and not for others?
    - One possibility - Nicotine Metabolism Genes *CYP2A6* and *CHRNA5*
- Chen et al 2014
  - 709 smokers randomized to placebo, bupropion, nicotine replacement therapy (NRT), or bupropion + NRT
    - Time to relapse associated with *CYP2A6* genotype-based estimates of nicotine metabolism

Fast metabolizers (n=501)
HR=0.50, 95%CI=0.38-0.68, p=4.41x10^{-6}



Slow metabolizers (n=208)
HR=0.93, 95%CI=0.59-1.46, p=0.75



With NRT [b]
Without NRT [c]

	Fast metabolizers	Slow metabolizers
With NRT[b]	363	149
Without NRT[c]	138	59

Chen et al. 2014

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Motivating behavior change by incorporating genetic risk into counseling

- Does disclosing a genetic predisposition to a major illness motivate patients to change a modifiable risk factor?

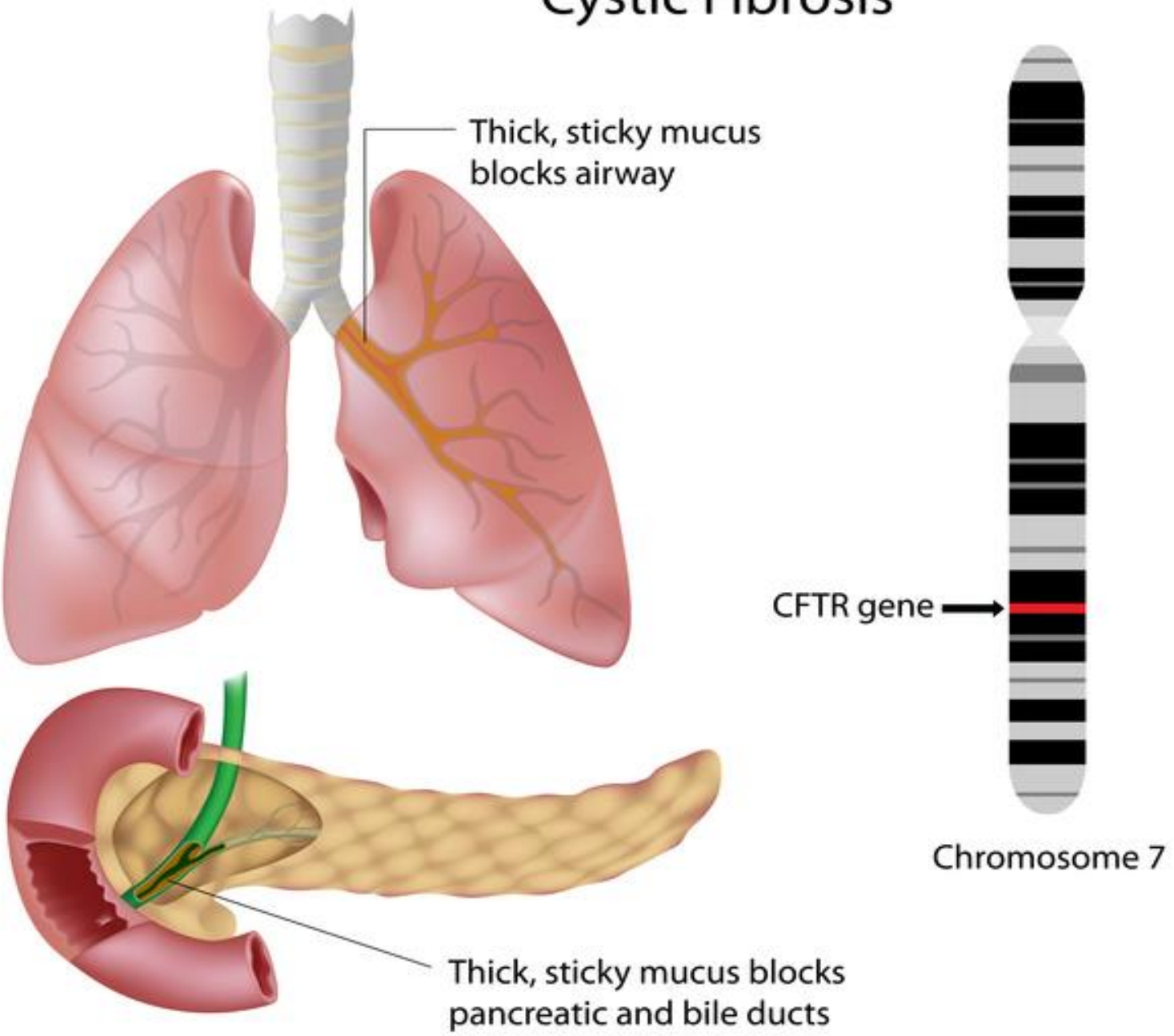
Alpha-1 antitrypsin (AAT) deficiency and smoking cessation

- AAT deficiency
  - Impaired production of alpha-1 antitrypsin, which inhibits neutrophil elastase
  - Increased risk of lung disease (COPD) in deficient patients, particularly those who smoke
- 199 smokers surveyed 3 months following AAT genotype disclosure
  - Patient with severe AAT deficiency more likely to report a 24 hour quit attempt (59%) vs. those who tested normal (26%)
    - At 3 months, no difference in 3-month smoking abstinence rates

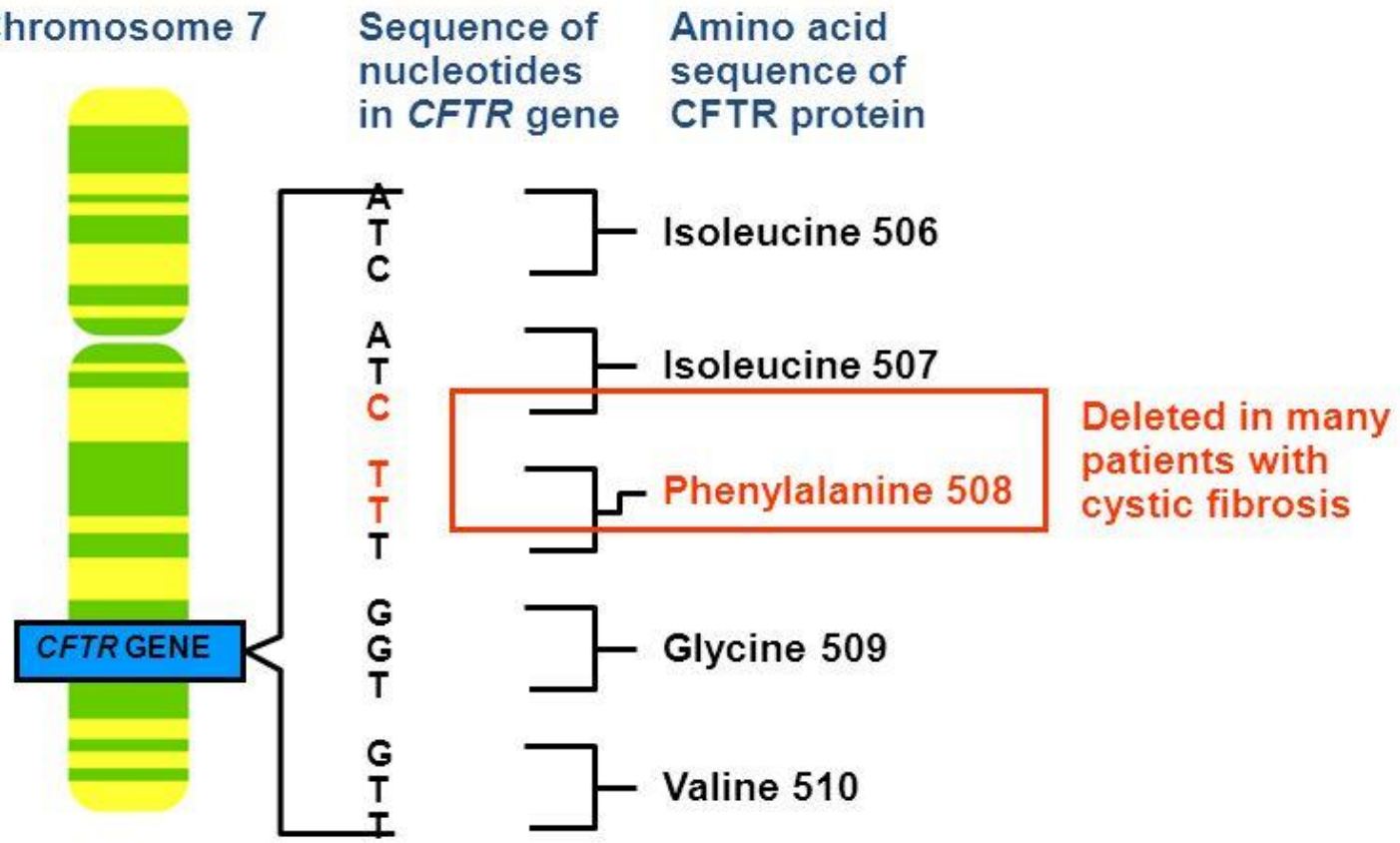
Carpenter et al. 2007;
Graves et al 2014

- Possible factors affecting how genetic information influence behavior
  - Mode of counseling
  - Frequency of counseling
  - High risk/low risk disease, perception of disease severity
  - Perception that behavioral change can significantly influence disease risks

Cystic Fibrosis



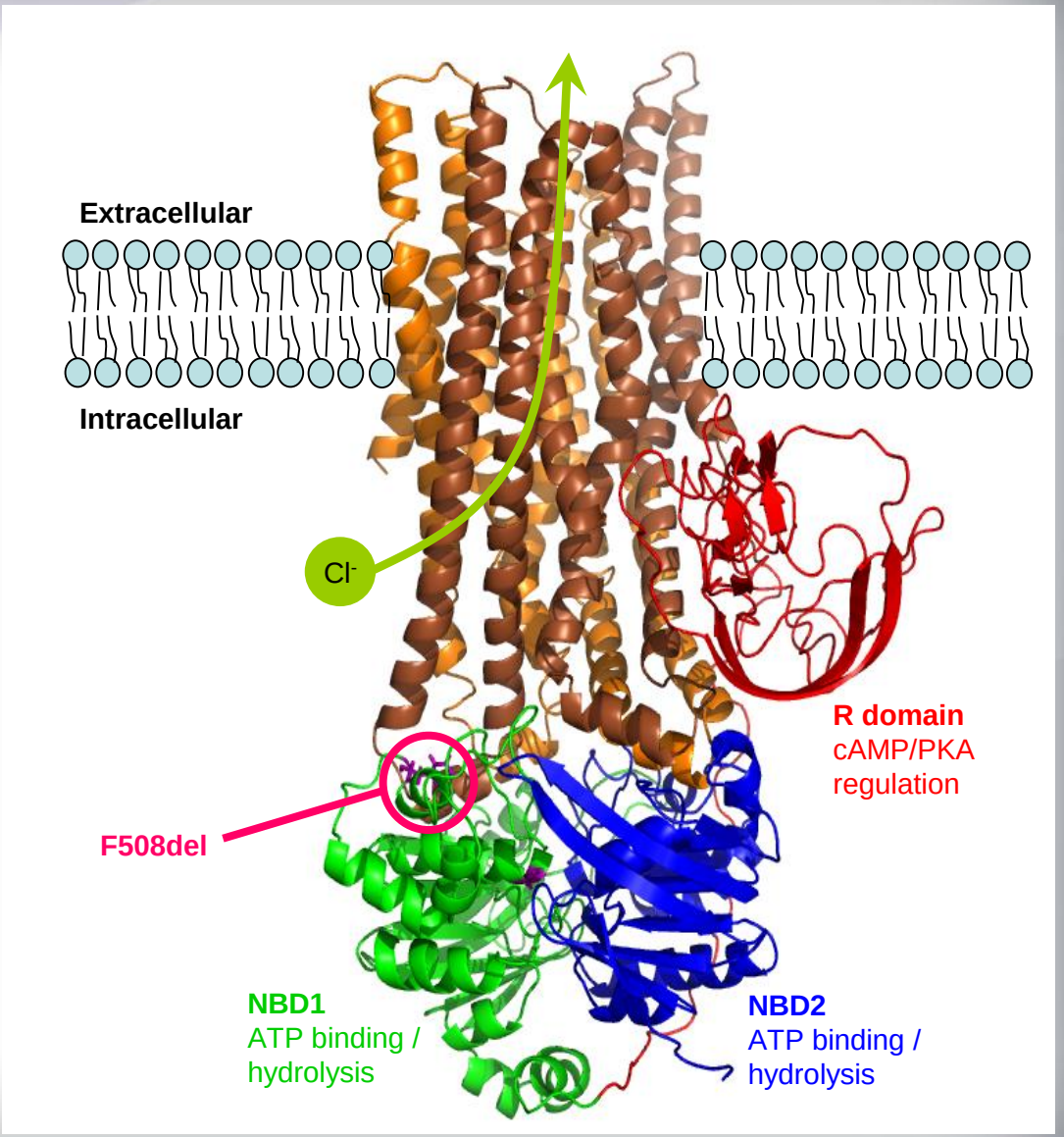
Cystic Fibrosis Gene



Welsh M, Smith A. *Sci Am.* 1995;273:24.

Cystic Fibrosis Transmembrane Regulator (CFTR) Protein

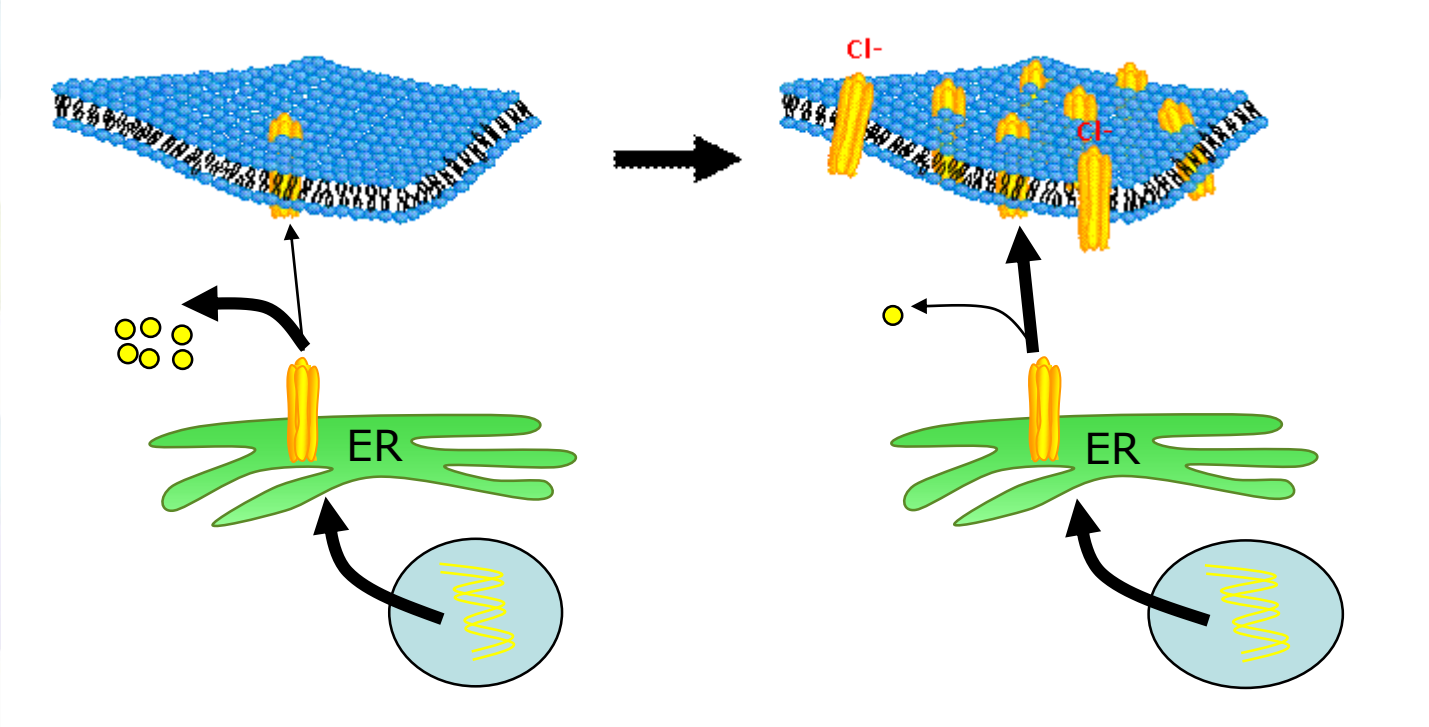
- ~90% of CF individuals have at least one F508del allele
- ~50% have 2 copies (homozygous); ~40% have one copy (heterozygous)
- F508del-CFTR has a protein-folding defect that
  - Inhibits trafficking
  - Enhances degradation
  - Reduces CFTR membrane channel function
- Little to no functional F508del-CFTR reaches the cell surface



Zhang et al. *J Struct Biol* 2009;167:242
CFF Patient Registry 2008 (US)O'Sullivan & Freedman. *Lancet* 2009;373:1891-1904

CFTR Correctors

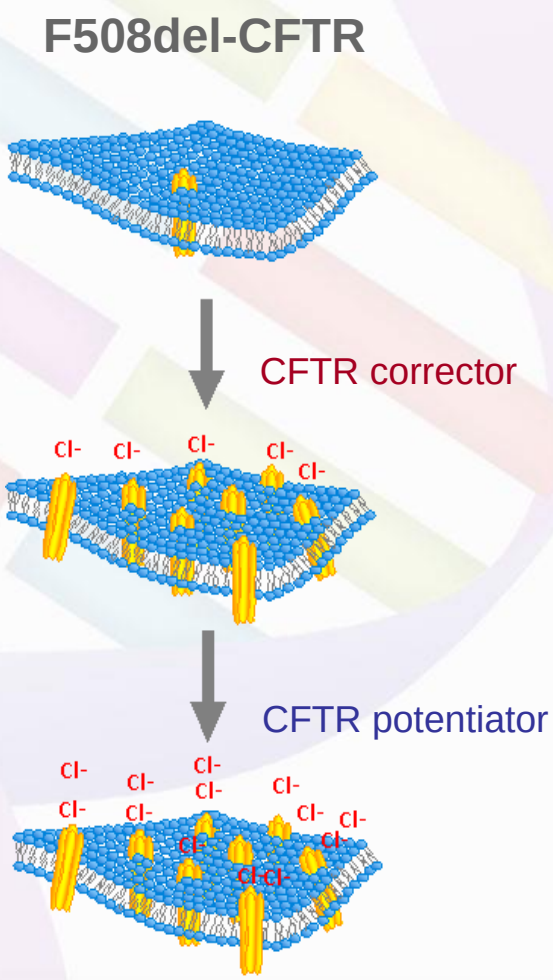
CFTR correctors aim to increase the delivery and amount of functional CFTR protein to the cell surface, resulting in improved ion transport

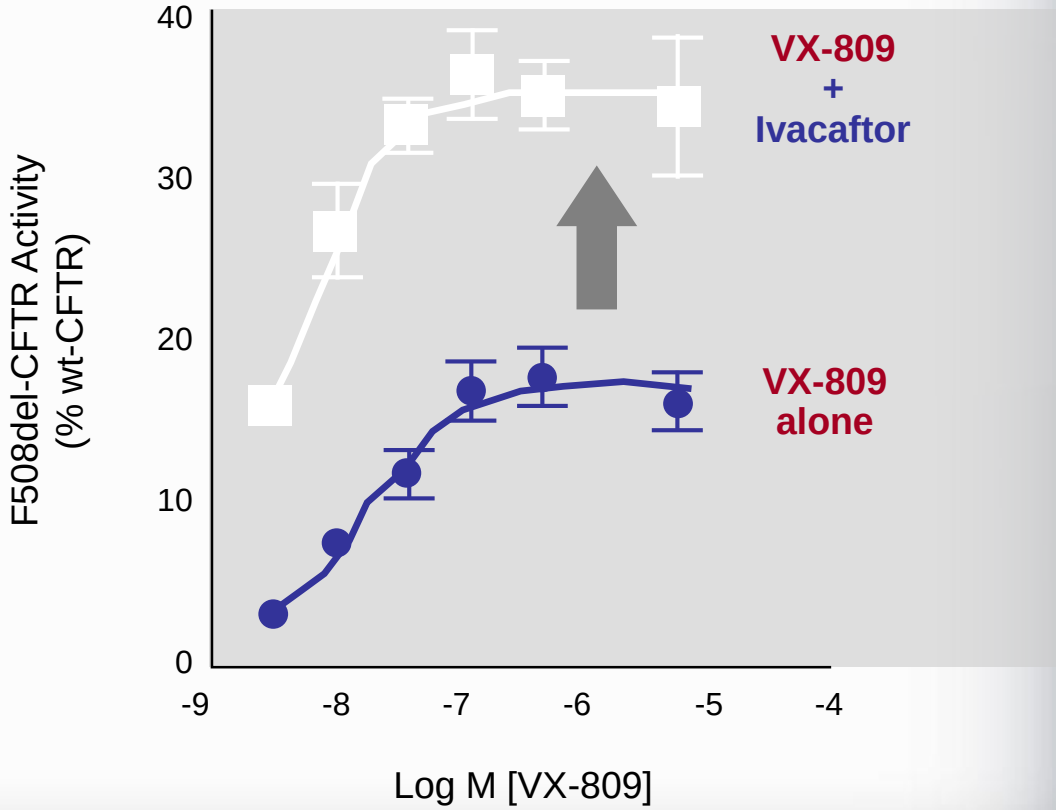


Lumacaftor resulted from a high-throughput screening and medicinal chemistry optimization program to generate F508del-CFTR corrector compounds

Combination Approach: CFTR Potentiator Ivacaftor (Kalydeco) Doubled the Activity of CFTR Corrector Lumacaftor (VX-809)

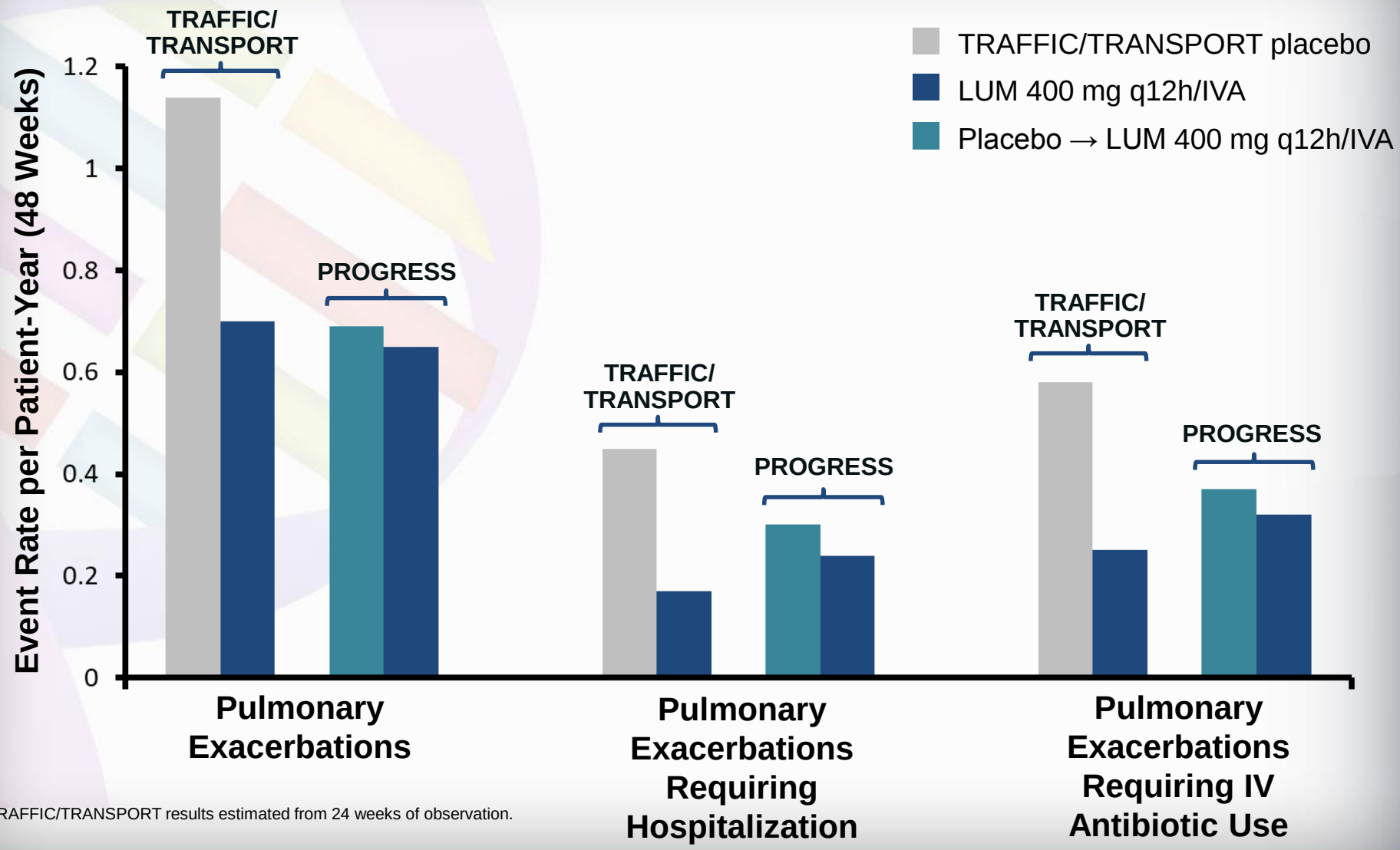
= Orkambi





Van Goor et al. *Pediatr Pulmonol* 2009;44(S32):154absS9.4

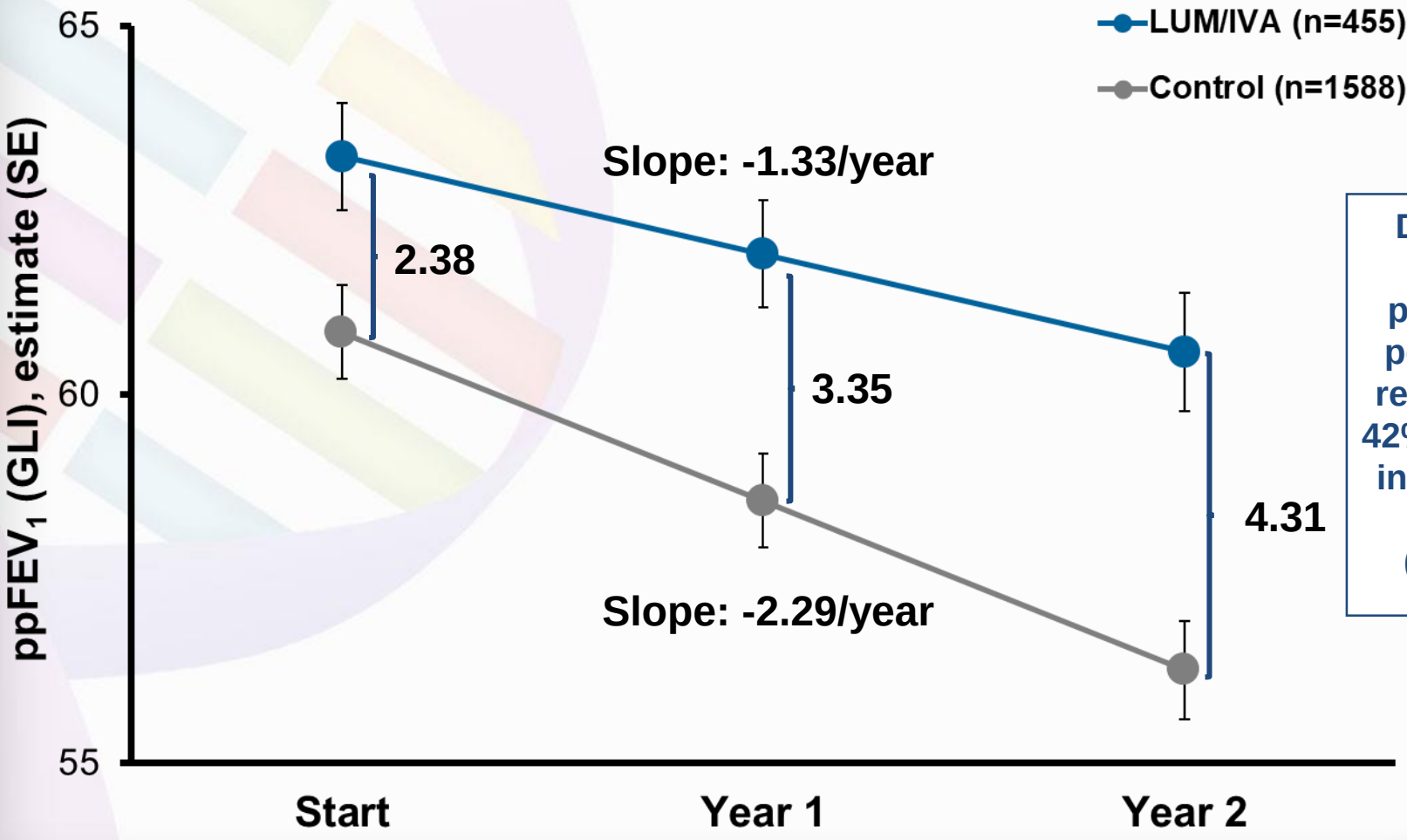
Pulmonary Exacerbation Rate Remained Low With Up to 120 Weeks of Treatment



TRAFFIC/TRANSPORT results estimated from 24 weeks of observation.

Konstan M et al, Lancet Respir Med 2017;5:107-118.

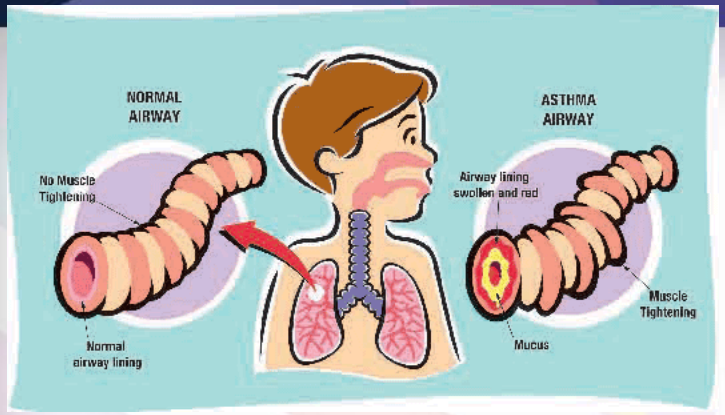
Orkambi Associated With a Slower Annual Rate of Lung Function Decline Than Matched Controls



Difference of 0.97 percentage points/year, representing 42% reduction in the rate of decline (*P*<0.001)

GLI equations. Postbaseline data limited to 2 years. To avoid inclusion of acute lung function improvement with LUM/IVA, visits ≤21 days of treatment initiation were excluded

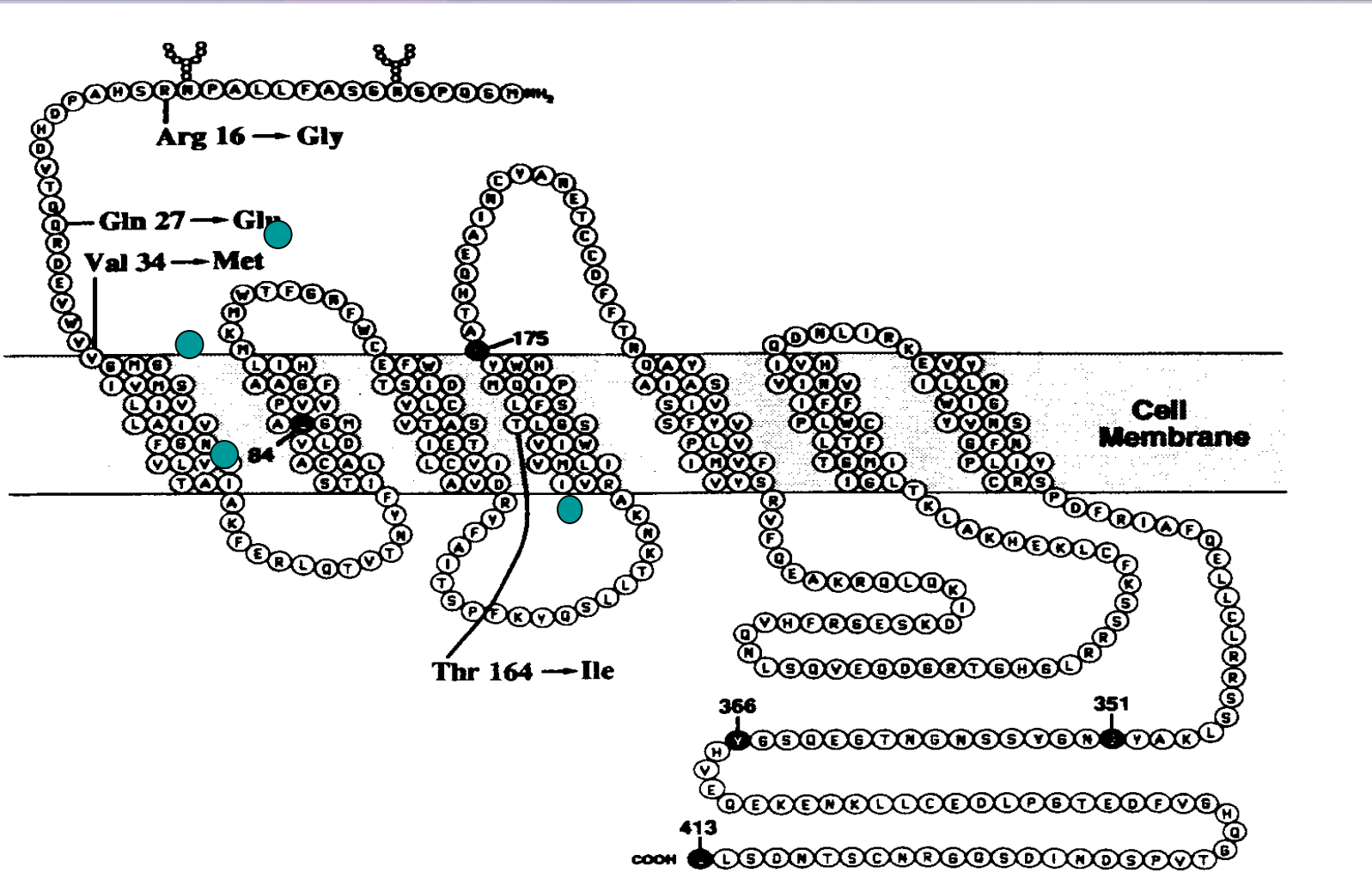
Konstan M et al, Lancet Respir Med 2017 Feb;5(2):107-118.



Pharmacogenomics and asthma

- As many as two-thirds of patients with asthma may not attain full control of their asthma.
- Up to one-third of patients treated with inhaled corticosteroids (ICSs) may not achieve objective improvements in airway function
- However, not simple because host factors such as age, disease severity, concomitant drugs, and disease etiology, can affect responses.

β_2-Adrenergic Receptor Polymorphisms



Reihsaus etal. *Am J Respir Cell Mol Biol.* 1993;8:334-339.

Beta Agonists

β-agonists are the most commonly used medications in the treatment of asthma

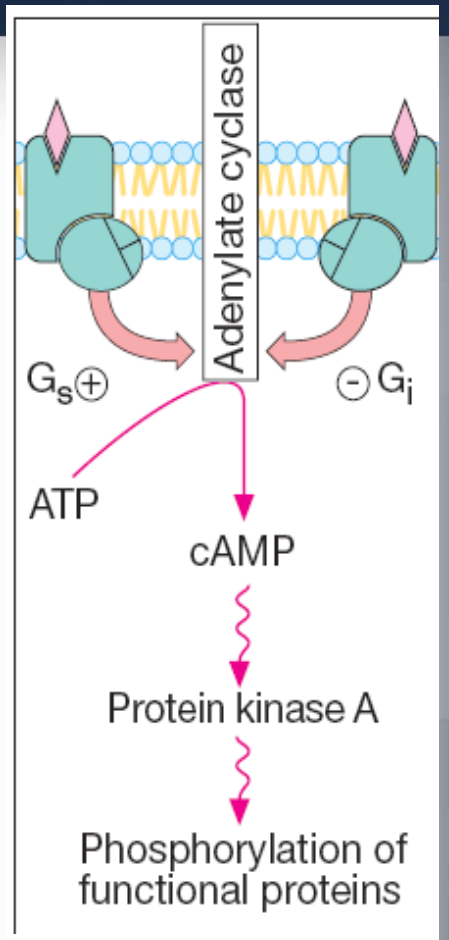
They act by binding to the β_2-adrenergic receptor (ADRB2)

- Receptor binding results in activation of adenylyl cyclase via stimulatory G proteins that activate protein kinase A (PKA)
- Active PKA phosphorylates several target proteins resulting in a decrease in intracellular calcium causing smooth muscle relaxation in the airways

Inter-individual variability in response to β_2-agonists has been reported since the early 1940s

The ADRB2 gene (which encodes ADRB2) has been found to be intronless with over 80 reported SNPs identified

- Two of these polymorphisms (non-synonymous), at amino acid positions 16 {arginine to glycine (Arg 16 Gly)} and 27 {glutamic acid to glutamine (Glu27Gln)} were found to alter receptor function, ligand binding and signal transduction
- Homozygotes of the Arg16 allele are more likely to respond to albuterol compared to homozygotes of Gly16 and heterozygotes



→ ↓ **intracellular calcium → smooth muscle relaxation in the airways**

Beta Agonists

Several other genes in the β_2-agonist pathway have also been investigated in pharmacogenetic studies

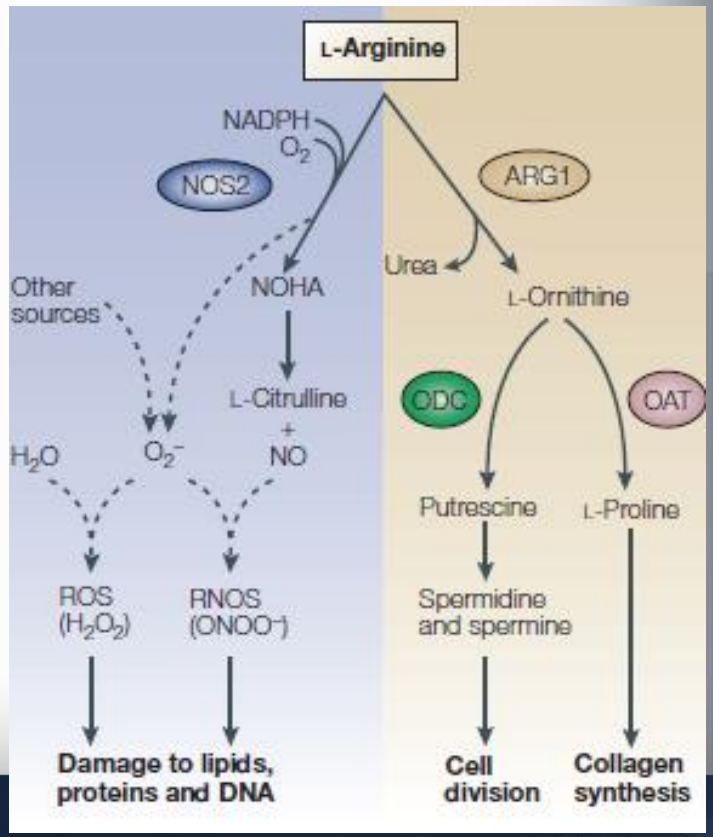
For example a nonsynonymous SNP (isoleucine to methionine at amino acid position 772 (Ile772Met) in the adenylyl cyclase type 9 gene predicts response to β_2-agonists in combination with ICS treatment

- The Met772 allele was associated with increased adenylyl cyclase enzymatic activity in response to β_2-agonists in the presence of an ICS

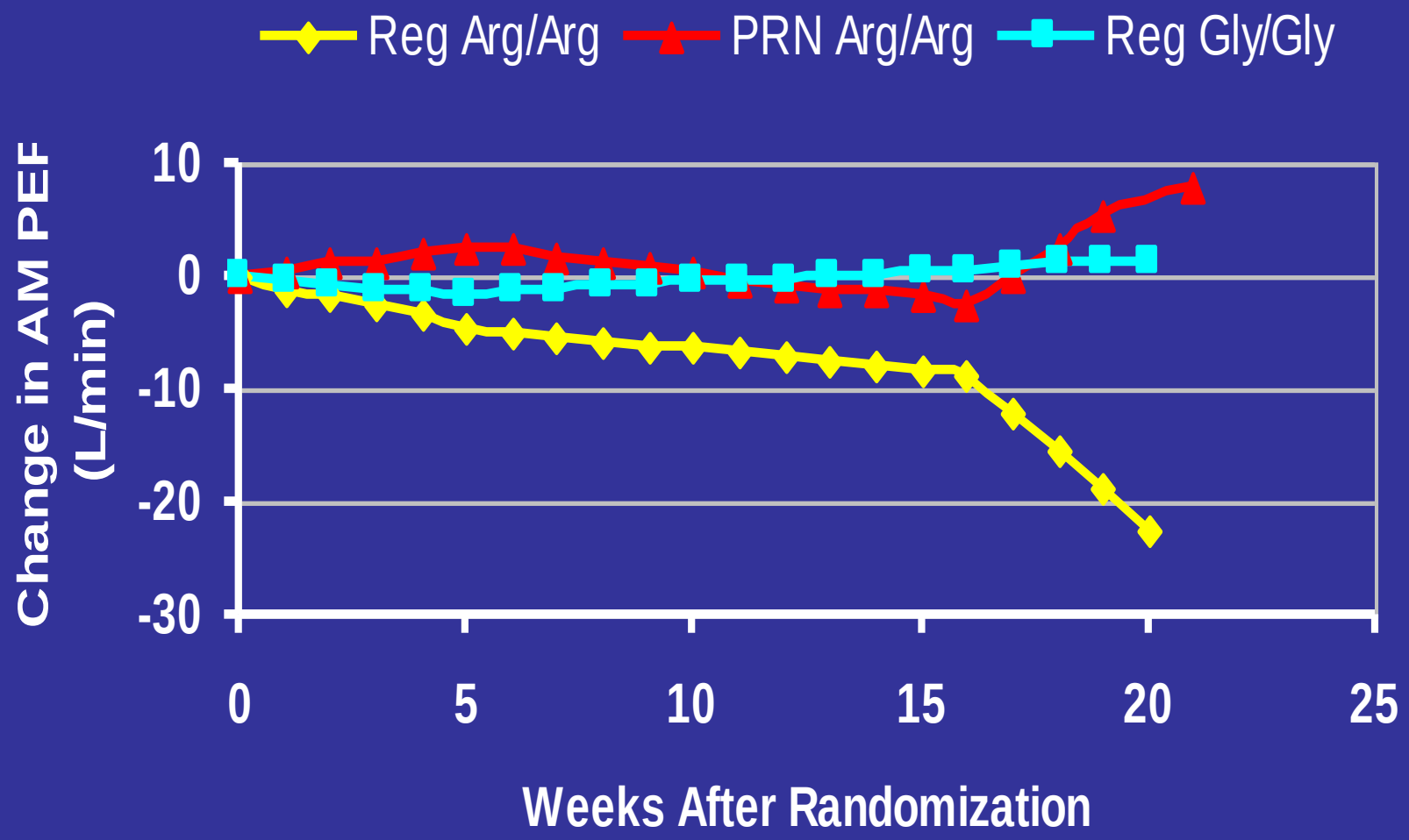
Genes outside the β_2-agonist pathway have also been associated with variable response to these drugs

For example, three SNPs on one haplotype block located in the promoter region of the arginase 1 (*ARG1*) gene were associated with variable β_2-agonist response. This enzyme been implicated in asthma --?

- *ARG1* metabolizes L-arginine, thereby decreasing the production of endogenous nitric oxide (NO; a potent smooth muscle relaxer), leading to the inhibition of smooth muscle relaxation



A Comparison of Response to Albuterol QID or PRN by Genotype



Israel E et al.: Am J Respir Crit Care Med 162; 75-80; 2000

Glucocorticoids

Glucocorticoids (GCs) are the most effective and commonly prescribed anti-inflammatory drugs for the treatment of chronic asthma

MOA: GC therapeutic effects result from the binding of such drugs to the intracellular receptor (GR-α) and other transcription factors to form a complex, which translocates into the nucleus where it regulates the expression of numerous genes

- For example, GCs suppresses the transcription of various pro-inflammatory proteins including interleukins (ILs) 1, 3, and 5
- In addition, GCs decrease the expression of muscarinic receptors on airway smooth muscles, resulting in bronchodilation and airway relaxation
- The therapeutic effects of GCs may also result from increasing the transcription of the β_2-AR in the human lung and bronchial smooth muscles

Despite their effectiveness as anti-inflammatory drugs, oral and inhaled corticosteroids (ICS) have also been associated with several ADRs, especially at higher doses, such as growth retardation among children, adrenal suppression, bone demineralization, immunosuppression, skin reactions and cataract formation

Therefore, reduced doses of ICS are often used in combination with a LABA as an effective and safe treatment option for asthma

Glucocorticoids, MOA in details

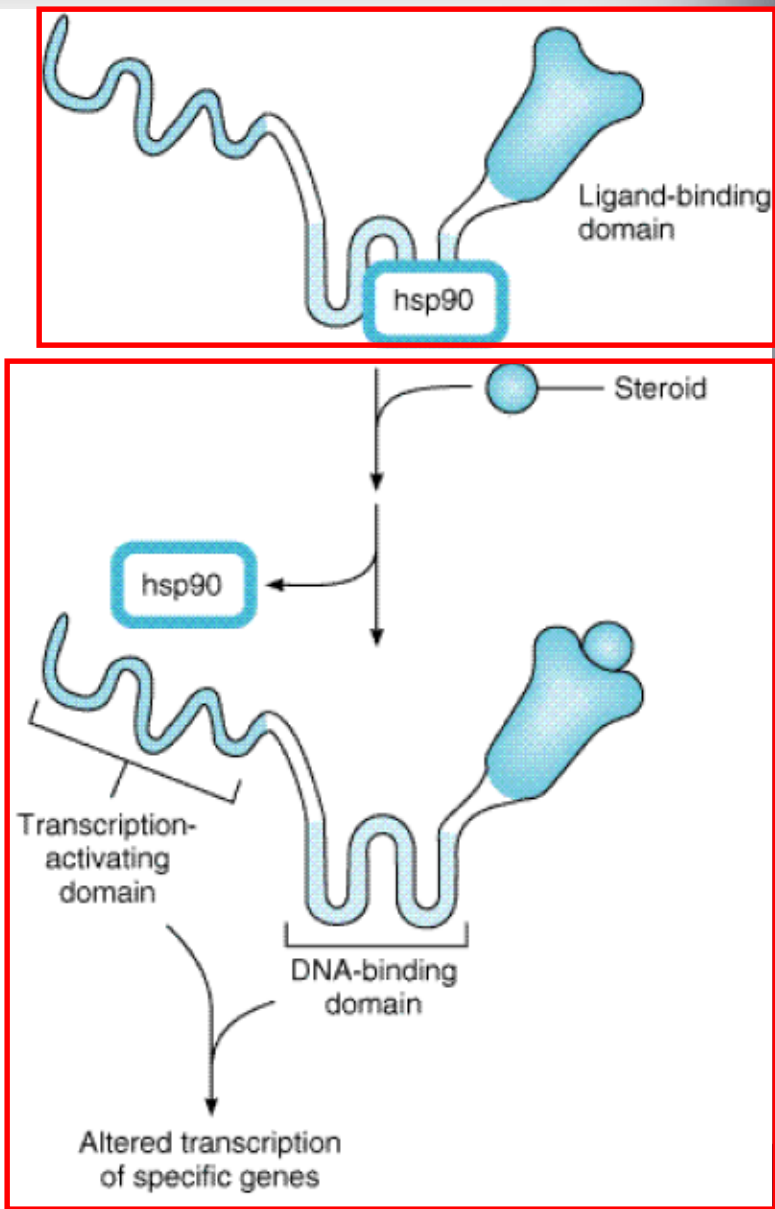
The glucocorticoid effects are initiated by interaction of the drugs with specific intracellular glucocorticoid receptor (GR-α) belonging to the nuclear receptor superfamily

in the absence of the hormone, a heat-shock protein, hsp90, binds to the glucocorticoid receptor polypeptide and prevents folding into the active conformation of the receptor

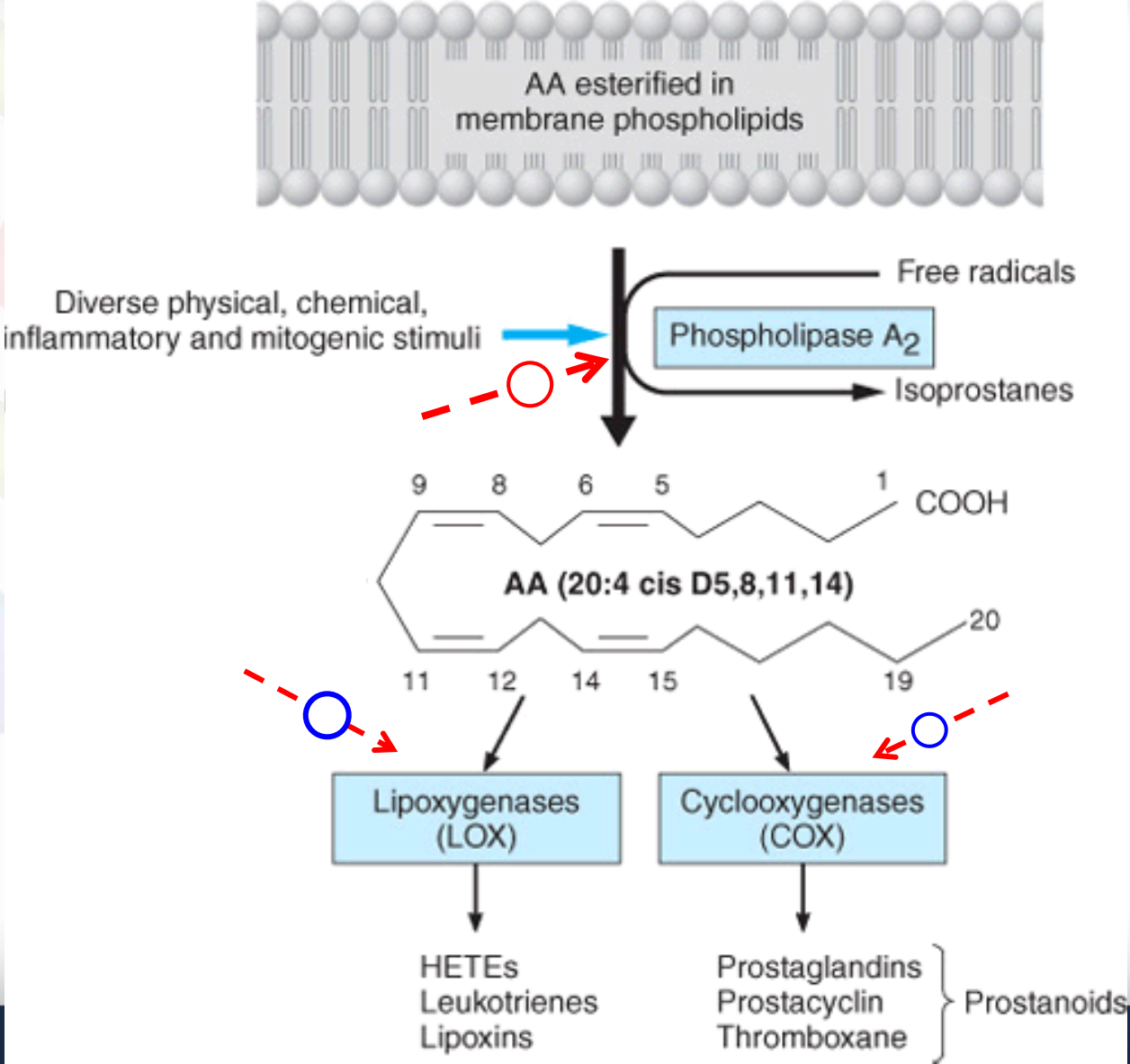
Binding of the hormone causes dissociation of the hsp90 stabilizer and permits conversion of glucocorticoid receptor to the active configuration

The active glucocorticoid receptor binds to +ve or -ve glucocorticoid response elements present in the promoters of target genes, thus bringing about corresponding changes (induction or repression) in transcription → actions (see next slide)

The receptor is eventually recycled in an ATP-dependent process and combined again with hsp90 in the cytoplasm to complete the cycle



Effect of GCs on arachidonic acid release & inflammatory mediator formation



Glucocorticoids, Pharmacogenomics

There is substantial inter- and intra-individual variability in the response to GCs.

- About 5-10% of all asthmatics and up to 35% of severe asthmatics exhibit reduced response to GC therapy
- The incidence of decreased response to GCs is higher among African Americans than Caucasians

Some patients do not respond to even high doses of oral or ICS, which is a condition known as GC resistance. True GC resistant asthmatics (i.e. non-responders to moderate to high daily doses of oral GCs) could have an eight fold higher expression of the GR-α compared to GR-β

GR-β inhibits GR-α -mediated transactivation of target genes. The increased expression of GR-β in inflammatory cells might be a critical mechanism for conferring GC resistance

A number of mutations (15 missense, 3 nonsense, 3 frame shift, 3 splice) in the GC receptor gene (NR3C1) has been found to be associated with GC resistance

- A valine to asparagine substitution at amino acid position 641 was associated with a 3 fold decrease in dexamethasone (DEX) affinity
- A valine to isoleucine change at position 729 resulted in a 4 fold decrease in DEX affinity
- Expression of NR3C1 is regulated by IL-4 and IL-5, which are significantly reduced among asthmatics who are sensitive to GC response compared to non-responders
  - Genetic variants found in IL genes were significantly associated with decreased response to GCs among asthmatics

Leukotriene Modifiers

Leukotrienes (LT- A4, C4, D4, E4) are a family of potent bronchoconstrictor proteins which mediate inflammation and other asthma symptoms

LTs are produced through the metabolism of arachidonic acids by enzymes 5-lipoxygenase (5-LO) and LT-C4 synthase (LTC4S) and are released into the airways by proinflammatory cells such as mast cells, eosinophils, neurophils

LTs bind to receptors such as Cysteine LT_1 to cause smooth muscle contraction and mucus hypersecretion

Leukotrienes modifiers (LTMs) which inhibit LT formation or receptor binding are useful in the treatment of asthma, including 5-LO inhibitors (e.g. zileuton) and leukotriene receptor antagonists (LTRA; e.g. montelukast, zafirlukast)

- This is an important class of asthma therapy due to their safety (especially LTRAs), efficacy, convenient administration (once daily oral intake)

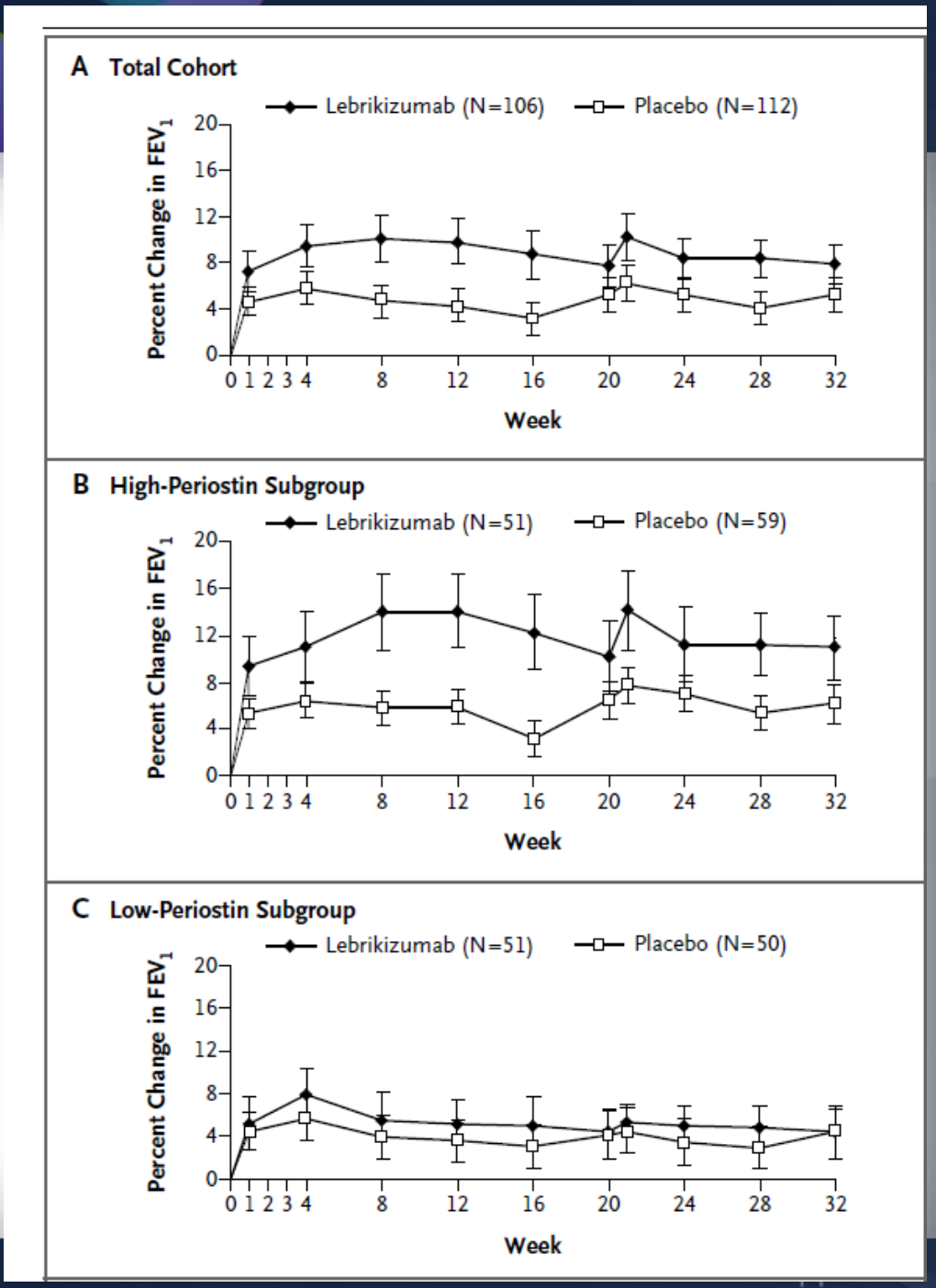
There is significant heterogeneity in response to LT modifiers among asthmatics

A repeat polymorphism in the promoter region of the 5-LO gene (ALOX5) is associated with decreased gene expression, which is associated with cellular and clinical changes in response to LTM therapy

A promoter SNP in the LTC4S gene (C-444A) was found to be more prevalent among severe asthmatics and was associated with increased LT production

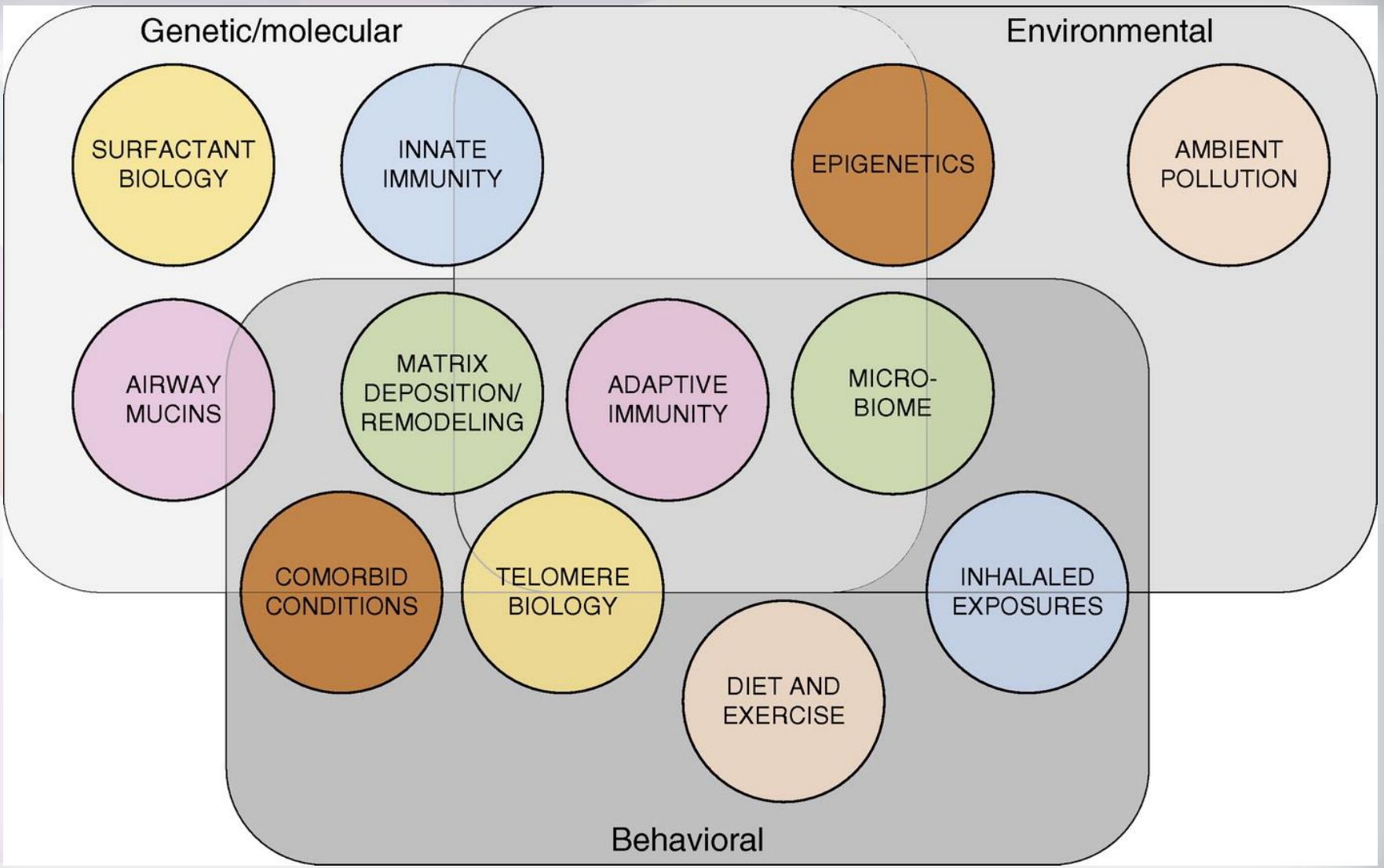
Lebrikizumab treatment in asthma : efficacy related to serum periostin

Lebrikizumab is a monoclonal antibody that neutralizes IL-13.
IL-13 induces bronchial epithelial cells to secrete periostin.
Patients with high serum periostin respond better.



Corren et al NEJM 2011

Idiopathic Pulmonary Fibrosis



https://doi.org/10.1164/rccm.201601-0169CI

Validated Genetic Variants Associated with Idiopathic Interstitial Pneumonias

Gene	Protein	Function	Study					
			Lead Author	Year	Type of Study	Cases	Controls	Ref
SFTPA1	SP-A1	Surfactant	Selman	2003	CGS	84 IPF	194 healthy	24
			Zhang	2012	CGS	1 FIP family		25
SFTPA2	SP-A2		Wang	2009	WGS	59 FIP families		30
			Coghlan	2014	CGS	132 IPF	192 COPD	33
SFTPC	SP-C	Surfactant	Thomas	2002	CGS	1 FIP family		14
			Chibbar	2004	CGS	1 FIP family		15
			Van Moorsel	2010	CGS	22 unrelated FIP, 20 sporadic IIP	100 healthy	16
			Ono	2011	CGS	1 FIP family		17
			Lawson	2004	CGS	89 IPF, 46 NSIP	104 healthy	18
ABCA3	ABCA3	Surfactant	Campo	2014	CGS	1 FIP family		32
			Coghlan	2014	CGS	132 IPF	192 COPD	33
TERT	TERT	Telomere	Armanios	2007	CGS	73 FIP probands	194 healthy	41
			Tsakiri	2007	CGS	46 FIP families	44 sporadic ILD	42
			Mushiroda	2008	GWAS	159 IPF	934	43
			Fingerlin	2013	GWAS	1,616 IIP	4,683	36
TERC	TR	Telomere	Armanios	2007	CGS	73 FIP probands	194 healthy	41
			Tsakiri	2007	CGS	46 FIP families	44 sporadic ILD	42
RTEL1	RTEL1	Telomere	Cogan	2015	WES	188 FIP families		44
			Stuart	2015	WES	99 FIP probands, 78 IPF	2,816	45
			Kannengiesser	2015	WES	35 FIP families	13 healthy	48
DKC1	DKC1	Telomere	Alder	2013	CGS	2 DC families with PF		51
			Kropski	2014	CGS	1 FIP family		52
			Hisata	2013	CGS	1 DC with PF		53
			Safa	2001	CGS	1 DC with PF		54
TINF2	TIN2	Telomere	Fukuhara	2013	CGS	1 DC with PF		56
			Alder	2015	WES	1 FIP family		57
MUC5B	MUC5B	Mucin	Seibold	2011	GWAS	152 IPF, 145 FIP	233	69
			Zhang	2011	CGS	341 IPF	802	71
			Noth	2013	GWAS	542 IPF	542	89
			Fingerlin	2013	GWAS	1,616 IIP	4,683	36
			Stock	2013	CGS	110 IPF, 440 SSc	416	72
			Borie	2013	CGS	142 IPF, 553 SSc	1,877	73

IPF and Precision Medicine

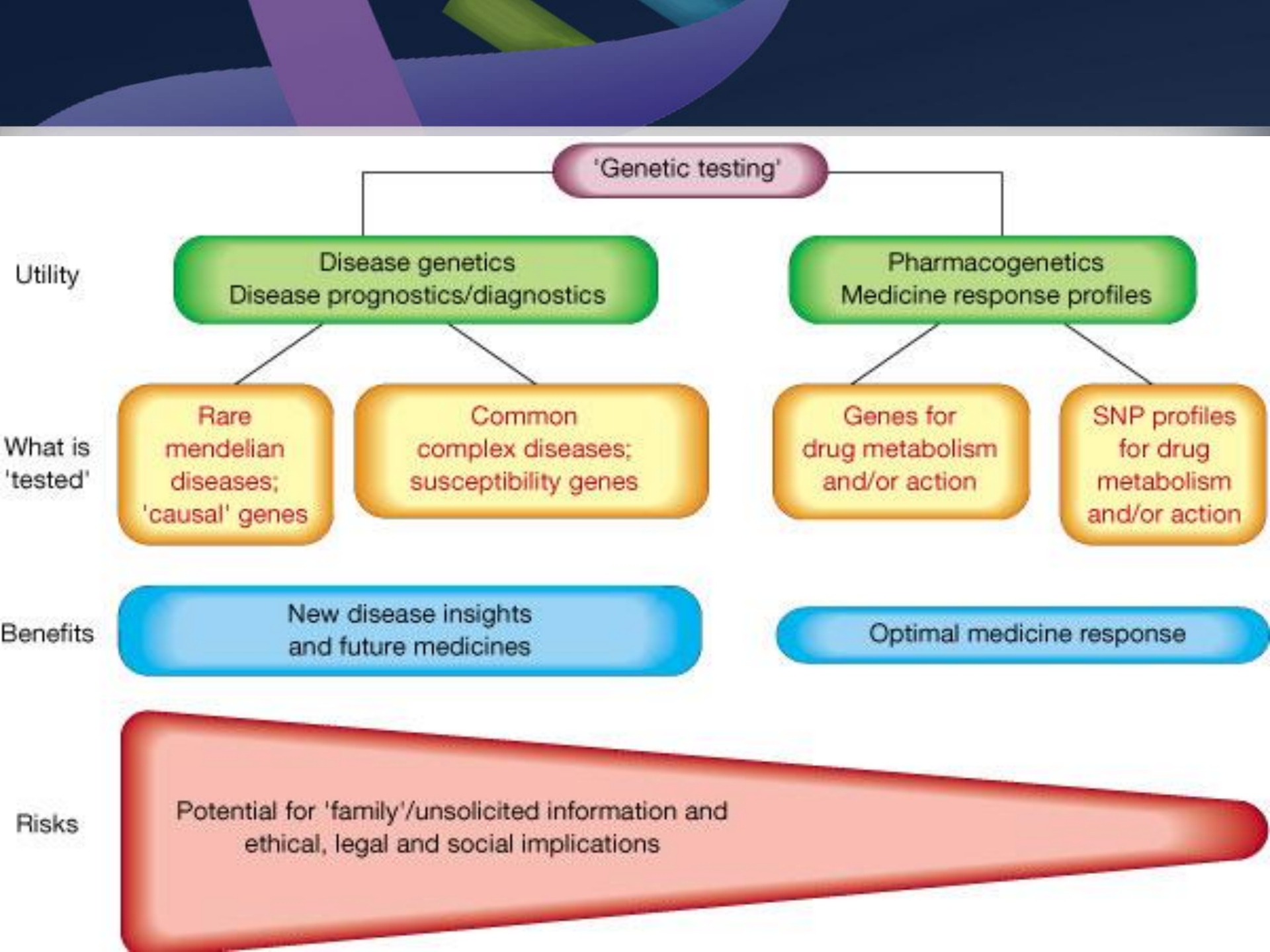
- TOLLIP, MUC5B, and the Response to N-Acetylcysteine
  - SNPs within TOLLIP and MUC5B have been associated with risk of IPF. A recent retrospective review of data from several completed clinical trials in IPF explored a possible pharmacogenomic relationship between these SNPs and response to N-acetylcysteine (NAC) .
- Oral Immunotherapy with Type V Collagen
  - Circulating autoantibodies against type V collagen are detectable in ~40% of patients with IPF. Injury to the lung may expose type V collagen to immune cells and autoimmune-mediated injury. On the basis of this hypothesis, a phase I clinical trial of oral immunotherapy with bovine type V collagen was performed in patients with IPF with circulating anti–type V collagen antibodies.
- Autoantibody Reduction Therapy
  - A subgroup of patients with IPF has circulating autoantibodies against epithelial cells (HEp-2 cells) and heat shock protein-70 that may contribute to parenchymal injury and progressive fibroproliferation. These observations have prompted a phase II clinical trial of rituximab (a chimeric monoclonal antibody against CD20) in IPF that is currently enrolling patients (www.clinicaltrials.gov, NCT01969409).
- Matrix-directed Therapy
  - Elevated levels of circulating LOXL2 (a regulator of collagen crosslinking) have been found in a subgroup of patients with IPF, and it is hypothesized that these patients might be responsive to LOXL2-directed therapy.

Precision Medicine and …

- Pulmonary hypertension
  - A modest proportion of PAH cases are strongly associated with rare genetic variations (mutations) in a single gene, although phenotypic expression of disease remains heterogeneous, even in this more focused genetic circumstance. For example, bone morphogenetic protein receptor type 2 gene (BMPR2) gene mutations are present in more than 75% of families with heritable PAH, as well as approximately 20% of idiopathic PAH cases; however, among subjects with the same (or different) BMPR2 gene mutation, there is reduced penetrance as well as clinical PAH variability, including age of onset.

Lung Cancer

TARGETED THERAPY FOR ADVANCED NSCLC		
AGENT	**TARGET**	**BIOMARKER**
EGFR tyrosine kinase, inhibitors (gefitinib [Iressa®], erlotinib [Tarceva®], afatinib [Gilotrif®])	EGFR tyrosine kinase	EGFR mutation
Anti-EGFR monoclonal antibodies (cetuximab [Erbitux®])	EGFR extracellular domain	EGFR protein expression (IHC)
ALK tyrosine kinase inhibitors (crizotinib [Xalkori®], Ceritinib [Zykadia®])	ALK fusion proteins	ALK protein expression (IHC)
Pan-kinase inhibitors (vandetinib [Zactima®/Caprelsa®])	VEGFR, EGFR, RET, BRAF, CRAF	KIF5B–RET fusion (translocation), KRAS and LKB1 mutation
ROS1 fusion protein (crizotinib [Xalkori®])	ALK gene fusion (translocation);	ROS1 gene fusion (translocation).
Anti-MET monoclonal antibodies (Onartuzumab [MetMab®])	MET receptor tyrosine kinase;	MET protein expression; MET gene copy number
HER2 inhibitors (trastuzumab [Herceptin®])	HER2 receptor tyrosine kinase	HER2 gene copy number or gene mutation.
VEGF-A inhibitors (bevacizumab [Avastin®]) (non-squamous lung cancer)	VEGF-A and VEGFR2	Plasma VEGF-A and VEGFR2


'Genetic testing'
Utility
Disease genetics
Disease prognostics/diagnostics
Pharmacogenetics
Medicine response profiles
What is 'tested'
Rare mendelian diseases; 'causal' genes
Common complex diseases; susceptibility genes
Genes for drug metabolism and/or action
SNP profiles for drug metabolism and/or action
Benefits
New disease insights and future medicines
Optimal medicine response
Risks
Potential for 'family'/unsolicited information and ethical, legal and social implications