# Genetic Testing in 2014

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# Conflict of Interest Disclosure

Dr. Lanpher has no financial interests, arrangements, affiliations, or any bias with any of the corporate organizations offering financial support or educational grants for this program.

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# Why is this Important

Genetic Testing expanding exponentially

So is the cost

Insurance coverage spotty and unpredictable

Results complex, unclear and may be misleading

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# Why Do Any Test

Determine diagnosis
Determine treatment
Determine prognosis
Determine risk
Determine recurrence/family risk

Genetic testing can help with all

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# Two Types of Testing

## Reactive

- Something is wrong with the patient and you want to find out what.
- Useful to know what else might go wrong
- Useful to know who else might have the same thing.

## Predictive or Proactive

- Want to know if something might go wrong or how someone will respond to an external stimulus (drugs)
- Very very early stages of utility
- Most advanced is pharmacogenetics
- Does not always produce actionable data
- Massive amounts of work before this is useful.

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# Test Selection Factors

Information quality

Cost

Utility of information

Ability to process information

Time to result

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# Testing: It's a matter of resolution

Karyotype or Chromosome Analysis is low resolution but very well established. Great for trisomies, rearrangements, large missing pieces. Can get fast. If testing all patients seen in genetics about 3-5% yield

Chromosome Microarray (CGH) is much higher resolution (latest 1 million probes). Very well established. Great for trisomies, and small duplications and deletions. If testing all patients seen in genetics about 26% yield. In non-syndromic developmental delay about 10-15%

Sequence Analysis very useful in targeted situations of suspected genes. Usually confirmatory. Newer whole exome sequencing returns about 5,000 positive results per patient. Whole genome about 10,000,000. Slow. Data processing most complex part.

# Cytogenetic Resolution

1 kb = 1,000 base pairs
1Mb = 1,000,000 base pairs

Metaphase karyotype = 5-10Mb
High resolution karyotype = 3-4Mb
FISH = 30-40 kb
CMA= 1-5 kb

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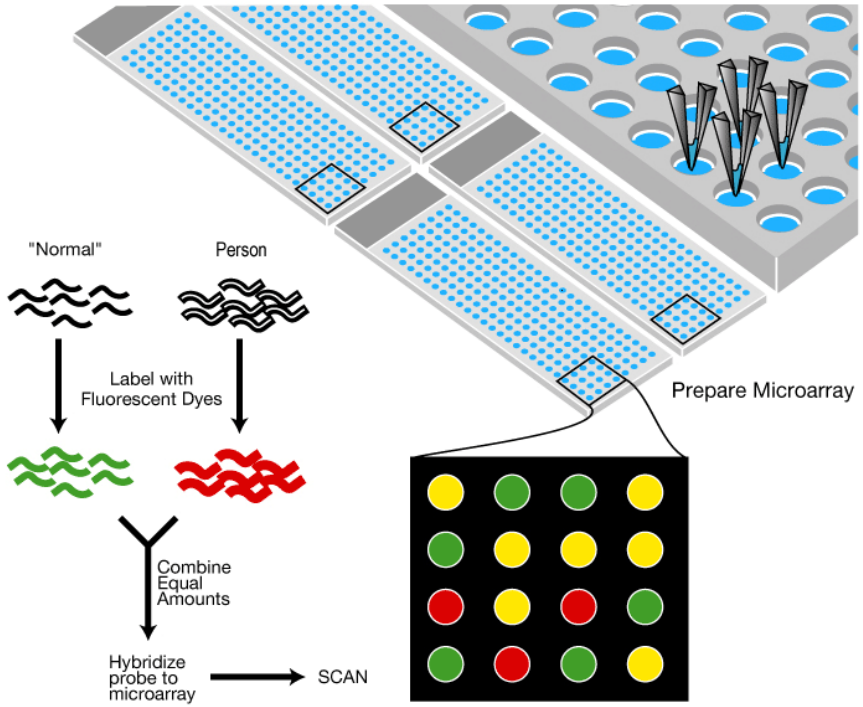
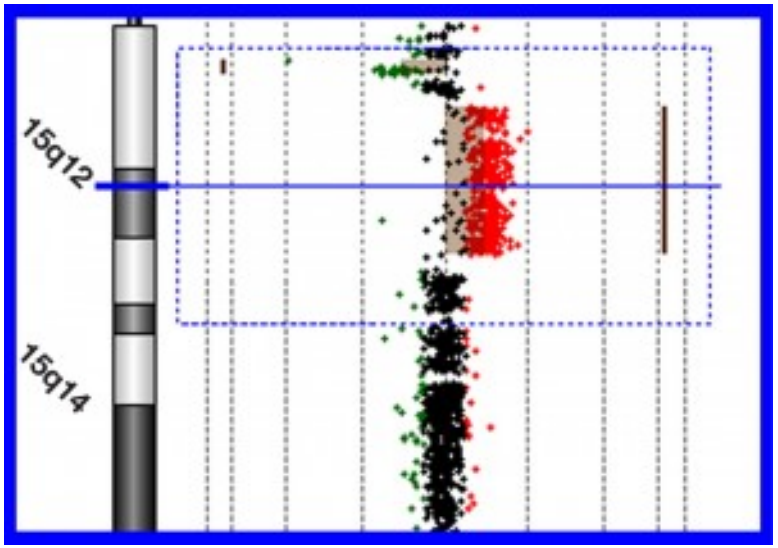
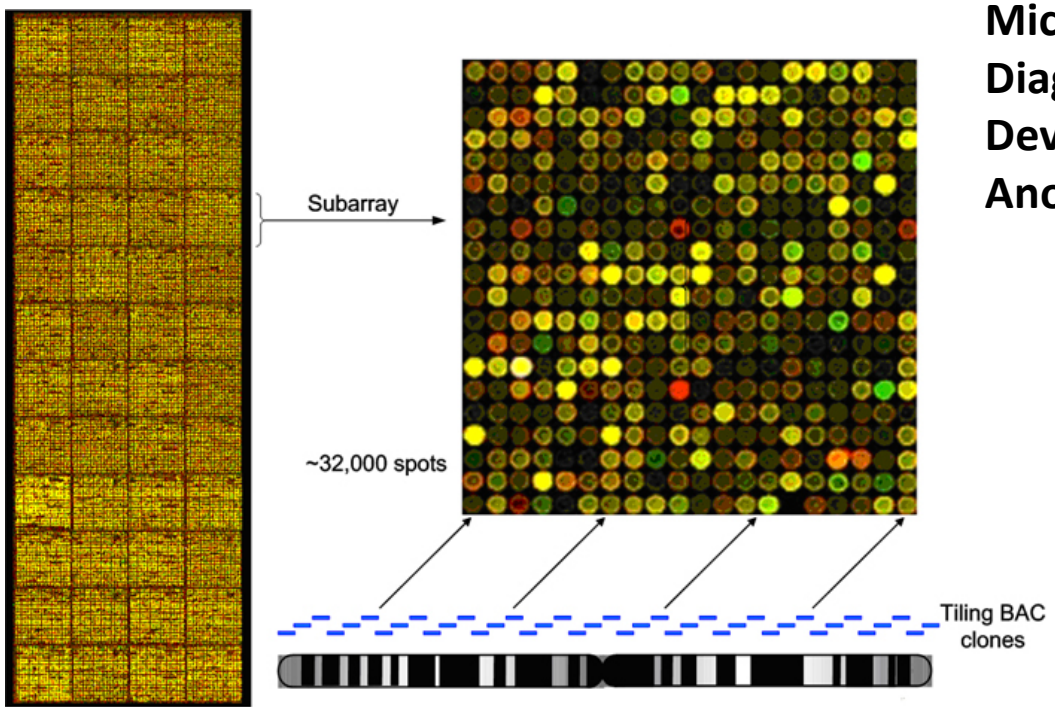



**Consensus Statement: Chromosomal Microarray Is a First-Tier Clinical Diagnostic Test for Individuals with Developmental Disabilities or Congenital Anomalies (AJHG, 2010)**

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# Chromsome Microarray

For patients with Developmental delay (including autism) the positive hit rate is 10-20%

Testing costs about $1500-$3000 and takes about 4 weeks to get back (getting better)

Many Variants of Unknown Signficance (VOUS) which require interpretation. About 20% but dropping.

Will not detect balanced rearrangements.

Variable detection of mosaicism

Is now the standard of care in genetics clinics for first line workup of Multiple Congenital Anomalies, DD, Autism, etc.

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# Complex results - CMA

Clinical History:Imperforate anus, multiple congenital anomalies

CYTOGENETIC RESULT: arr[hg19]2q21.1(131,477,947-131,933,576)x1

INTERPRETATION and COMMENTS: Copy Number Variation Identified: Unclear Clinical Significance (Interpret with caution). Genes involved: GPR148, AMER3, ARHGEF4, FAM168B, PLEKHB2 (http://www.ncbi.nlm.nih.gov/omim) An approximately 456 kb loss on chromosome 2 at 2q21.1 was detected. This deletion has recently been described as a rare, recurrent deletion that may be associated with developmental delay (DD)/intellectual disability (ID), ADHD, epilepsy and other neurobehavioral abnormalities [Dharmadhikari AV, et al., Hum Mol Genet. 2012 Aug 1;21(15):3345-55. doi: 10.1093/hmg/dds166. Epub 2012 Apr 27. PMID:22543972]. However, the clinical significance of this deletion in a newborn is unclear and ongoing genotype-phenotype correlation is recommended.

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# Importance of Definitions

POLYMORPHISM vs MUTATION vs VARIANT

- Old Common usage: >1% in the population is a polymorphism
  - Polys are "non-deleterious"
- Mutations are supposed to cause molecular pathophysiology.
- The lines are blurring:
  - common changes have deleterious effects in one situation and beneficial in another.
  - Example: hemochromatosis (c282y) change found in 10% of caucasian population. Affects iron storage
- Common report terminology is Variant with a comment on its effect.
  - If unknown then "Variant of Unknown Significance

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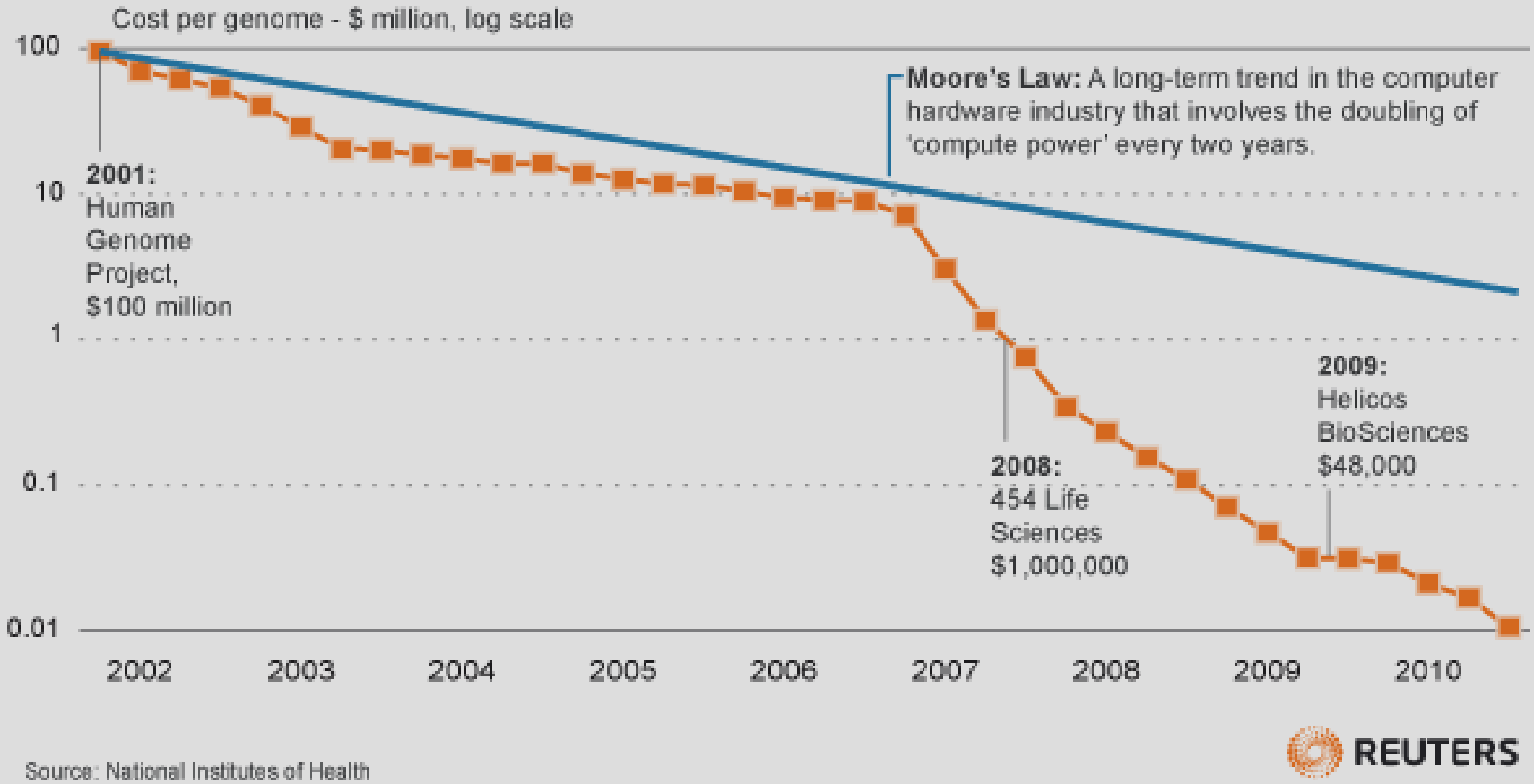
# DNA sequencing costs have gone down




Source: National Institutes of Health

Reuters graphic/Van Tsui 05/01/12

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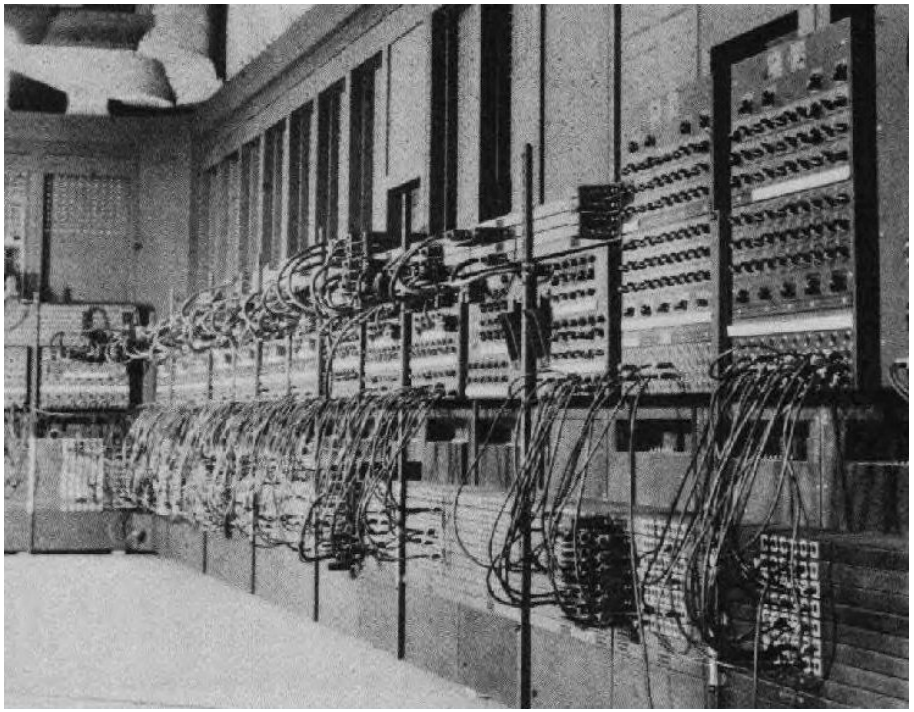
# Challenge: informatics

If you want to store the data in a raw format for later re-analysis, you're looking at **between 2 and 30 terabytes** (one terabyte = 1,000 gigabytes). A much more user-friendly format, though, would be as a file containing each and every DNA letter in your genome, which would take up around **1.5 gigabytes**



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# Limitations of Genetic Testing

Variable penetrance.  Changes may not always lead to disease.

Software systems for “friend or foe” determination of sequence variation are only fair.

Existing tests often look for the most common mutations, some disease causing mutations will not be detected in different ethnic groups.

Small chance of errors in testing procedure.

Testing is not always matched by treatment.

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# Functional Testing as a Surrogate for DNA testing

Biochemistry (blood/urine/CSF levels)

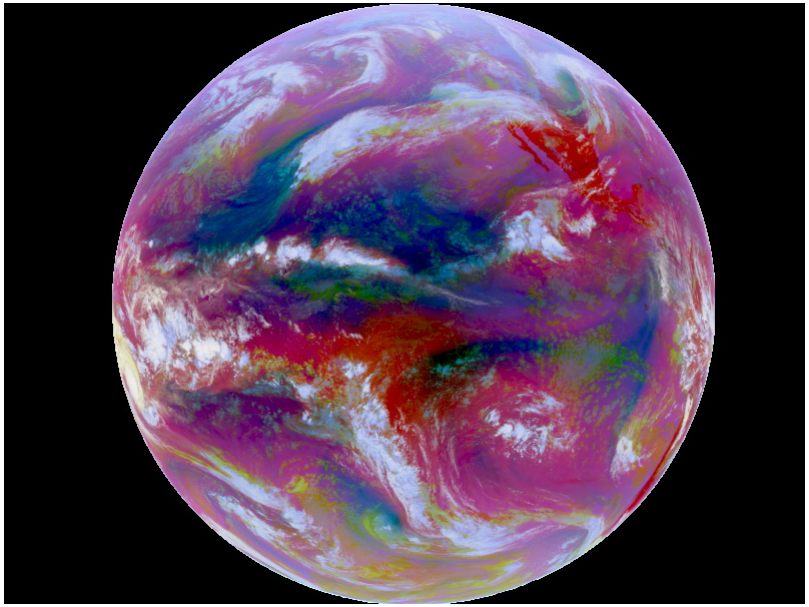
Newborn Screening

Enzyme function

Tissue staining

Protein Characteristics

A good exam.



Advantages

- One test many mutants
- Biologic relevance is clear

Example

- High ammonia reflects 8 urea cycle genes and at least 6 organic acid genes

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# Whole Exome (typically 18-22K genes)

Sounds great right?

Nature Genetics 2010 (N Genetics 42, 969-72, 2010)

- 200 normal adult Danes
- 18,654 genes sequenced per individual
- 121,870 single nucleotide variations
- 53,081 were coding changes

The biggest cost/burden of whole exome is interpretation and informatics. Non-deleterious changes vary from population to population. Expect up to 5000 variants per individual.

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# Whole Exome Sequencing – In Practice

Need trios (both parents and patient)

Results never completely normal

Most often with possible answers, rarely definite

- Functional studies may not be possible

Significant issues with incidental findings

- Adult onset disease
  - Cancer, cardiac, neurodegenerative
- Carrier status

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*Test(s) Requested:* Diagnostic Testing / XomeDx / Whole Exome Sequence Analysis

*Clinical Indication:* One-year-old male with a history of ataxia, chorea, seizures, optic atrophy, brain atrophy, hypomyelination, growth retardation, hypotonia, microcephaly, motor delay, speech delay, stiffness, nystagmus, and twitching of eyes. Pelizaeus-Merzbacher disease was included in the differential diagnosis.

A sample from this individual's mother (GeneDx# 1332000) and father (GeneDx# 1332001) were also submitted for variant segregation analysis by whole exome sequencing.

*Result Summary:*

**1. No definitive explanation for the cause of the phenotype in this patient was identified by this analysis.**

**2. Variants in genes possibly associated with the reported phenotype:**

- **Homozygous for the R751G variant of unknown significance in the AARS gene**

**3. Variants in the candidate genes with a potential association to the phenotype:**

- **Hemizygous for the C301S variant of unknown significance in the TAF1 gene**

**The results of the mitochondrial genome sequencing and deletion analysis are provided in the attached report.**

**1. Definitive Mutations in Disease Genes Associated with Reported Phenotype:**

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# Specific Testing in Practice: Ground Rules

A Genetics Consult is cheaper than any one genetic test. ($300 vs $3-10,000+)

Genetic counseling must be done before and after the testing. Manage expectations (takes time!)

Since they take awhile to return make sure someone is tracking the results. (return time is months)

Anticipate that the answer may be ambiguous. The reports are purposefully done this way. (average review time >2-3 hrs)

Fill out the clinical profile for the test. This will greatly help interpretation by the lab.

Remember that a negative test does not completely rule any genetic disease

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# How Can We Help

Children's National Genetics and Metabolism

- 202-476-6287
- 13 Medical Geneticists (11 double in Biochemical)
- 15 Genetic Counselors
- Tracking Following Counseling Diagnosis Testing
- Genetics@childrensnational.org

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# Personalized Medicine

## The Promise

- Determine health risk
- Drug metabolism
- Best care practices
- Better health

## But

- Needs correlation between DNA sequence and risk
- What is actionable?
- Population and environment specific.
- Ethics


Not there yet.

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# Personalized Medicine by the Numbers

## Growth

- 13 prominent examples of personalized medicine drugs, treatments and diagnostics products available in 2006
- 72 prominent examples of personalized medicine drugs, treatments and diagnostics products available in 2011

## Drug Use

- 1% of marketed drugs have a companion diagnostic
- 10 % of marketed drugs inform or recommend genetic testing for optimal treatment
- 33 pharmacogenomic biomarkers are included on FDA-approved drug labels

Personalized Medicine Coalition. The Case for Personalized Medicine. 2011

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# Economics

34% reduction in chemotherapy use would occur if women with breast cancer receive a genetic test prior to treatment

17,000 strokes could be prevented each year if a genetic test is used to properly dose the blood thinner warfarin

$604,000,000 annual cost savings to the health care system if patients with metastatic colorectal cancer receive a genetic test for the KRAS gene prior to treatment

Personalized Medicine Coalition. The Case for Personalized Medicine. 2011

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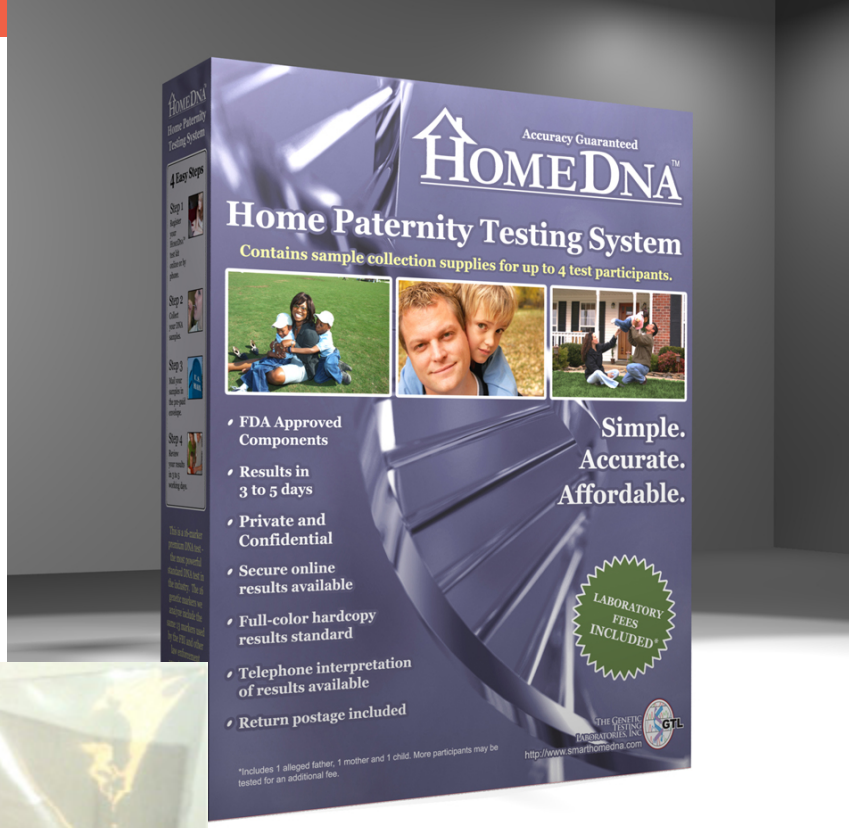





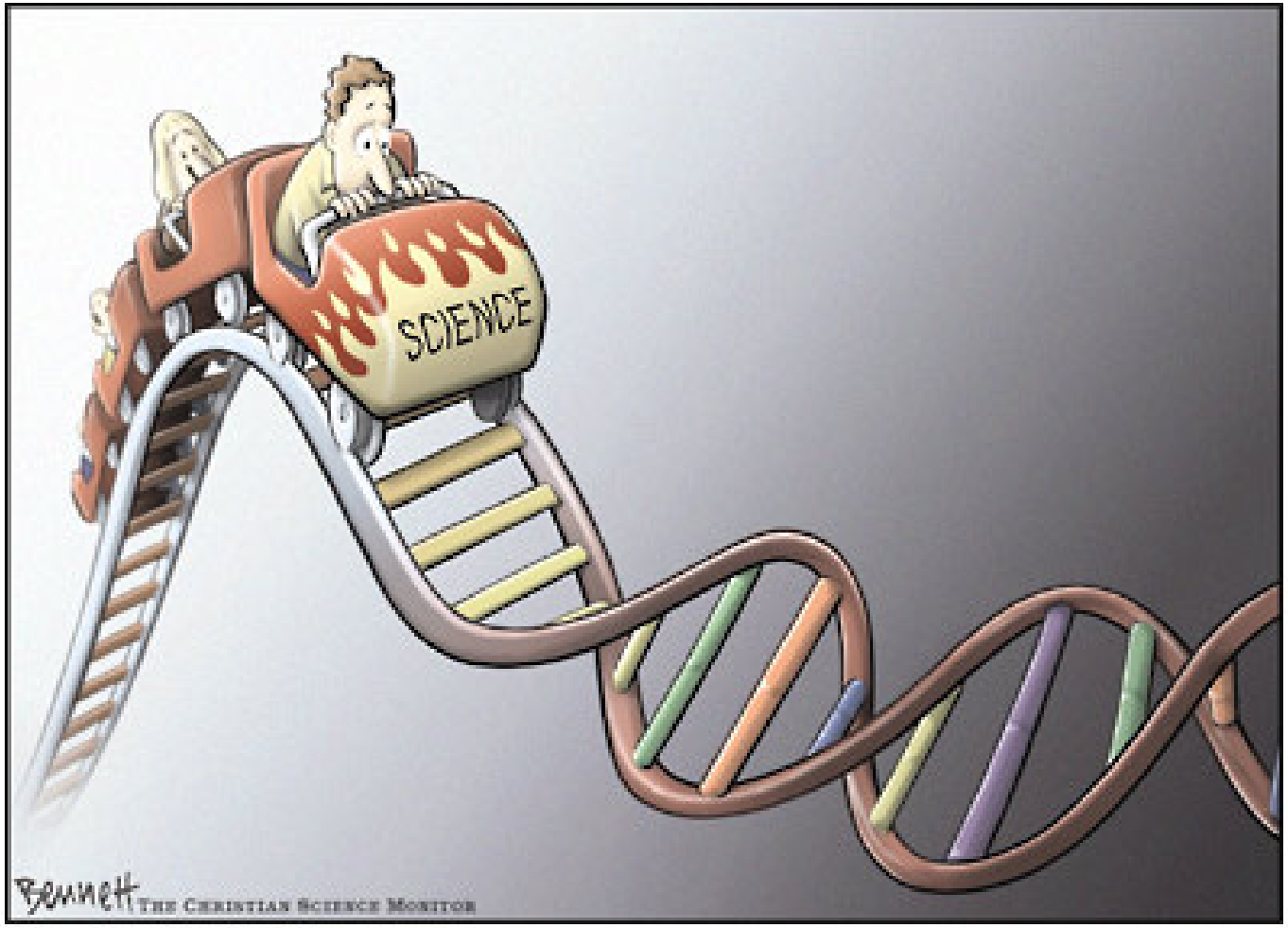


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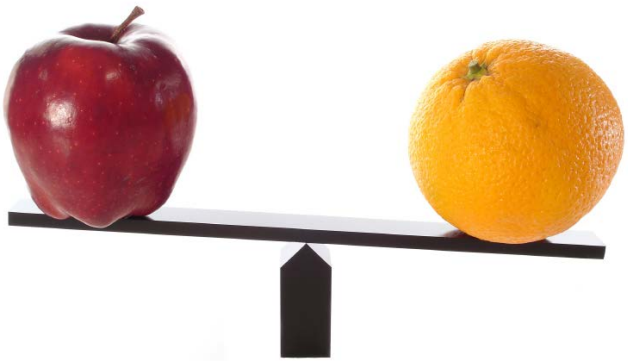
# Consumer Based Testing



Direct to Consumer

- 23andMe, KnowMe, Navigenics

Nutrigenomics

- Sciona, Genelex, Market America, Suracell

Ancestry Testing

- Genographic,GeneTree, DNAPrint

Skin and Hair Care

- HairDx, Dermagenetics

Canine Breed Analysis

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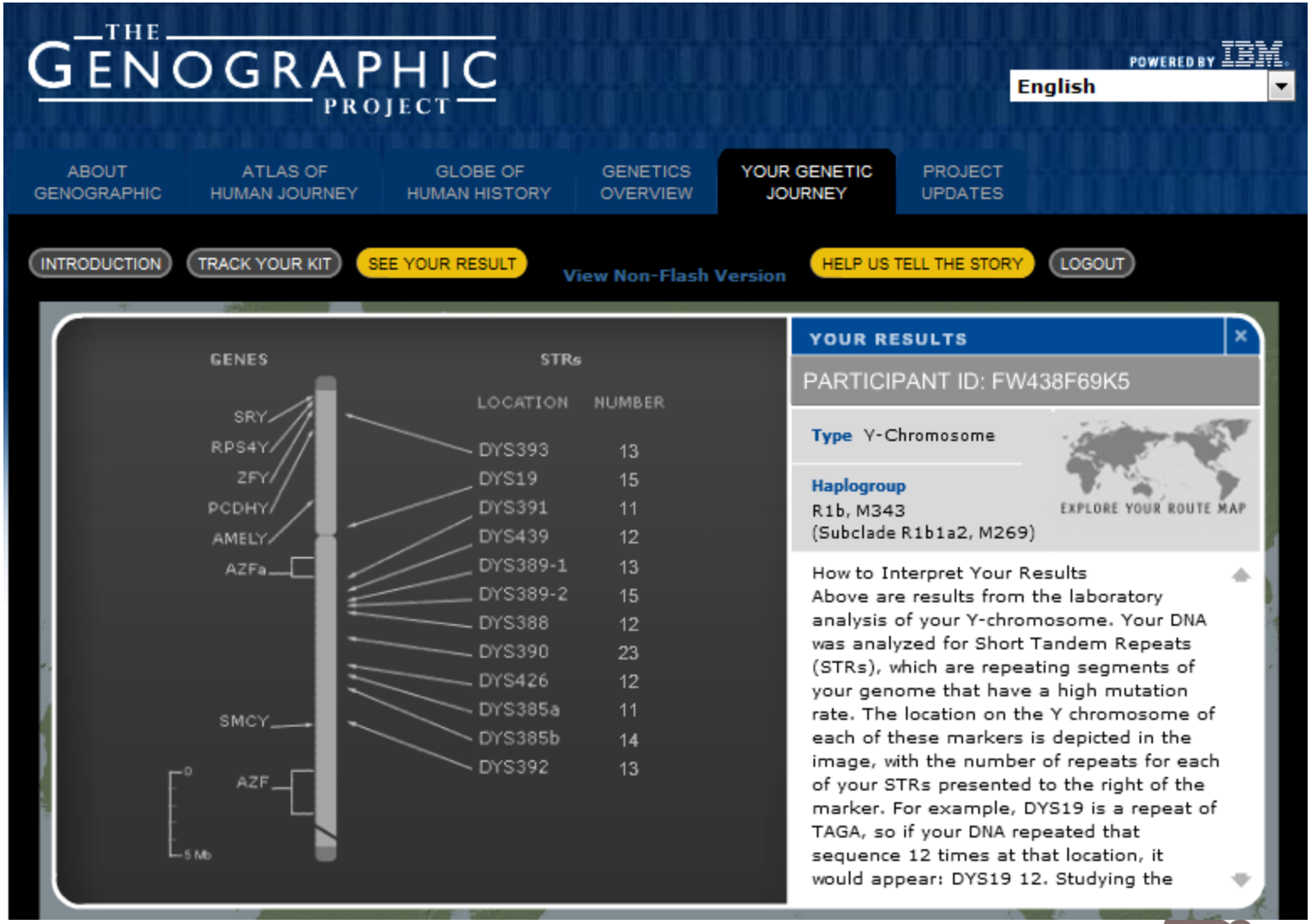


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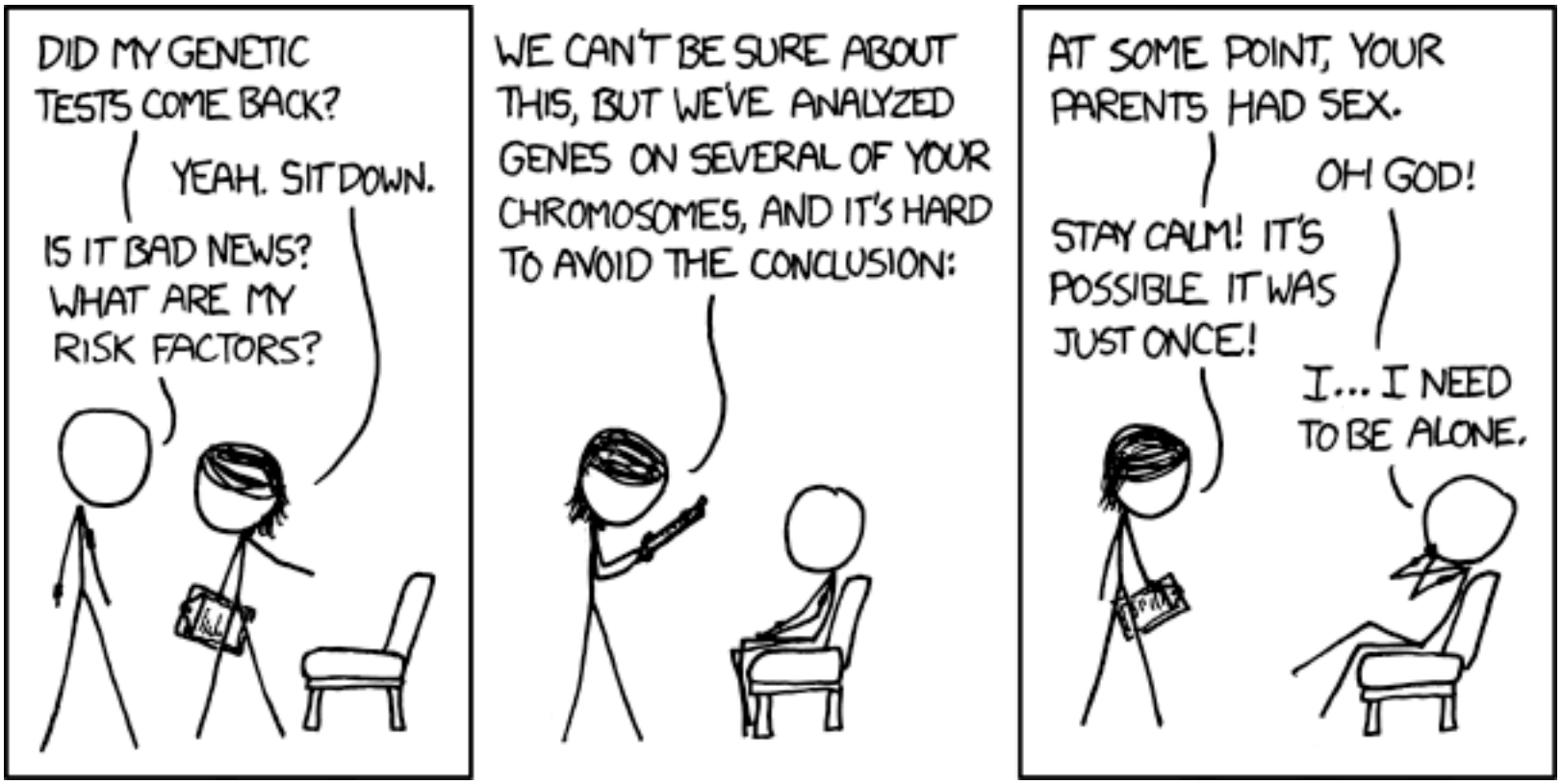
# Questions?

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