Low Dose Aspirin Therapy

An Example of Personalized Medicine

- In patients with a history of cardiovascular disease (CVD), aspirin therapy reduces the risk of serious cardiovascular events by about 16 per 1000 person-years
- In healthy people, aspirin therapy prevents only about 0.6 CVD events and causes about 0.3 major gastrointestinal bleeding events per 1000 person years
- The United Stated Preventive Services Task Force published guidelines for aspirin use in primary prevention that are intended to prevent a greater number of cardiovascular events than the number of major bleeding events caused

Aspirin in Primary Prevention of CVD

"Encourage women age 55 to 79 years to use aspirin when the potential benefit of a reduction in ischemic strokes **outweighs** the potential harm of an increase in gastrointestinal hemorrhage."

"Encourage men age 45 to 79 years to use aspirin when the potential benefit of a reduction in myocardial infarctions **outweighs** the potential harm of an increase in gastrointestinal hemorrhage."

Men		Women	
Age	10-Year CHD Risk, %	Age	10-Year Stroke Risk, %
45–59 y	≥4	55–59 y	≥3
60–69 y	≥9	60–69 y	≥8
70–79 y	≥12	70–79 y	≥11

Aspirin Therapy: Balancing Prevention and Harms

USPSTF Task Force Recommendations for Men

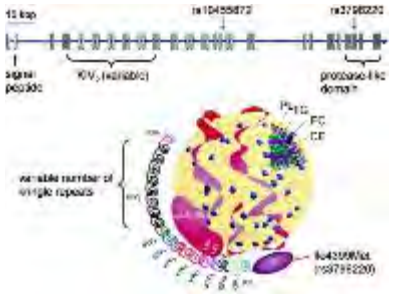
10-Year CHD Risk (%)	MIs Prevented (per 1000 men)
20	64
19	60.8
18	57.6
17	54.4
16	51.2
15	48
14	44.8
13	41.6
12	38.4
11	35.2
10	32
9	28.8
8	25.6
7	22.4
8	19.2
5	16
4	12.8
3	9.6
2	6.4
1	3.2

Harms*	Age
37	70 to 79
25	60 to 69
9	45 to 59

*GI bleed or hemorrhagic stroke

USPSTF *Annals Intern. Med.* 2009; **150**:396

Risk Variants in the *LPA* Gene



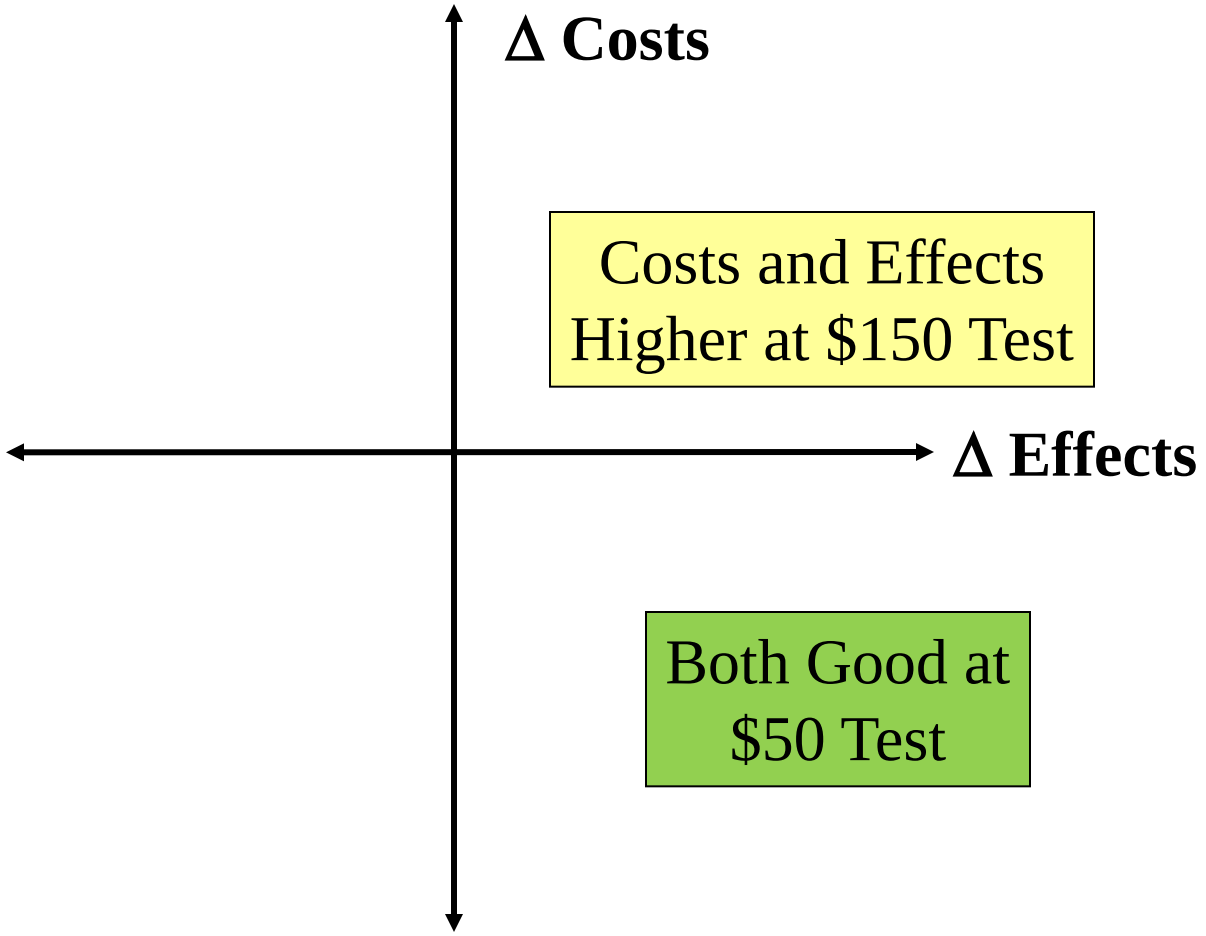
- Two SNPs in the *LPA* gene, which encodes apolipoprotein(a), are associated with both risk of CVD and with concentrations of lipoprotein(a), a plasma lipoprotein that is associated with CVD
- One variant, present in 3.2 % of people, confers an increased risk of 69%. The other variant, present in 6% of people, confers an increased risk of 42%
- Genetic information was combined with traditional CVD risk factors to produce a modified 10 year risk estimate which was applied to the USPSTF guidelines for aspirin use in primary prevention of CVD in a representative USA patient population
- The incremental cost effectiveness of testing *vs* no testing was estimated in terms of the incremental cost per quality-adjusted life-year (QALY) gained

LPA Cost Effectiveness Analysis Model

Final Result for a Theoretical 1,000,000 Person Plan

Patients tested for LPA	20,510
CVD events Prevented	65
GI events caused	49
Cost of testing	$3,076,521
Costs of events	($1,066,662)
Total Cost	$2,009,859
Cost/CVD event prevented	**$30,846**
Cost/QALY	**$24,942**

Interpretation of LPA CEA Results



Reimbursement of Genomic Tests

- Absent evidence of clinical utility and cost-effectiveness, private and public payors may default to non-reimbursement
- Basis for reimbursement of WGS is uncertain; at $1,000 - $15,000 per interpreted indication, single clinical indications may not be cost-effective (except perhaps for cancer indications). How to assess the cost-effectiveness of WGS for multiple clinical indications & payors over a lifetime?
- Due to inaccuracy issues (at current WGS error rate of 0.01%, 300,000 variants will be false) targeted confirmatory testing of some actionable variants may be necessary and will increase overall costs

Other Reimbursement Issues

- FDA approval of a test does not necessarily mean it will be reimbursed by medical insurers
- Have payors (Blue Cross, United Healthcare, Medicare), Government Benefits Administrators (Palmetto), Pharmacy Benefit Managers (CVS Caremark), professional associations (ASCO, NCCN[1]), and patient support groups (American Melanoma Association[2]) taken on the role of determining which diagnostics and therapies will be paid for (and therefore provided) rather than what a patient's physician decides is medically indicated?

[1] onco*type* DX® breast cancer assay - likelihood of distant recurrence

[2] ZELBORAF® - BRAF V600E positive metastatic melanoma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Obesity
New genetic tests can point to risks—but not always a cure
BY BONNIE ROCHMAN

Disclosure, Privacy, and Ethical Issues

- How much genetic information should be disclosed, to whom, and when?
- In the Facebook era: “Privacy is dead; deal with it”, is genetic privacy important to people?
  - Health Information Privacy and Protection Act (HIPPA)
  - Genetic Information Non-Discrimination Act (GINA)
  - Personal Genome Project (participants forego privacy)
- Non-Invasive Prenatal Testing and reproductive rights
- Changing standards of Informed Consent
  - Genome data, health and trait information create a risk for re-identification

Typical Academic Informed Consent for Research

Please feel free to ask questions and discuss your preferences with the study team members. They will help you complete the table. If you do nothing, you will be told. However, if you wish not to be told, please initial where indicated below.

What choices do I have for receiving these other results that do not have direct impact on care of my current cancer?	**If you do NOT want to be told of these results, please initial the boxes below.**
1) Results that may have **significance for biological family members**.	
2) Results that are **not related to your cancer,** but may have **potential medical impact for you**.	

5.2 What are the risks of genetic research?

There are some risks to receiving genetic results. Participants could experience risks such as psychological or emotional distress, loss of insurance, loss of employment, discovery of previously unknown health conditions, discovery that you are not the biological parent of a child(ren), or discovery that you could carry a gene for a certain disease, etc. Therefore, we offer **genetic counseling** before participation in the study as part of the informed consent process.

The Institute of Medicine's Model Case

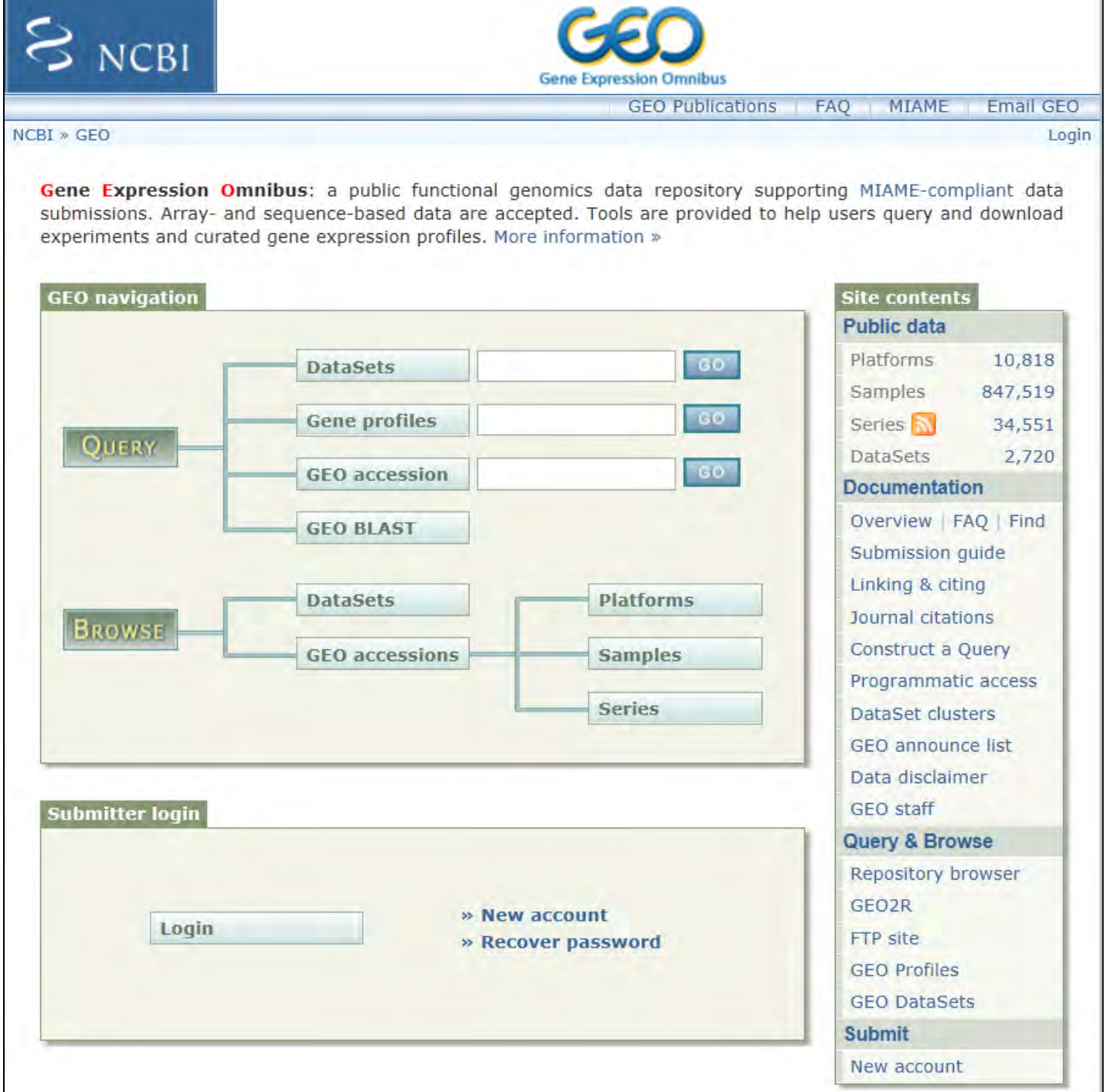
- Preconception visit of a 30 year old Ashkenazi female smoker. Targeted testing reveals that she is a carrier of a mutation that causes Tay Sachs Disease. WGS identifies variants that confer elevated risk for Alzheimer's Disease and deep vein thrombosis (DVT), and two variants that indicate she is likely to be at high risk of bleeding from a standard dose of anticoagulation therapy
- At age 40, she presents with a DVT and will receive anticoagulation therapy
- At age 50, she presents with a lung mass that reveals a non-small cell lung cancer. A WES of her tumor (compared to her previous germline WGS) finds variations that suggest treatment with a targeted therapy

Scenarios for Disclosing WGS/WES Results

- Disclose only the results immediately relevant to the person's current clinical needs
  - Pre-conception test: Carrier for Tay Sachs
- Disclose both the results that are immediately relevant and other results that are "actionable"
  - Carrier for Tay Sachs
  - Elevated risk for DVT: avoid oral contraceptives & HRT
  - If DVT, treat with a lower dose of warfarin
- Disclose all the results
  - Carrier for Tay Sachs; tumor has EML4-ALK variant
  - Elevated risk for DVT & Alzheimer's; Rx lower dose warfarin

Impact of Genomic Research on Drug Discovery

- Genetic variants associated with a disease will be more rapidly analyzed as targets for new drugs
- An NIH database can be searched to see whether the gene is expressed in relevant tissue(s) and phenotypes
- Reagents (protein, siRNA, antibody, cellular) and biological assays may be available for study of the variant's (or potential drug's) mechanism of action
- An animal model with the modified gene may exist for testing the effect of potential new drugs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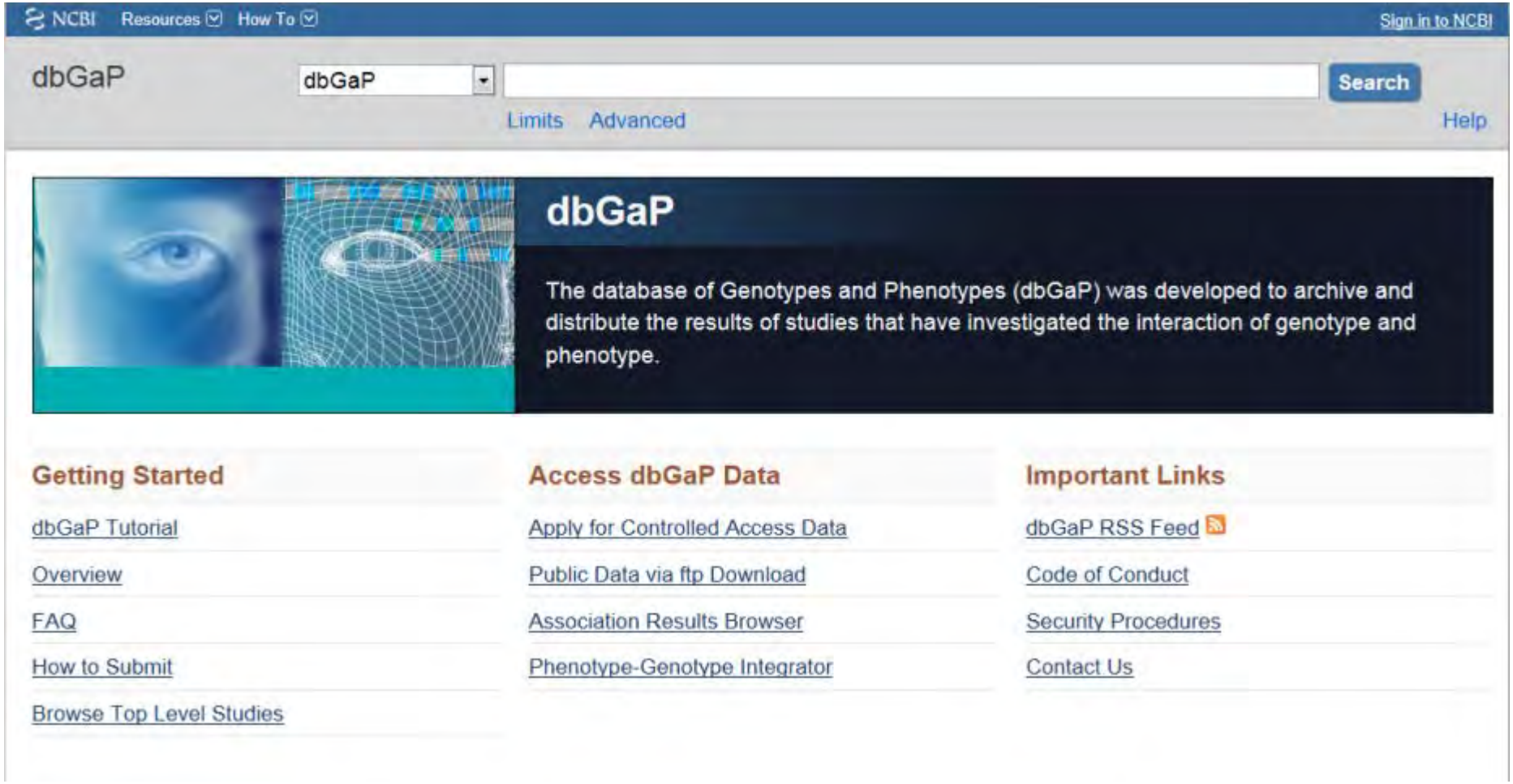
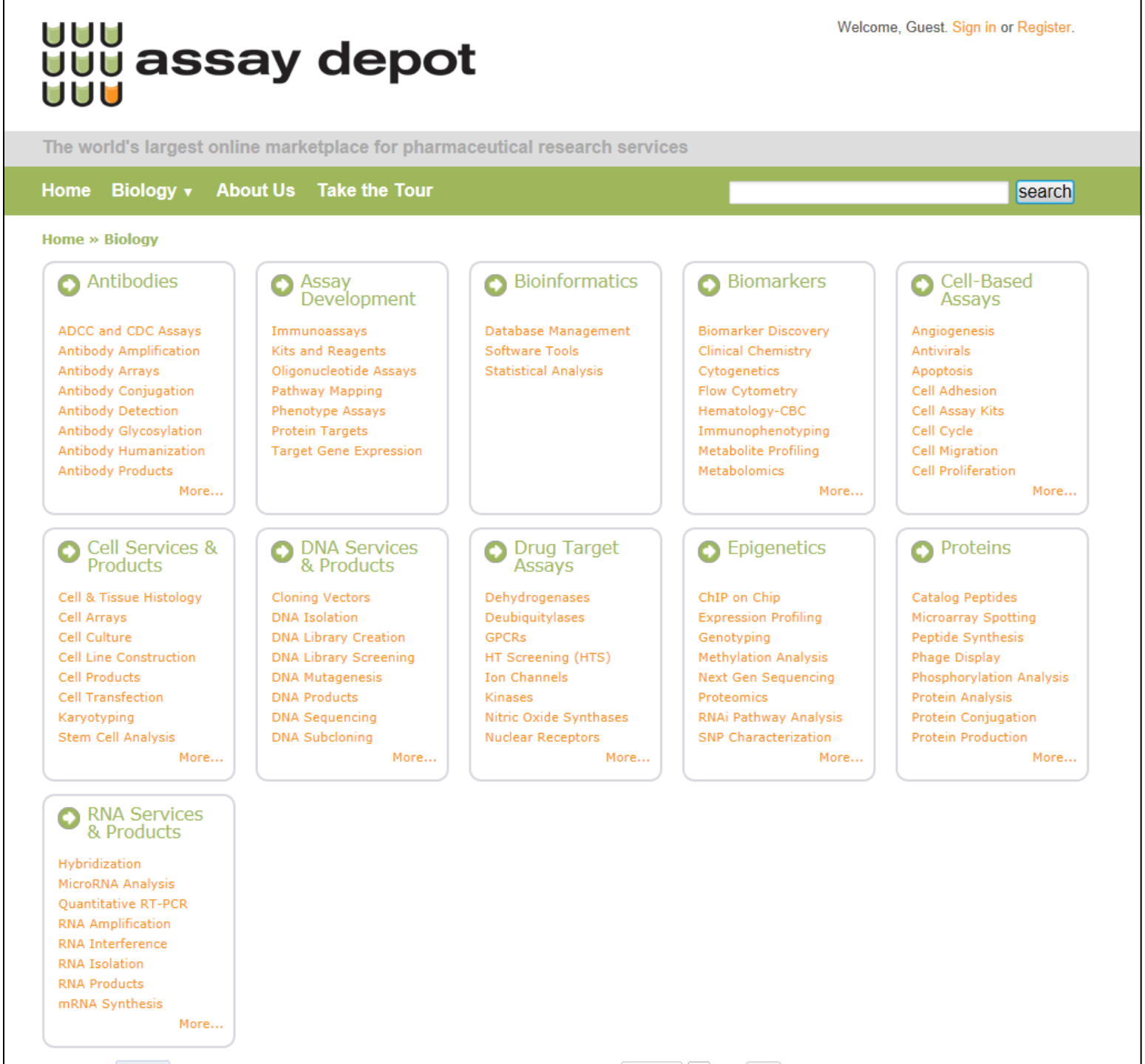
Database of Genotypes & Phenotypes

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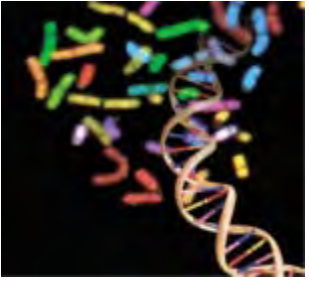
Related links

At the Jackson Laboratory

- Technical Support resources

Steps to Move Genomic Research to the Clinic

- Professional organization guidelines for reporting genetic variants
- Acceptance by stakeholders of different evidentiary standards for clinical utility of tests for different medical conditions
- A national, dynamically updated, interpretative database of evidence for clinical utility of genetic variants
- Government-sponsored prospective randomized clinical outcome studies: e.g., NHLBI's clinical trial (COAG) of warfarin dosing by clinical + genetic information vs clinical information alone. Studies funded by the Patient-Centered Outcomes Research Institute
- Cost-effectiveness models based on simulated clinical outcome studies



Summary

- Whole Genome/Exome Sequencing (not reimbursed) is initially entering clinical practice informally via academic medical centers, biotech, and CLIA labs. Large CLIA labs may offer WGS depending on the market, reimbursement, and content of test reports
- Approval of an FDA-approved WGS instrument / reagent system is currently unlikely, with complex intended use(s), accuracy problems, no gold standard for comparison, rapid technical obsolescence (uncompetitive with LDTs), and a potential requirement for lengthy and costly prospective treatment-by-genotype clinical outcome studies
- Need a patient-oriented, medical value-based system of test reimbursement rather than a technology-based system
- A major impact of genomics will be in drug discovery

James Evans' Take on the Genomics Scorecard

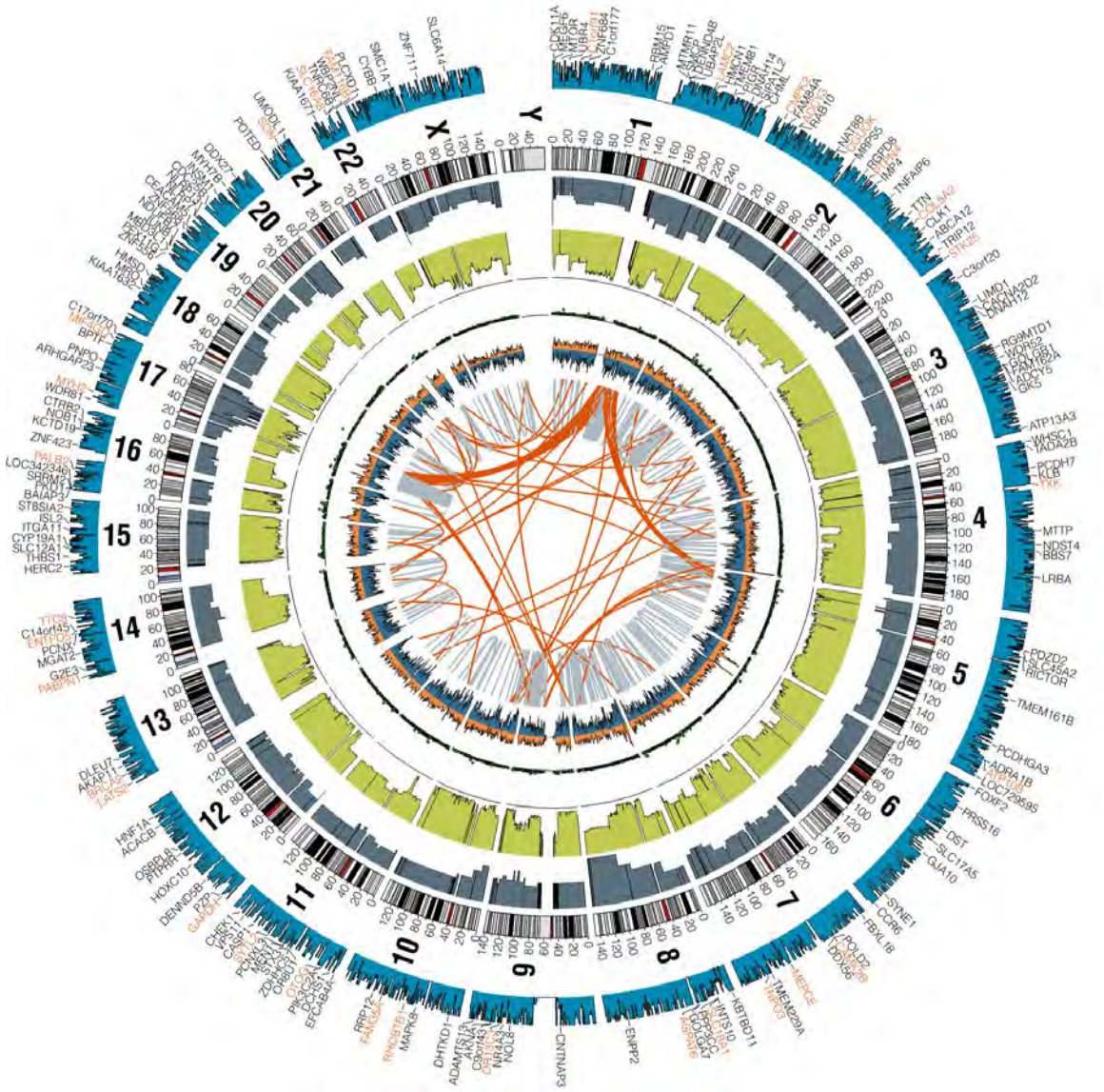
- ☑ Improved treatment of cancer through genomic somatic analysis
- ☑ Powerful diagnostic tool for patients with primary genetic disorders
- ☑ Prevention of rare diseases through selective genomic discovery of highly penetrant mutations
- ☑ Pre-conception screening to inform reproductive choice
- ☑ Utility in newborn screening
- ☒ Broad preemptive pharmacogenomics application
- ☒ Prevention of common diseases through genomic risk assessment

An Optimistic Viewpoint

“I think there's a time in the near future when every individual will have a complete understanding of the genetic content of their tumors, and that will help guide us not only to develop new medicines but to specifically identify those patients that are most likely to respond”.

- Gary Gilliland, Senior Vice President and Global Head of Oncology at the pharmaceutical company Merck & Co., quoted on National Public Radio: Science Friday, 01/11/13

Breast Cancer Genome



Conclusions

Technology is moving so quickly that genomic medicine risks bypassing the type of rigorous evidence for safety and effectiveness that an FDA-approved test system would provide, with the result that insurers will probably not reimburse most genomic tests, requiring individuals to self-pay for information that may be of unproven clinical or economic benefit in diagnosis or treatment, and the interpretation of the test results dependent on the perspectives of various government, professional and commercial organizations

Acknowledgements

- US biomedical research organizations
- Individual investigators and the peer-review system
- Institute of Medicine (National Academy of Sciences)
  - David Veenstra (University of Washington)
  - James Evans (University of North Carolina)
- Association for Molecular Pathology
- National Center for Biotechnology Information (NCBI)
- John Sninsky, Dov Shiffman & Mike Zoccoli (Celera)

References

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- *de novo* mutations and father's age: *Nature* 488: 471 (2012)
- Rare functional variants: *Science* 337: 100 (2012)
- Personal Genome Project: *PNAS* 109: 11920 (2012)
- WGS in prenatal diagnosis: *N Engl J Med* 367: 23 (2012)
- ENCODE Project: *Nature* 489: 46-113 (2012)
- Aspirin & LPA test CEA: *Clinical Therapeutics*: 34: 1387 (2012)
- Molecular portraits of breast cancer: *Nature*: 490: 61 (2012)
- Pres Comm on Privacy & Progress in WGS: www.bioethics.gov
- EuroGentest Clinical Utility Cards: *Eur J Hum Gen*: 21: 1 (2013)
- Translating Genes into Health: *Nature Genetics:* 45: 5 (2013)

Additional Slides

Questions About the Alzheimer's Discovery

- The mother of a 50 year old man had late-onset Alzheimer's at age 85; should he be tested for the specific protective (and risk) mutations?
- Where is testing available, what will it cost, and will his health insurance cover it?
- Although the Genetic Information Non-Discrimination Act prohibits his test results from being used to deny employment and health insurance, what about disability, life and long-term care insurance?

Questions About the Lung Cancer Discovery

- Since 96% of NSCLC patients' tumors do not carry the EML4-ALK variant, is it worthwhile to be tested for it?
- Must a patient's tumor have the variant in order to receive the drug?
- Are there other genetic variants in the tumor that could be used to select other targeted therapies?
- Is there intra-tumor genetic heterogeneity?
- Should the tumor be studied by Whole Exome Sequencing (WES)?

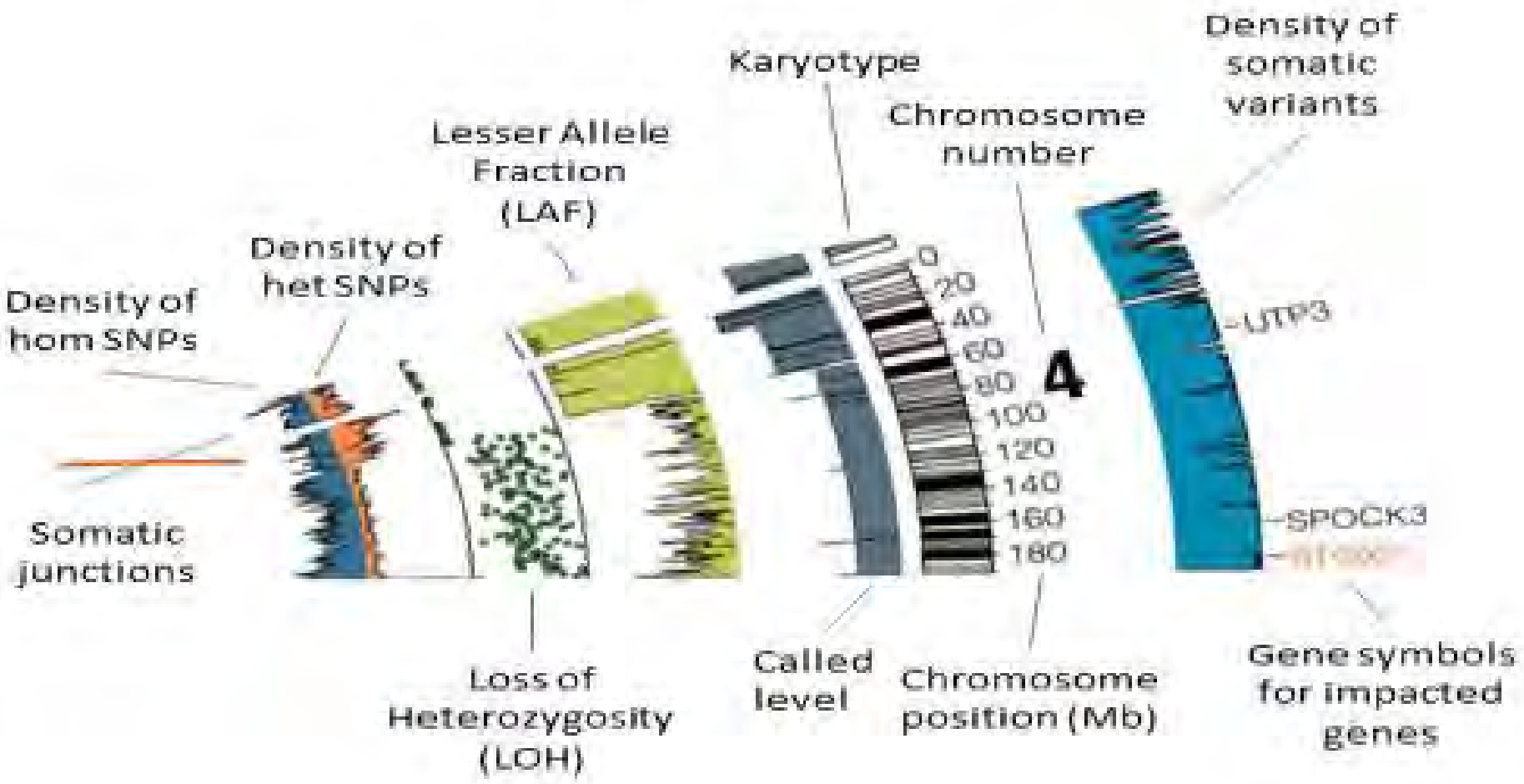
Questions About the Autism Discoveries

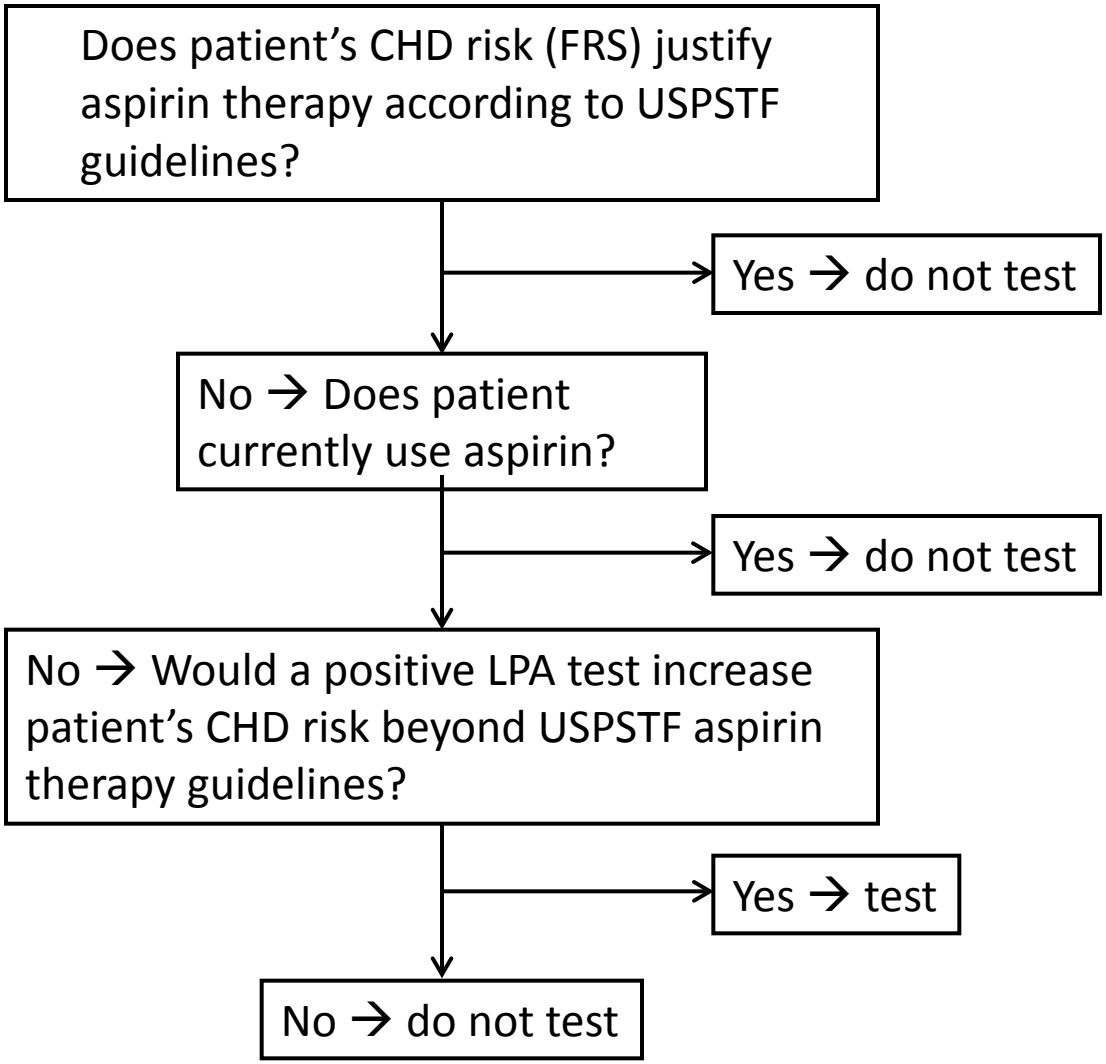
- What are "*de novo*" variants?
- Can they be detected by Non-Invasive Prenatal Testing?
- If most of the known autism variants are not inherited, why are the children of older fathers at greater risk?
- Is it worth having a Whole Genome Sequence (WGS) done on an autistic child to identify variants if there is no targeted therapy?
- How will Variants of Unknown Significance be reported?
- Will the discovery of these variants potentially lead to new drugs for autism?

Other Terms

- NCCN – National Comprehensive Cancer Network
- CPT Code – Current Procedural Terminology
- QALY – Quality-adjusted life year gained. The product of a patient's view of the quality of his life (1 being perfect health, and 0 being dead) multiplied by the number of years of life gained compared to the standard treatment. When the incremental cost of the new treatment/test is divided by the QALY, one gets a measure of the cost-effectiveness of a new Rx/Dx
- NHANES - National Health and Nutrition Examination Survey
- *Post hoc* analysis consists of looking at the data—after the experiment has concluded—for patterns that were not specified *a priori*

Key to Figure




Does patient's CHD risk (FRS) justify aspirin therapy according to USPSTF guidelines?
Yes → do not test
No → Does patient currently use aspirin?
Yes → do not test
No → Would a positive LPA test increase patient's CHD risk beyond USPSTF aspirin therapy guidelines?
Yes → test
No → do not test

Result	Total Population	Men	Women
Patients tested for LPA (n)	20,510	11,602	8,909
CVD events prevented (n)	65	51	14
Major bleeding events caused (n)	49	38	11
Cost of testing ($)	3,076,521	1,740,230	1,336,291
Cost saving of events ($)	1,066,568	947,745	118,823
Total Cost ($)	2,009,953	792,485	1,217,468
Cost per CVD event prevented ($)	30,846	15,749	87,206
Incremental cost per QALY ($)	24,942	13,283	58,193

- **Anecdotal study**
  - Replication rarely reported
- **Case control**
  - Retrospective in design
  - Susceptible to masked bias (e.g. survivorship, selection, ascertainment, drug treatment)
  - Most GWAS studies use this design
- **Observational cohort**
  - Prospective in design
  - Less likely to have masked bias
- **Randomized control trial**
  - Prospective in design
  - High level of evidence
  - *Post hoc* analysis possible (e.g. pre-specified, avoid subgroups, use primary endpoint)
- **Meta-analysis of randomized control trials**
  - High level of evidence **(if similar trials/designs)**

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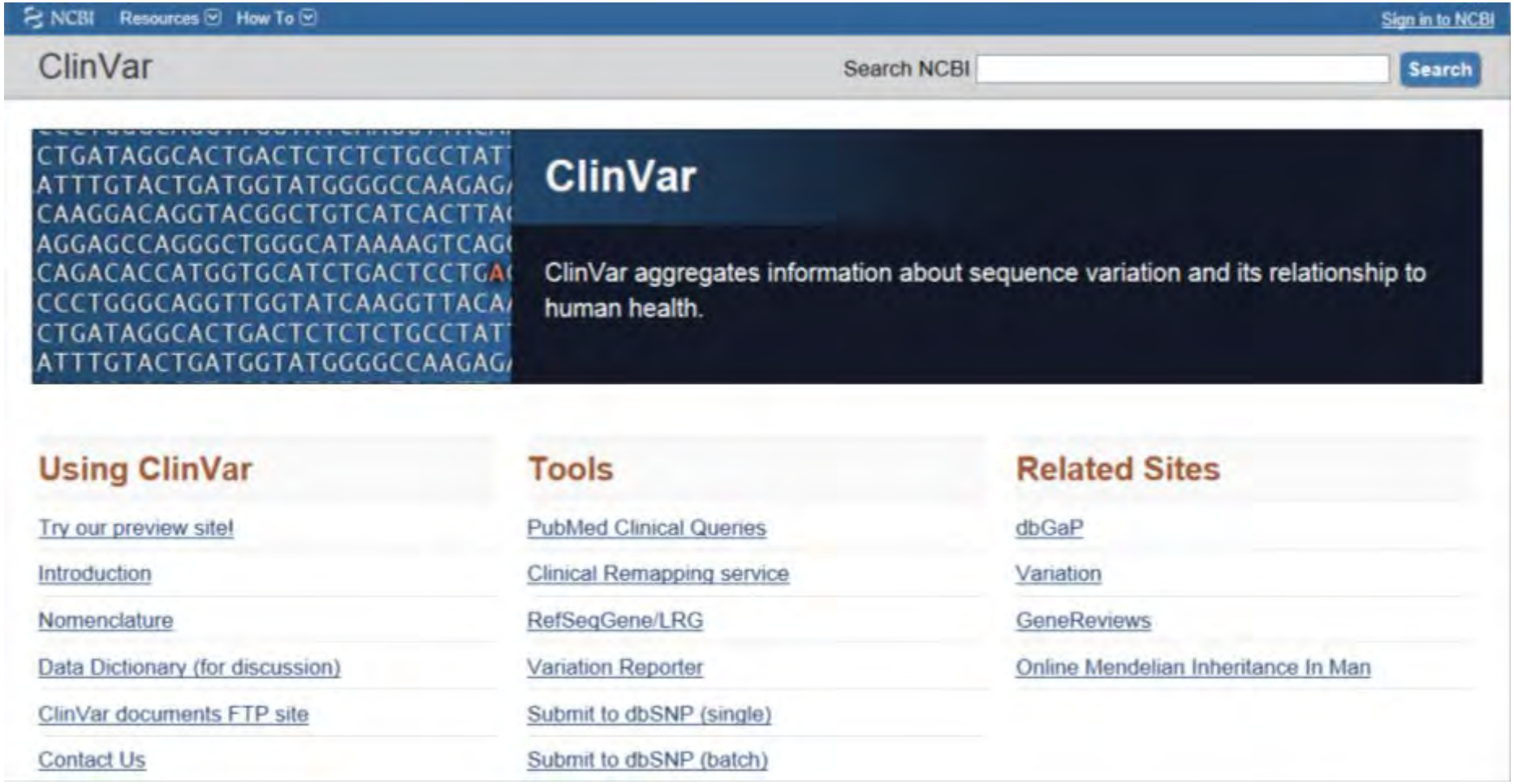

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