Clinical Sequencing
@
Medical College of Wisconsin

Howard J. Jacob, Ph.D.

http://www.mcw.edu/HMGC

Children's Hospital and Health System™

Medical College of Wisconsin

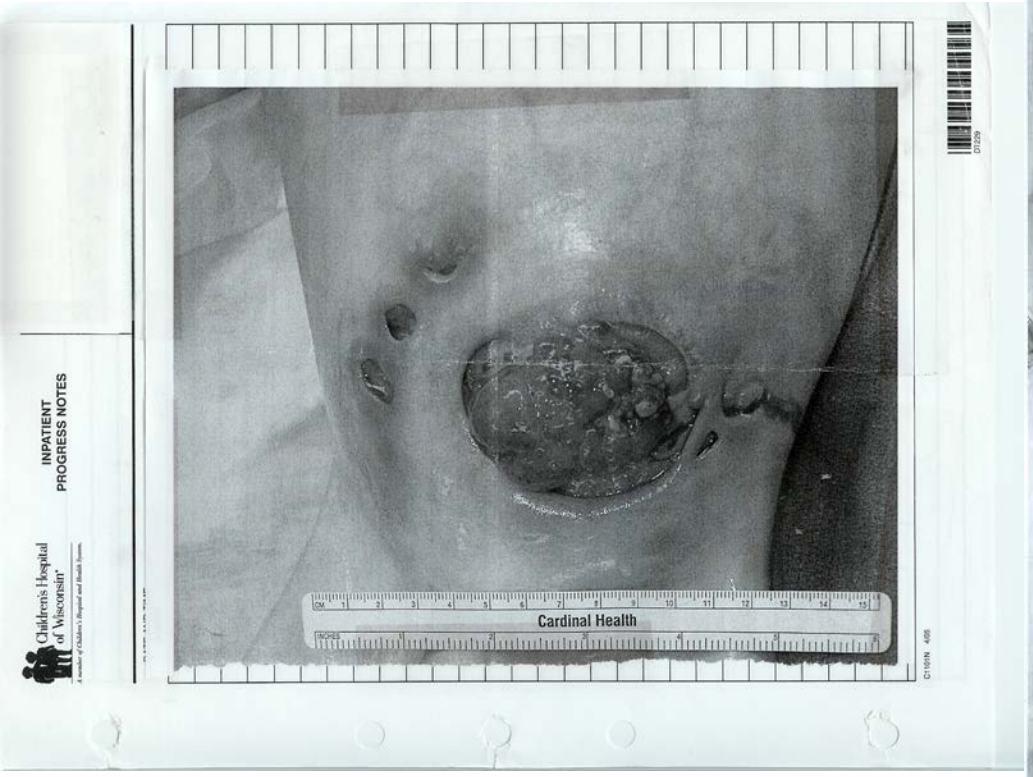
Human and Molecular Genetics Center

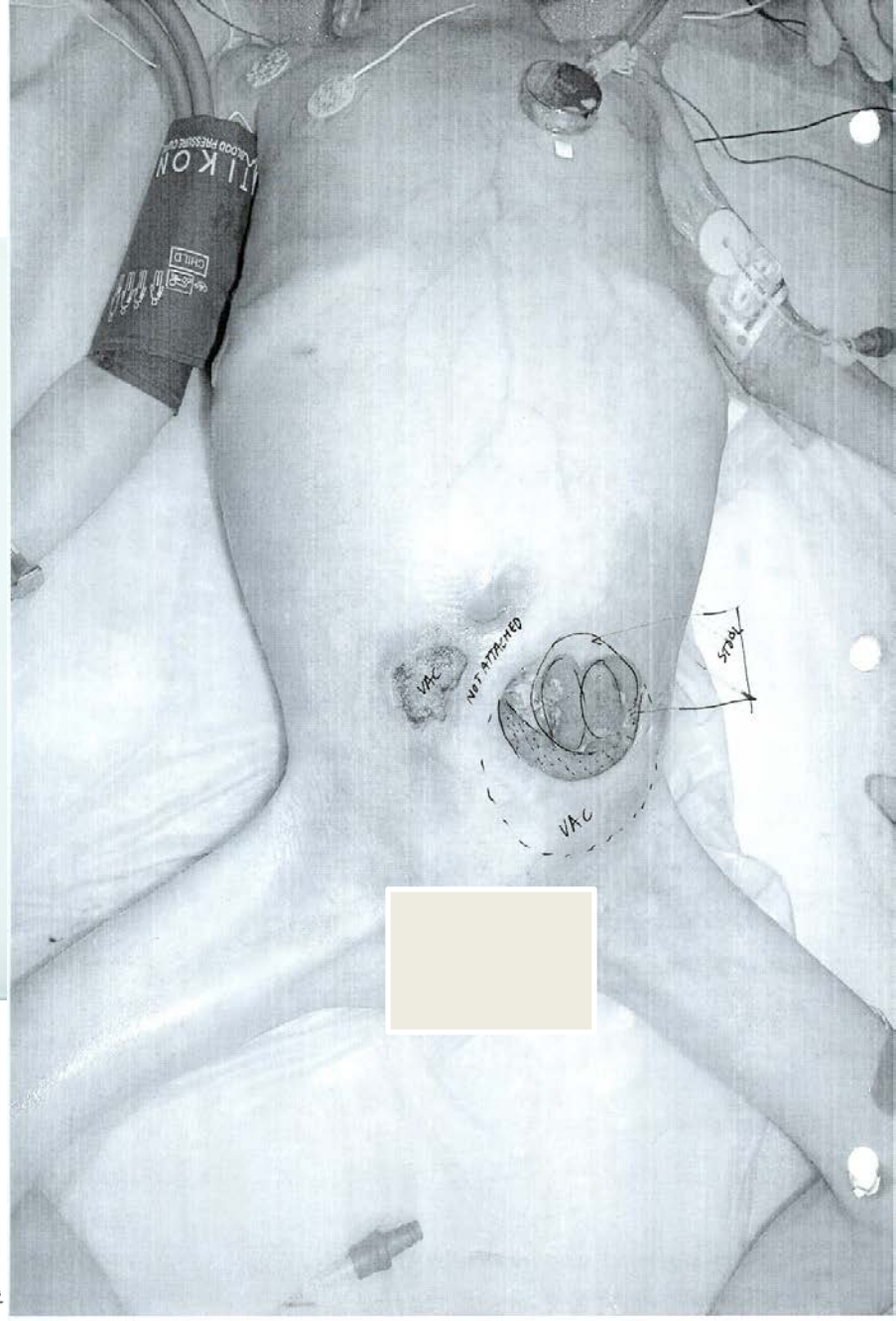
Overview of my talk

- Diagnostic Odyssey Program.
  - Initial case
  - Laboratory certification sequencing lab and analysis tool
  - Selection of patients—why we have a clinical board
  - Consent and Ethics
- Whole Genome Sequence Analysis
  - Limitations.
  - Opportunities
- Genomic sequencing in the clinic as another laboratory method
  - Clinical delivery and getting it paid for

Mission Statement (Oct. 1999)

- **Enable researchers and clinicians at MCW to use the genomic sequence to understand disease, improve diagnosis and ultimately improve treatment of our patients in our affiliated hospitals.**
- **2004 Goal: Genomics Sequence in the Clinic in 2014**





Children's Hospital and Health System™

MEDICA
COLLEG
OF WISCON

Science 4 February 2011:
Vol. 331 no. 6017 p. 546
DOI: 10.1126/science.1202894

ESSAYS ON SCIENCE AND SOCIETY

GENOME-SEQUENCING ANNIVERSARY

Faces of the Genome

Francis S. Collins

Author Affiliations

Director, National Institutes of Health, Bethesda, MD, USA.

When the draft sequence of the human genome was published in February 2001, *Nature* and *Science* featured human faces on their covers. As striking as these images were, they could be seen as more art than science, because systematic genome-wide sequencing had yet to be applied to individuals for medical purposes. What a difference a decade makes. Real faces are now appearing that demonstrate the medical value of comprehensive genome sequencing.

CREDIT: *MILWAUKEE (WISCONSIN) JOURNAL SENTINEL*

View larger version:
» In this page » In a new window
» Download PowerPoint Slide for Teaching

Children's Hospital and Health System™

MEDICAL COLLEGE OF WISCONSIN

Human and Molecular Genetics Center

Milwaukee Approach

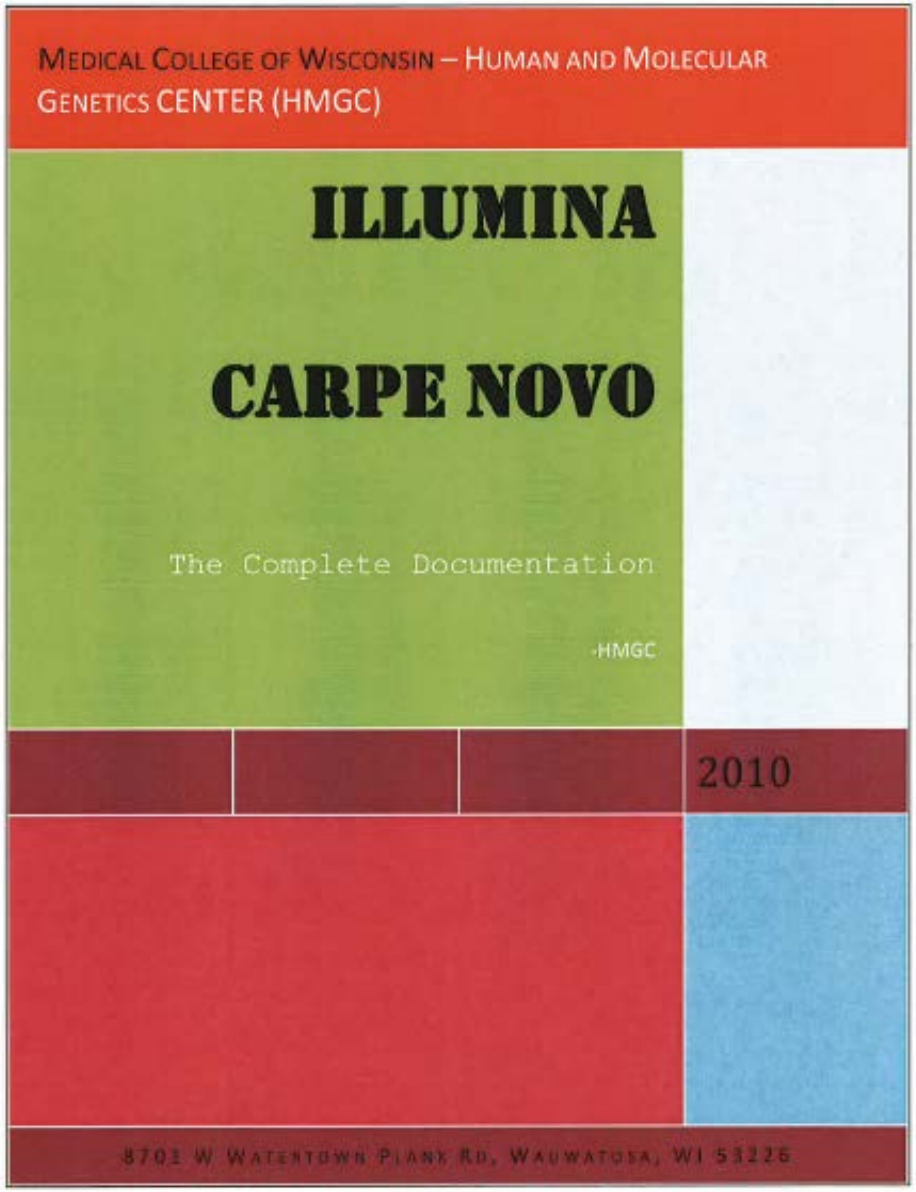
- Nominated by Two Physicians
  - End a diagnostic odyssey
  - Actionable
- Case Review
- Consent
- Genome Sequencing
- Data Analysis
- Follow-up Counseling

Case Assessment: Guiding Principles

- Reasonable clinical testing has been performed*
- Likely to obtain a genetic etiology:
  - Monogenic etiology
  - Distinctive/unique phenotypes more likely to have definable result
- Ability of WGS to assist/enhance medical decision-making
- Ability to conclude WGS assessment:
  - Parent(s) available
  - Appropriate tissue/DNA available for confirmation
- Monetary cost/benefit consideration

Genetics Consent

- Genetics Assessment
  - Evaluation by MD geneticist (if not done)
  - Pedigree by Genetic Counselor (4 generation)
- Consent Process and discussions of data return
  - Multiple consent counseling sessions
  - Family has time to consider testing and data return
  - Followed by written consent
- Total Average Time: 6-8 hours



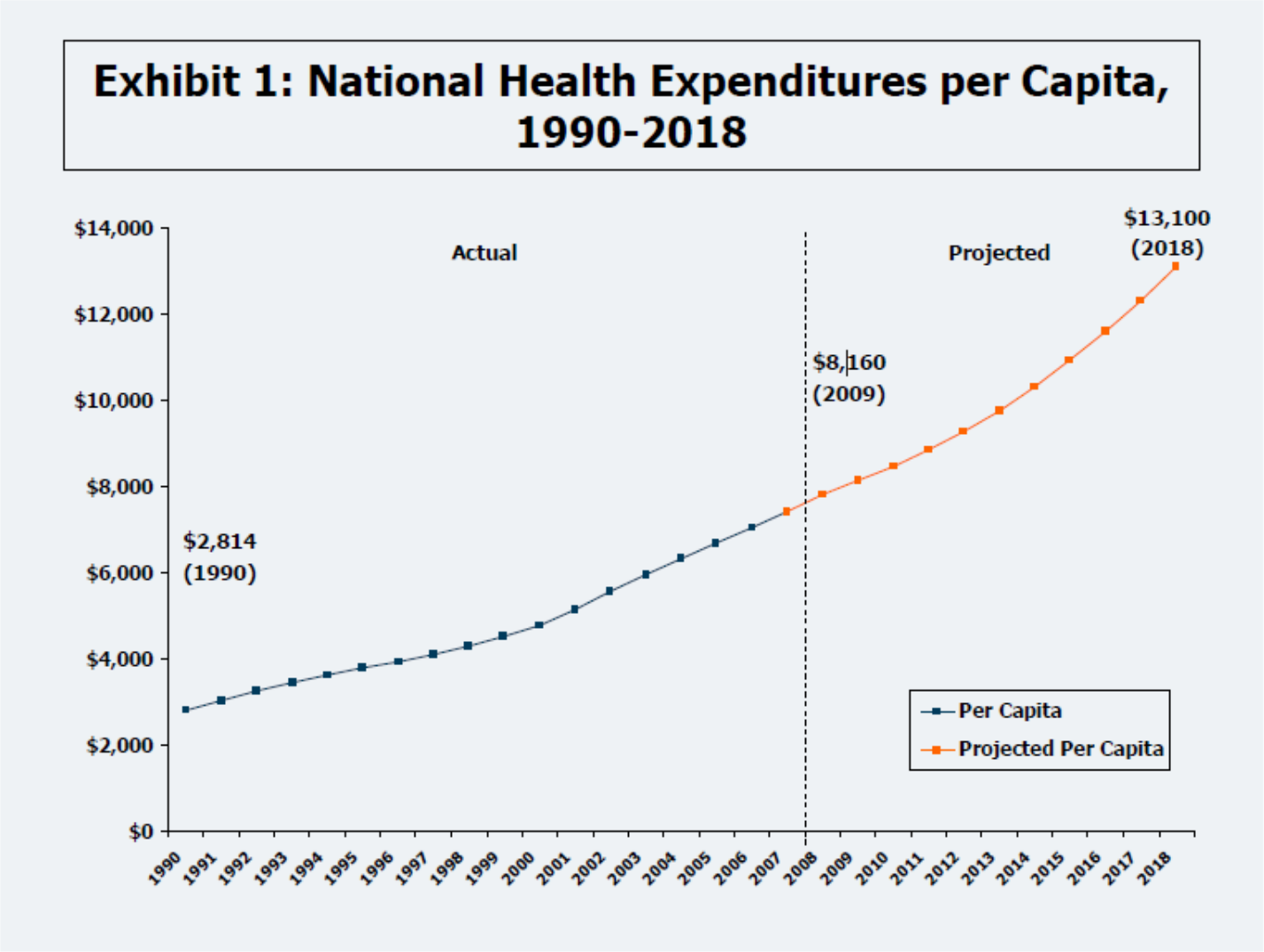
Children's Hospital and Health System™

MEDICAL COLLEGE OF WISCONSIN

Human and Molecular Genetics Center

Limitations

- What does actionable mean?
- Alignment vs. de novo assembly
- Limited availability of genomic sequence
- Little clinical data available
- Questions of clinical utility and value



Kaiser Family Foundation March 2009

Children's Hospital and Health System™

MEDICAL COLLEGE OF WISCONSIN

Human and Molecular Genetics Center

CONGRESSIONAL BUDGET OFFICE
U.S. Congress
Washington, DC 20515

Douglas W. Elmendorf, Director

August 7, 2009

Honorable Nathan Deal
Ranking Member
Subcommittee on Health
Committee on Energy and Commerce
U.S. House of Representatives
Washington, DC 20515

Dear Congressman:

This letter responds to the question you asked at a July 16, 2009, committee markup concerning the Congressional Budget Office's (CBO's) analysis of the budgetary effects of proposals to expand governmental support for preventive medical care and wellness services. Specifically, you asked whether the agency's scoring methods reflect potential reductions in federal costs from improvements in health that might result from expanded support for those activities.[1]

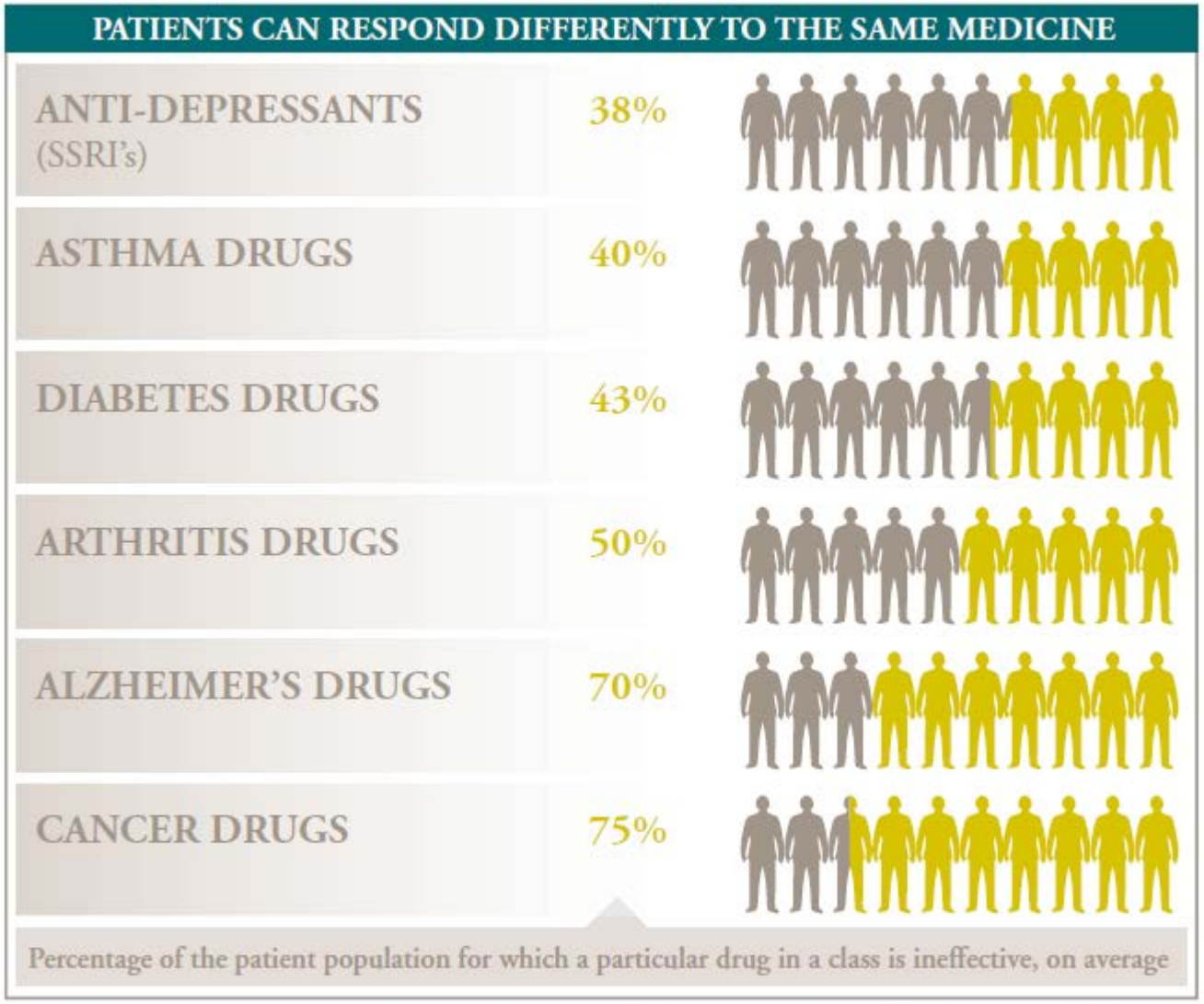
Preventive Medical Care

Preventive medical care includes services such as cancer screening, cholesterol management, and vaccines. In making its estimates of the budgetary effects of expanded governmental support for preventive care, CBO takes into account any estimated savings that would result from greater use of such care as well as the estimated costs of that additional care. Although different types of preventive care have different effects on spending, the evidence suggests that for most preventive services, expanded utilization leads to higher, not lower, medical spending overall.

That result may seem counterintuitive. For example, many observers point to cases in which a simple medical test, if given early enough, can reveal a condition that is treatable at a fraction of the cost of treating that same illness after it has progressed. In such cases, an ounce of prevention improves health and reduces spending—for that individual. But when analyzing the effects of preventive care on total spending for health care, it is important to recognize that doctors do not know beforehand which patients are going to develop costly illnesses. To avert one case of acute illness, it is usually necessary to provide preventive care to many patients, most of whom would not have suffered that illness anyway. Even

[1] For additional information on both topics, see Congressional Budget Office, *Key Issues in Analyzing Major Health Insurance Proposals* (December 2008), pp. 132–139.

Figure 1: One Size Does Not Fit All



Source of data: Brian B. Spear, Margo Heath-Chiozzi, Jeffrey Huff, "Clinical Trends in Molecular Medicine, Volume 7, Issue 5, 1 May 2001, Pages 201-204.

Children's Hospital and Health System™

MEDICAL COLLEGE OF WISCONSIN

Human and Molecular Genetics Center

Plavix

Used for patients with MI and CAD after stent.
Less effective in ~30% of patients

Estimation:

1. Current Population: 300 pts on Plavix (based off LWC and LQG)
   ~100 pts will have the genetic abnormality
   ~50 pts will have complications
2. Cost for a MI:
   50 people * $50,000 = $2,500,000
3. Cost for WGS and one gene analysis for $1,000.
   Total: 300 patients X $1000 = $300,000
4. Let's just switch all patients off Plavix to another compound (e.g. Ticagrelor). Additional savings likely.

Plavix

5. Plavix comes of patent in 2011 assuming a drop of price of just $100 per month. Current price is $1,500 per month.
6. New distribution of prescriptions:
   200 pts on Plavix 200 x $100 x12months = $240,000 in year 1!
   100 pts on Ticagrelor
7. Advantage of this genetics screen
   Savings for avoiding an MI in 50 people: $2,500,000
   Savings for lower prescription prices: + $240,000
   Year 1 savings: $2,740,000
   Lifetime savings over 5 years ($240K per year, plus $10K per year in follow on MI care and loss of productivity) =
   $2,740,000 + $1,250,000 = $3,990,000
   Discount to 10% = $399,000 or savings of $99,000 minimum.
8. Bonus for using a WGS: Analyzes of other PGX genes or clinical traits

Children's Hospital and Health System™

MEDICAL COLLEGE OF WISCONSIN

Human and Molecular Genetics Center

One Gene Test at a Time

Is not cost effective!

WGS can be cost effective

What is the value of a patient's WGS?

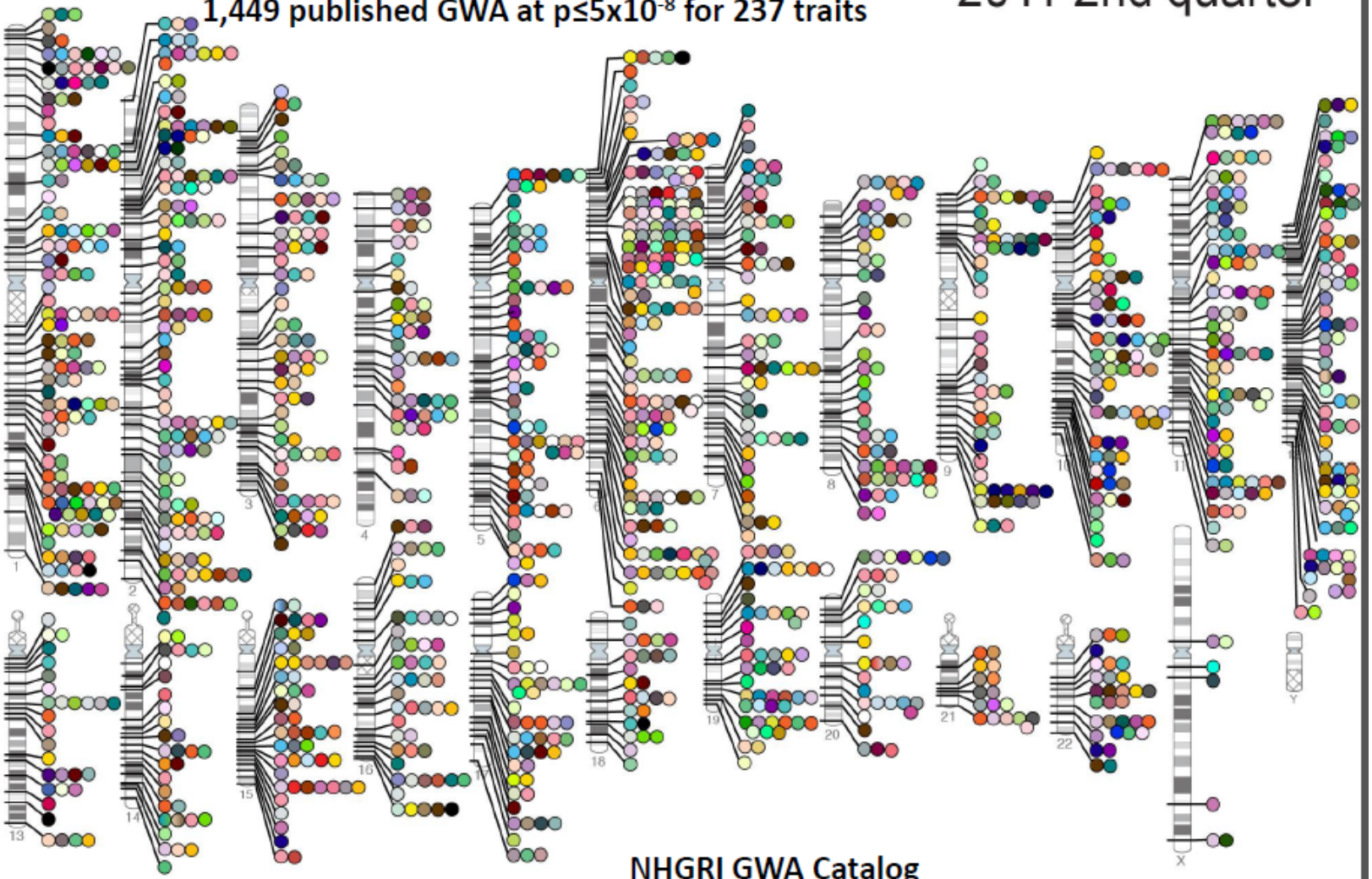
WGS = Family History With Data!

370 Drugs/Compounds PharmGKB

How many diseases or clinical phenotypes?

Published Genome-Wide Associations through 06/2011,
1,449 published GWA at p≤5x10^{-8} for 237 traits

2011 2nd quarter



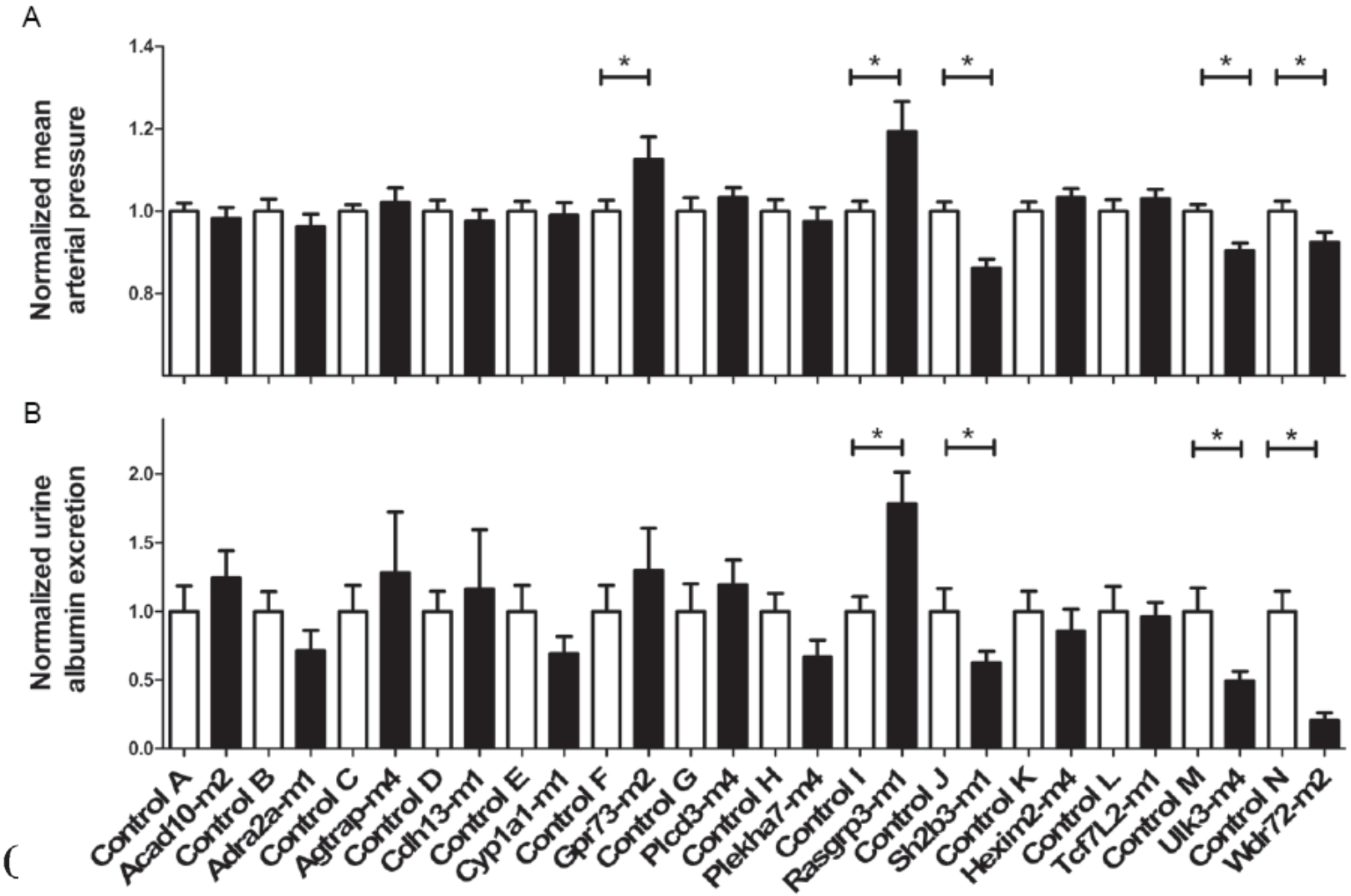
NHGRI GWA Catalog
www.genome.gov/GWAStudies

Children's Hospital and Health System™

MEDICAL COLLEGE OF WISCONSIN

Human and Molecular Genetics Center

Modification of some GWA genes can alter relevant phenotypes in the sensitized rat



ARTICLE

Risk Prediction of Complex Diseases from Family History and Known Susceptibility Loci, with Applications for Cancer Screening

Hon-Cheong So,[1] Johnny S.H. Kwan,[1] Stacey S. Cherny,[1,2,3] and Pak C. Sham[1,2,3,*]

Risk prediction based on genomic profiles has raised a lot of attention recently. However, family history is usually ignored in genetic risk prediction. In this study we proposed a statistical framework for risk prediction given an individual's genotype profile and family history. Genotype information about the relatives can also be incorporated. We allow risk prediction given the current age and follow-up period and consider competing risks of mortality. The framework allows easy extension to *any* family size and structure. In addition, the predicted risk at any percentile and the risk distribution graphs can be computed analytically. We applied the method to risk prediction for breast and prostate cancers by using known susceptibility loci from genome-wide association studies. For breast cancer, in the population the 10-year risk at age 50 ranged from 1.1% at the 5th percentile to 4.7% at the 95th percentile. If we consider the average 10-year risk at age 50 (2.39%) as the threshold for screening, the screening age ranged from 62 at the 20th percentile to 38 at the 95th percentile (and some never reach the threshold). For women with one affected first-degree relative, the 10-year risks ranged from 2.6% (at the 5th percentile) to 8.1% (at the 95th percentile). For prostate cancer, the corresponding 10-year risks at age 60 varied from 1.8% to 14.9% in the population and from 4.2% to 23.2% in those with an affected first-degree relative. We suggest that for some diseases genetic testing that incorporates family history can stratify people into diverse risk categories and might be useful in targeted prevention and screening.

The American Journal of Human Genetics *88*, 548–565, May 13, 2011

Salt and Hypertension

reduction trials. Over the long-term, low-salt diets, compared to normal diets, decreased systolic blood pressure (the top number in the blood pressure ratio) in healthy people by 1.1 millimeters of mercury (mmHg) and diastolic blood pressure (the bottom number) by 0.6 mmHg. That is like going from 120/80 to 119/79. The review concluded that "intensive interventions, unsuited to primary care or population prevention programs, provide only minimal reductions in blood pressure during long-term trials." A 2003 Cochrane review of 57 shorter-term trials similarly

Diseases reported that the number of people who experience drops in blood pressure after eating high-salt diets almost equals the number who experience blood pressure spikes; many stay exactly the same. That is because "the human kidney is made, by design, to vary the accretion of salt based on the amount you take in," explains Michael Alderman, an epidemiologist at the Albert Einstein College of Medicine and former president of the International Society of Hypertension.

WHOLE GENOMIC SEQUENCING

It will be along time before this is used clinically! **50+ nominations**

NO ONE WILL PAY FOR IT!

Children's Hospital and Health System™

MEDICAL COLLEGE OF WISCONSIN

Human and Molecular Genetics Center

Letter from Insurance Group

February 23, 2011

David Dimmock, M.D., Associate Professor
David Bick, M.D., Associate Professor
Division of Genetics, Dept of Pediatrics
Medical College of Wisconsin
HRC, Rm. H5865
8701 Watertown Plank Road
Milwaukee, WI 53226

To date 4 of 10 pre-approval

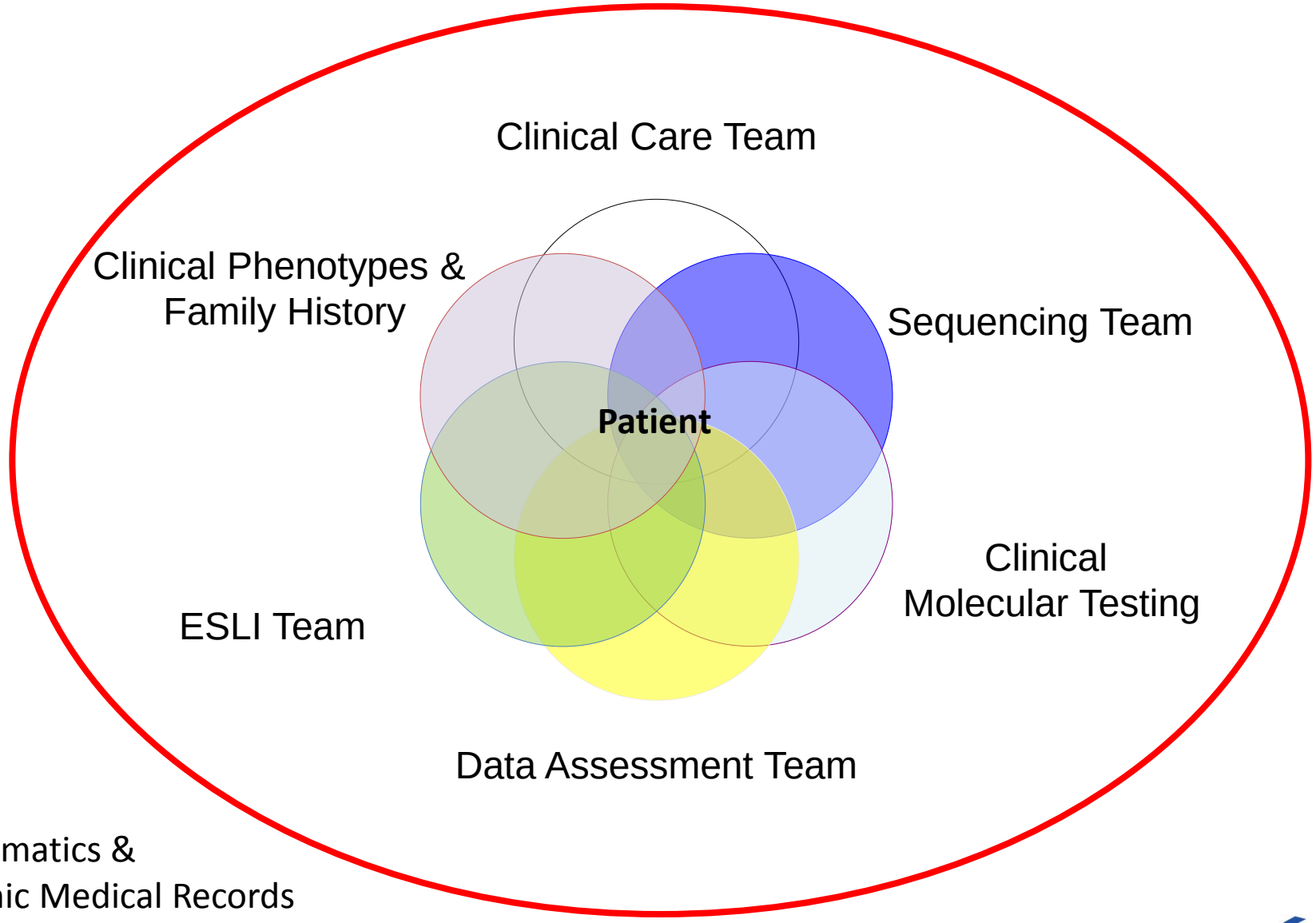
We are interested in the development of an evaluation clinic where you will assess our insured children and adults before expensive diagnostic testing is performed and evaluate the likely expected costs of routine testing. As we have discussed, in the situations where you determine that on average the costs of routine testing will exceed the current contract price of whole genome sequencing we will authorize whole genome sequencing as the first line clinical test.

We are committed to continuing to establish the utility of whole genome sequencing beyond these currently agreed indications, and are excited about the ongoing clinical utility monitoring you have established as part of your clinical whole genome sequencing program.

Children's Hospital and Health System™

MEDICAL COLLEGE OF WISCONSIN

Human and Molecular Genetics Center

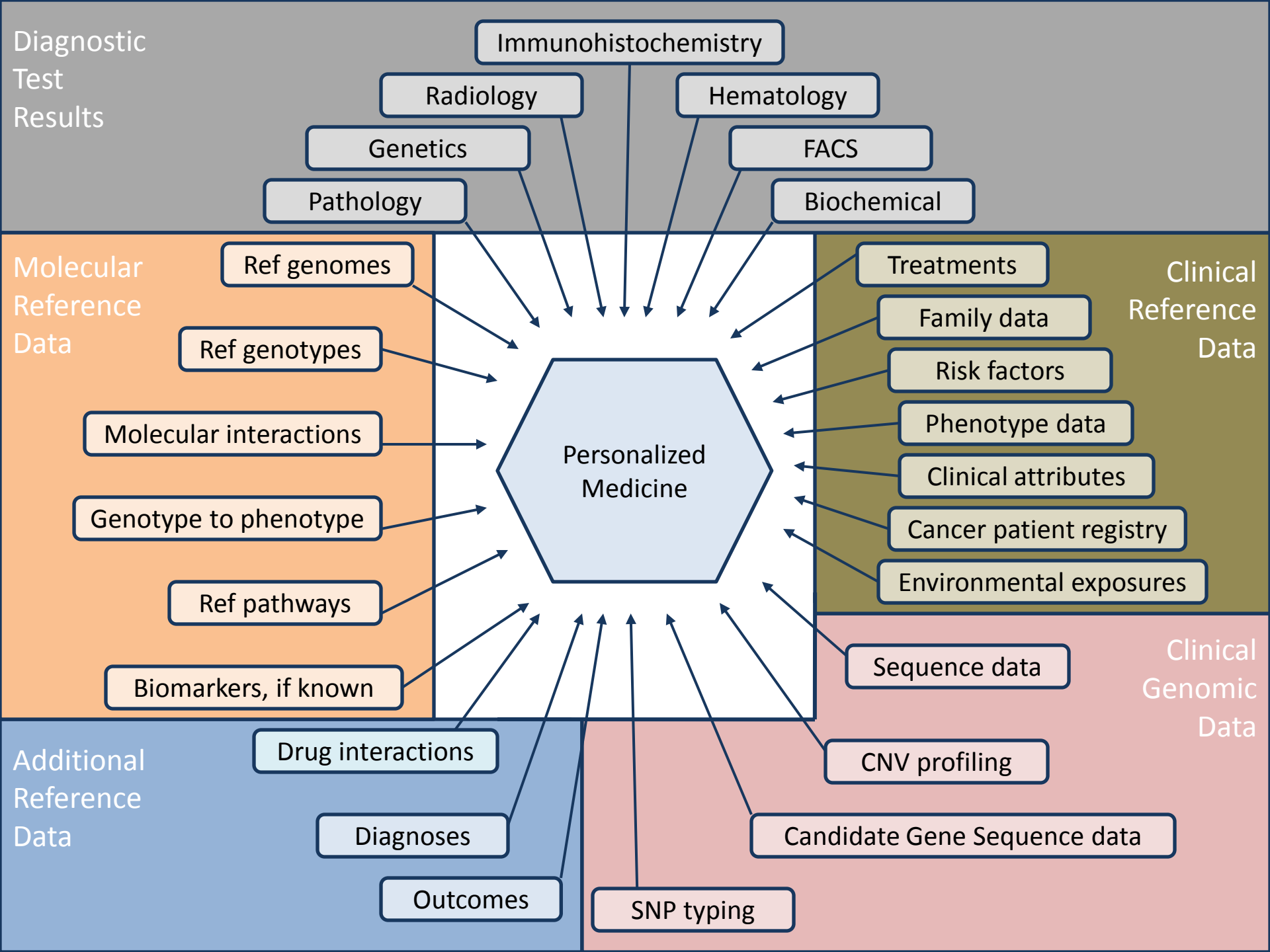


BioInformatics &
Electronic Medical Records

Children's Hospital and Health System™

MEDICAL COLLEGE OF WISCONSIN

Human and Molecular Genetics Center


Diagnostic Test Results
Immunohistochemistry
Radiology
Hematology
Genetics
FACS
Pathology
Biochemical
Molecular Reference Data
Ref genomes
Ref genotypes
Molecular interactions
Genotype to phenotype
Ref pathways
Biomarkers, if known
Personalized Medicine
Clinical Reference Data
Treatments
Family data
Risk factors
Phenotype data
Clinical attributes
Cancer patient registry
Environmental exposures
Clinical Genomic Data
Sequence data
CNV profiling
Candidate Gene Sequence data
SNP typing
Additional Reference Data
Drug interactions
Diagnoses
Outcomes

Rapidly Changing Landscape

Whole Exome Genome Sequence for clinical use will accelerate uptake!

Children's Hospital and Health System™

MEDICAL COLLEGE OF WISCONSIN

Human and Molecular Genetics Center

Children's Research Institute

Hospital
h System™

MEDICAL COLLEGE OF WISCONSIN

HumHuman and Molecular Genetics Center

Summary

- The cost of data generation will continue to fall. Within the year about $2000 per whole genome sequence.
- Data management and clinical decisions is the challenge.
- It is just another lab value, whose context with respect to clinical presentation is critical to utility. It has value now! A family history with data!
- It is cheaper to develop a single platform rather than individual genes.
- Data return is part of personalized medicine.
- Lots of education needed—this is the biggest challenge.

Needs

- Access to Results from Whole Genome Sequence
- Access to WGS with clinical information
- What is the VALUE of having a WGS for an individual?
- Demonstration projects to show cost effectiveness and utility
- Tools for integrating with family history
- Follow-up validation—how much?
- Decision support tools
- More powerful EHRs
- LOTS OF EDUCATION

Children's Hospital and Health System™

MEDICAL COLLEGE OF WISCONSIN

Human and Molecular Genetics Center

Children's Hospital and Health System™

MEDICAL COLLEGE OF WISCONSIN

Human and Molecular Genetics Center

Children's Hospital and Health System™

MEDICAL COLLEGE OF WISCONSIN

Human and Molecular Genetics Center

Special Case for WGS?

- Misdiagnoses – happens every day– due to lack of knowledge about the disease.
- Not actionable – stress on the patient
  - End stage renal disease <25% alive in 5 years
  - Stage 4 cancer, etc.
- Evidence based medicine
  - Population vs. individual
  - How do you show clinical utility?
- On average we are making progress

Children's Hospital and Health System™

MEDICAL COLLEGE OF WISCONSIN