

Clinical Sequencing @ Medical College of Wisconsin

Howard J. Jacob, Ph.D.

<http://www.mcw.edu/HMGC>

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)

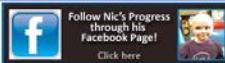
- **Enable researchers and clinicians at MCW to use the genomic sequence to understand disease, improve diagnosis and ultimately improve treatment of our patients in our affiliated hospitals.**
- **2004 Goal: Genomics Sequence in the Clinic in 2014**

INPATIENT
PROGRESS NOTES

Children's Hospital
of Wisconsin
A Division of Children's Hospital and Health System



Groundbreaking News: New Genetic Test leads to a life-saving treatment for one little boy
One in a billion



One in a Billion: A boy's life, a medical mystery - Part 1
 Nicholas Volker is a little boy with a rare, devastating disease. In a desperate bid to save his life, Wisconsin doctors must decide: Is it time to push medicine's frontier?
[Read More...](#)

Sifting through the DNA haystack - Part 2
 Driven by the urgency of Nicholas' condition, researchers seek clues in his DNA and find more than they expected.
[Read More...](#)

Gene Insights Lead to a Risky Treatment - Part 3
 Sequencing Nicholas' DNA has given his family and doctors a diagnosis and more worries. Now they hope a new immune system can stop his disease.
[Read More...](#)

DNA Series: "One in a billion" chat with Howard Jacob
 Howard Jacob, director of the Medical College of Wisconsin's Human and Molecular Genetics Center, answered questions about the Journal Sentinel series "One in a billion: A boy's life, a medical mystery," in a chat.
[Read More...](#)

Doctors use genetic code to make groundbreaking diagnosis
 In work that advances medicine's ability to search for genes for the causes of disease, researchers from Wisconsin have sequenced a young boy's genes and pinpointed the genetic trigger of an illness that had baffled doctors.
[Read More...](#)

JSONline
NIH director touts Volker DNA research at Medical College
 Feb. 3, 2011: Nic, a 6-year-old whose story was chronicled in a Journal Sentinel series, is one of three patients highlighted in an essay by Francis S. Collins, director of the National Institutes of Health.
[Read More...](#)

JSONline
Nic Volker case may be the leading edge of a wave moving across genetic medicine
 Feb. 27, 2011: "In a sign that medicine is crossing a technological threshold, a few hospitals and medical centers around the country are taking their first steps to follow up on the success of doctors in Wisconsin."
[Read More...](#)

Forbes
Sequencing A Child's DNA - And Convincing An Insurance Company To Pay
 March 2, 2011 - Genebioat Elizabeth Worthley worked on DNA sequencing, helping doctors decide to give a bone marrow transplant to a 6-year-old boy who had suffered through more than a hundred operations.
[Read More...](#)

HMGC Featured on Today Show
 Cord blood transplant as boy, 6, from rare illness.
[Read More...](#)

POPSCI
For the First Time, DNA Sequencing Technology Saves A Child's Life
 Popular Science - 1/16/2011
 Proponents of genetic medicine say DNA sequencing is the future of medicine and that every truly sick person will have his or her genome sequenced.
[Read More...](#)

R&D
At 10, Forbes Faces Reality
 R&D Magazine Blogs: In February 2001, the journal Science published two scientific papers that, for the first time, described parts of the newly sequenced human genome.
[Read More...](#)

Genetics Medicine
Genetics in Medicine: A milestone arrival for genomic medicine.
[Read More...](#)

MWJW
DNA Sequencing, Persistent Mom & Dedicated Doc Save Boy
 Milwaukee Public Radio, February 9, 2011: Major medical advances in DNA sequencing is offering promise to some patients - and their doctors. Howard Jacob is the head of the genetics center at the Medical College of Wisconsin.
[Read More...](#)

technology
Anticipating the Next Decade of the Genome - Francis Collins, Director of NIH
 NIH/NIH/NIH hosted a day-long scientific symposium on Friday, Feb. 11, 2011. NIH Director Francis Collins speaks on the Clinical Application of Genomic Analysis.
[Read More...](#)

JSONline | **A baffling illness**

Forbes
Matthew Harper
The Medicine Show
 necessitating a hundred surgeries including the removal of his colon.
[Read More...](#)

Medical Mystery: DNA Breakthrough in Milwaukee
 TODAY'S TH34 is teaming up with the Milwaukee Journal Sentinel to bring you a story of hope, enhanced by the power of science. It's a desperate bid to save a little boy's life, involving an idea years ahead of its time.
[Read More...](#)

technology
The Human Genome, 10 Years Later
 What have we learned about the genome and what hurdles still remain? It's been ten years since Science and Nature, the two most prestigious science journals in the world, published the first detailed look at the sequence of the human genome.
[Read More...](#)

Genetics Medicine
Genetics in Medicine
 Making a definitive diagnosis: Successful clinical application of whole exome sequencing in a child with intractable inflammatory bowel disease.
[Read More...](#)

Office of Public Affairs

Global Links
EL PAÍS
exclusiva
impresia

La secuencia de ADN que salvó al pequeño Nicholas
 (en Español): EE UU usa por primera vez esta técnica para evitar la muerte de un enfermo.
[Read More...](#)

Tendencias

La historia del primer paciente salvado por su ADN
 (en Español) Desde los dos años que Nicholas Volker tenía una rara enfermedad.
[Read More...](#)

accesso
accesso
contatto

El primer niño salvado por el ADN
 Acceso, January 31, 2011: La secuenciación del ADN del niño Nicholas Volker, ha permitido detectar la rara enfermedad que padecía y poder llevar a cabo el trasplante con células madre de cordón umbilical que necesitaba.
[Read More...](#)

Die Presse.com

Wo blieb die Genom-Revolution
 Die Presse.com, 2/4/2011: Zehn Jahre nach der Sequenzierung der DNA des Menschen macht sich Ernüchterung breit: Der erhoffte Nutzen für die Medizin ist weithin ausgeblieben. Ärzte beklagen mangelndes Wissen. Sie fühlen sich überfordert.
[Read More...](#)

Neues Deutschland

Vom Genom zur Epigenetik
 Vor zehn Jahren wurde die vollständige Sequenz des menschlichen Erbguts veröffentlicht. Nic Volker aus Madison (USA) war gerade zwei Jahre alt, als sich in seinem Darm so viele Fisteln bildeten, dass er kaum noch etwas essen konnte.
[Read More...](#)

分子基因组学

让基因组测序造福临床诊断
 威斯康星医学院的研究人员们正迈出开创性的步骤，使全基因组测序成为罕见遗传性疾病的儿童诊断测试标准的一部分，这些疾病不易被传统方法诊断。自从投资30亿美元的人类基因组计划发布以来，该技术十年内获得了长足的进步，事实上，这种进步足以使一个健康保险公司愿意支付测序的费用，条件是它比传统的基因检测更便宜。
[Read More...](#)

ivida

El primer niño salvado por el ADN
 Feb. 15, 2011: La secuenciación del ADN del niño Nicholas Volker, ha permitido detectar la rara enfermedad que padecía y poder llevar a cabo el trasplante con células madre de cordón umbilical que necesitaba.
[Read More...](#)

GESTIÓN EN SALUD PÚBLICA

Sociedad Europea de Genética Médica :: El Médico Interactivo, Diario Electrónico de la Sanidad
 March 21, 2011: La Sociedad Europea de Genética Médica pide a España la inclusión de la especialidad en nuestro país
[Read More...](#)

Agence Science-Presse


Nicholas Volker, 6 ans, sauvé grâce au déchiffrement de son ADN
 Depuis l'âge de 15 mois, Nicholas Volker souffre d'inflammation intractable des intestins.
[Read More...](#)

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.



View larger version:
[» In this page](#) [» In a new window](#)
[» Download PowerPoint Slide for Teaching](#)

CREDIT: MILWAUKEE (WISCONSIN) JOURNAL SENTINEL

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

MEDICAL COLLEGE OF WISCONSIN – HUMAN AND MOLECULAR
GENETICS CENTER (HMGC)

ILLUMINA

CARPE NOVO

The Complete Documentation

-HMGC

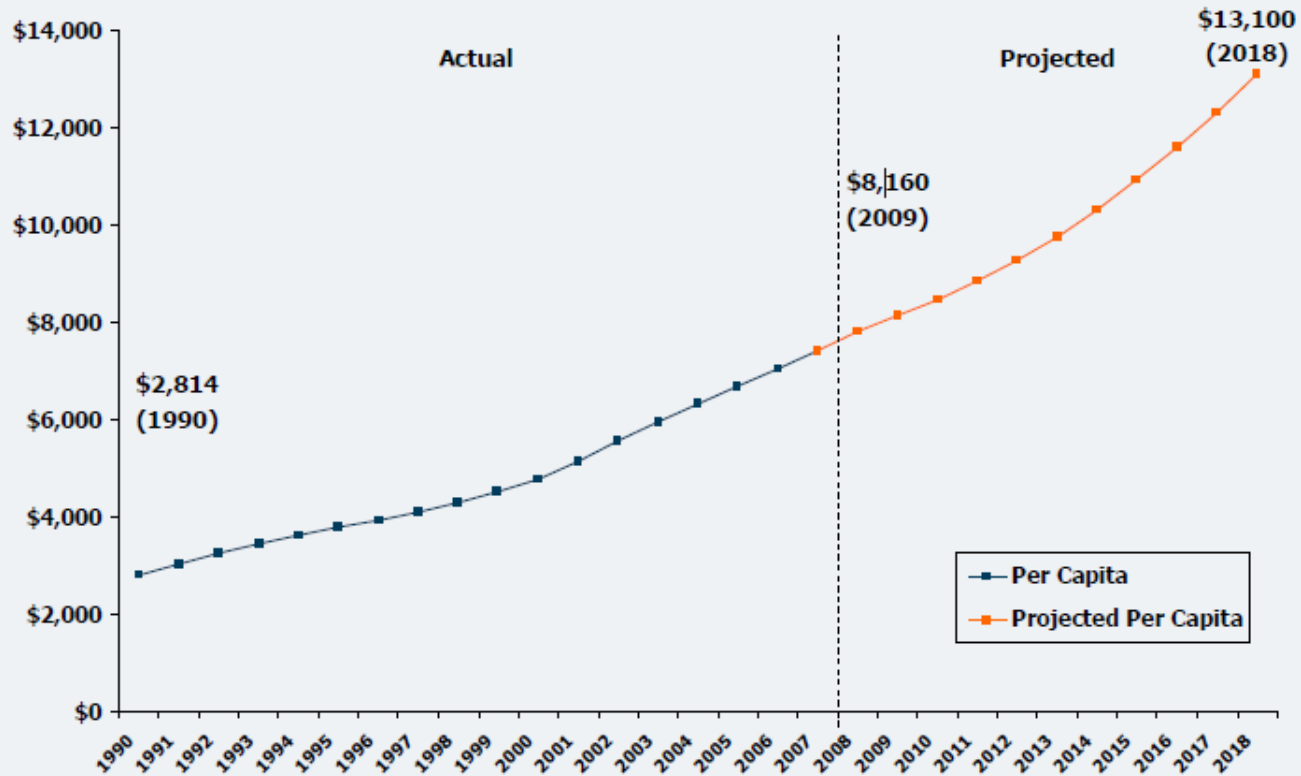
2010

8701 W WATERTOWN PLANK RD, WAUWATOSA, WI 53226

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

Exhibit 1: National Health Expenditures per Capita, 1990-2018



Kaiser Family Foundation March 2009



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

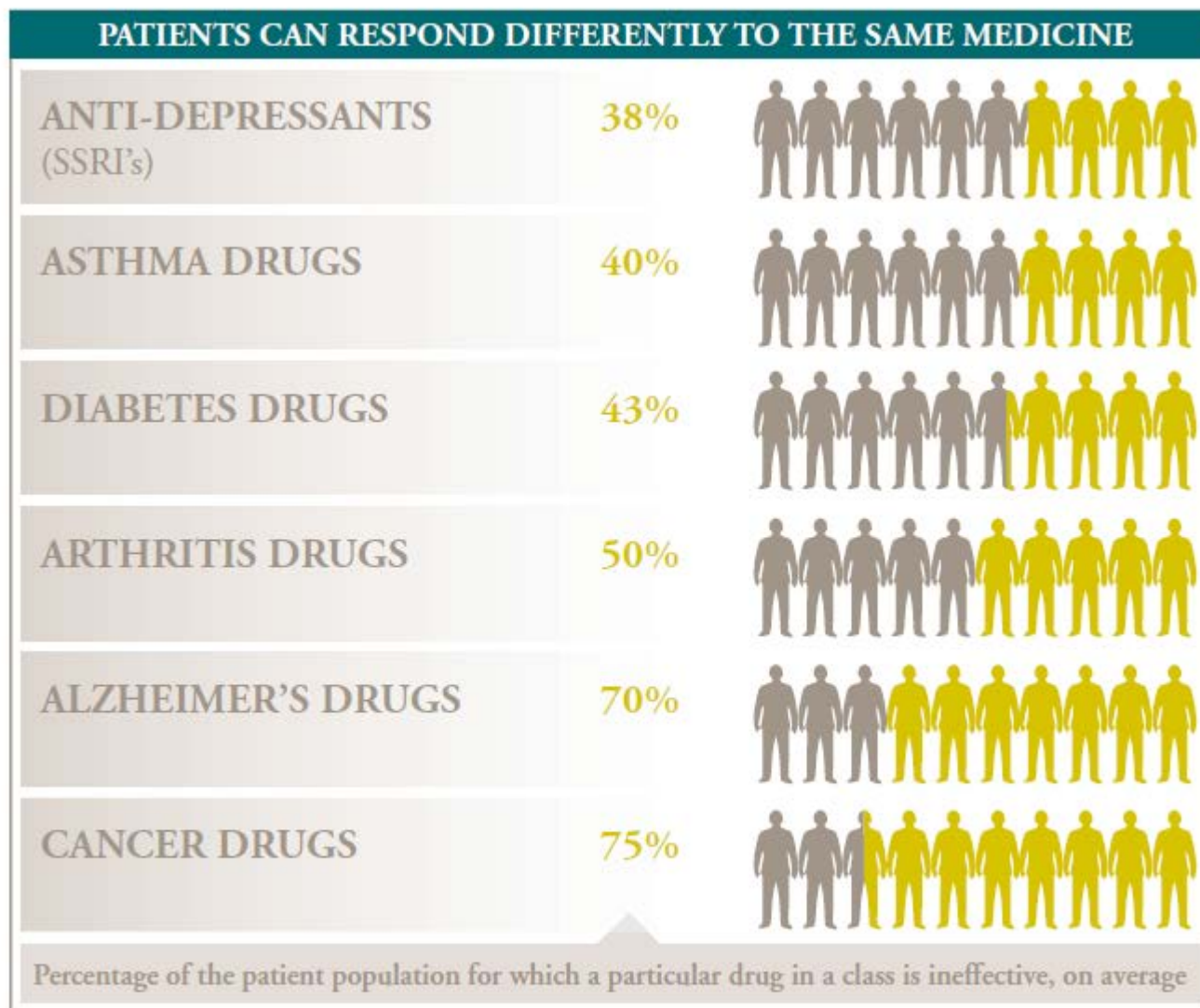
Preventive medical care includes services such as cancer screening, cholesterol management, and vaccines. In making its estimates of the budgetary effects of expanded governmental support for preventive care, CBO takes into account any estimated savings that would result from greater use of such care 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.

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

- Plavix comes off patent in 2011 assuming a drop of price of just \$100 per month. Current price is \$1,500 per month.
- New distribution of prescriptions:
200 pts on Plavix $200 \times \$100 \times 12 \text{ months} = \$240,000$ in year 1!
100 pts on Ticagrelor
- 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.
- Bonus for using a WGS: Analyzes of other PGX genes or clinical traits

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!

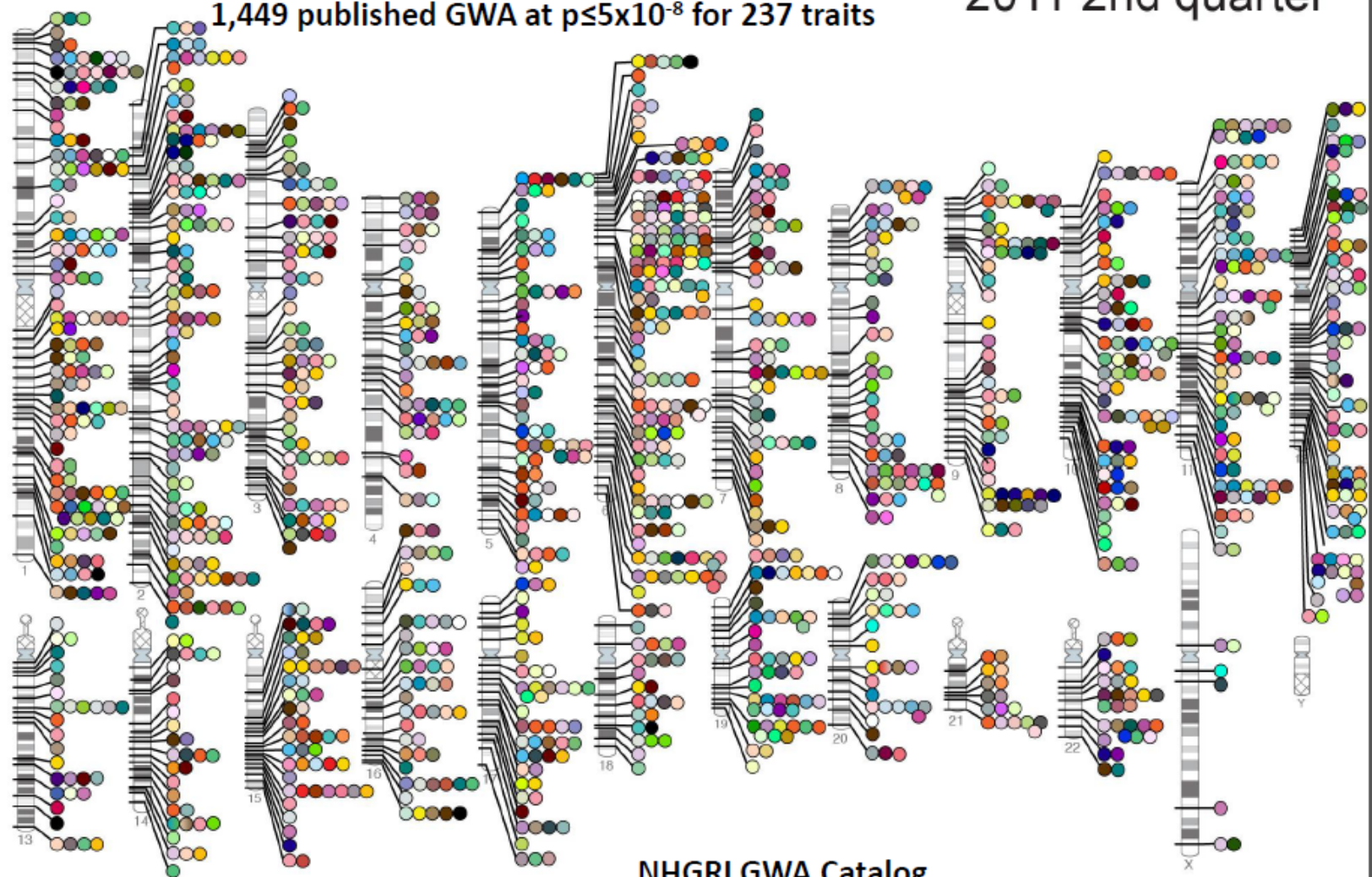
370 Drugs/Compounds PharmGKB

How many diseases or clinical phenotypes?

Published Genome-Wide Associations through 06/2011,

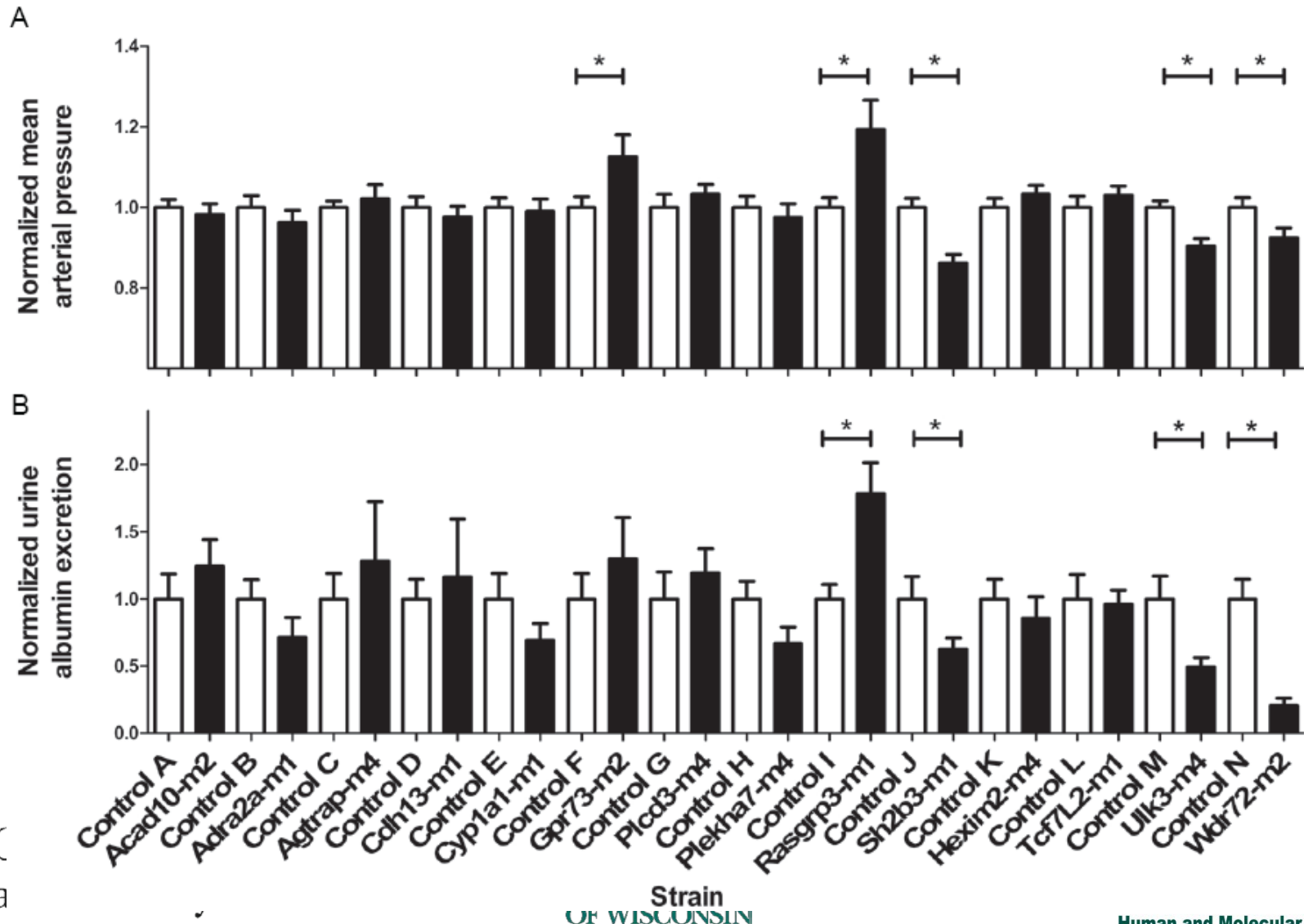
1,449 published GWA at $p \leq 5 \times 10^{-8}$ for 237 traits

2011 2nd quarter



NHGRI GWA Catalog
www.genome.gov/GWAStudies

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



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

WHOLE GENOMIC SEQUENCING

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

NO ONE WILL PAY FOR IT!

Letter from Insurance Group

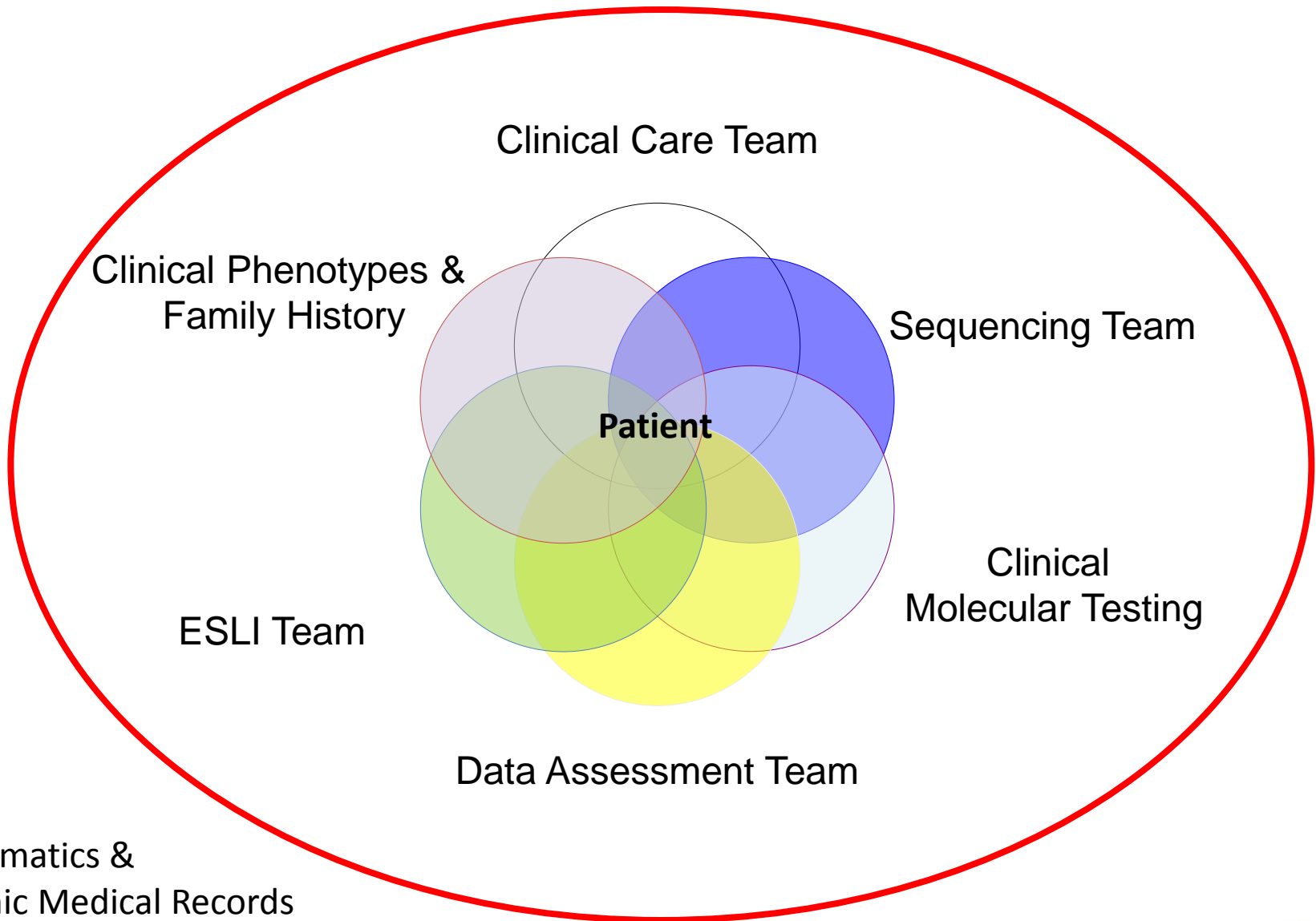
February 23, 2011

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

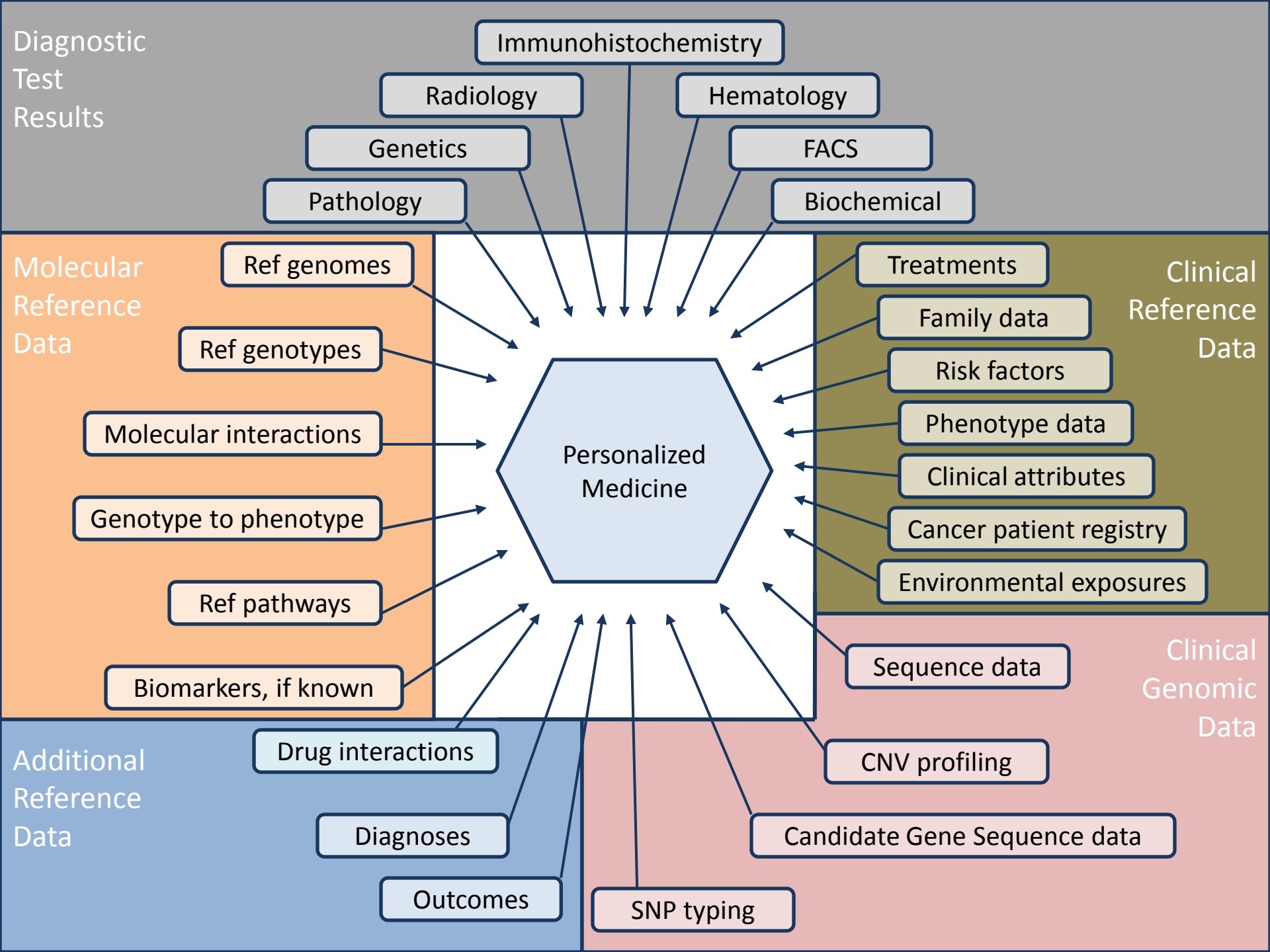
To date 4 of 10 pre-approval

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.



Bioinformatics &
Electronic Medical Records



Rapidly Changing Landscape

Whole Exome Genome Sequence for
clinical use will accelerate uptake!



NIH Director Highlights Volker Case in Testimony

by medicalcollegeofwi



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





Name: Anto Nedic
Date of Birth: 13.09.1968 (30yrs)
Male, 183 cm, 79.0 kg

REST ECG / Standard Page (1)

Patient ID: 1309968

marquette HELLIGE CardioSoft V3.03

HR [BPM]

Page 1

72

Trace Window: Contig2

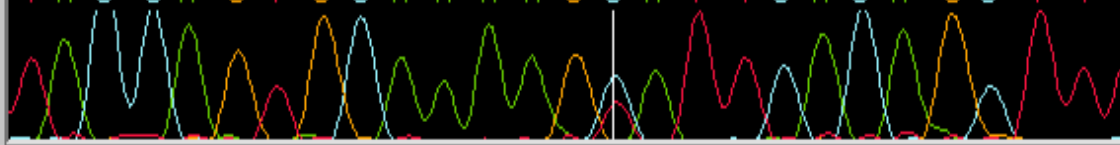
Dismiss

5htr_a1818.s1 con rd

5	1030	1035	1040	1045	1050
5	260	265	270	275	280

H []
V []

T A C C A G T G C A A A A G T A T T C A C A G C T T T
T A C C A G T G C A A A A G C A T T C A C A G C T T T
T A C C A G T G C A A A A G C A T T C A C A G C T T T



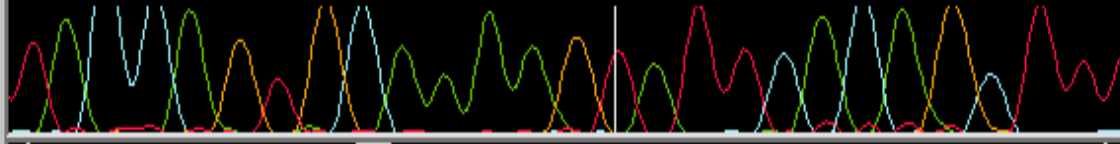
Scroll Together? Yes No
Remove Undo

5htr_a1717.s1 con rd

5	1030	1035	1040	1045	1050
9	264	269	274	279	284

H []
V []

T A C C A G T G C A A A A G T A T T C A C A G C T T T
T A C C A G T G C A A A A G T A T T C A C A G C T T T
T A C C A G T G C A A A A G T A T T C A C A G C T T T



Scroll Together? Yes No
Remove Undo

Help Insert

prev

Dismiss

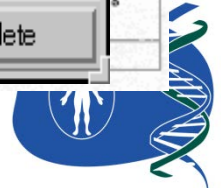
next

Help Delete



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

