Public Engagement, Policy, and Oversight while the Science Accumulates

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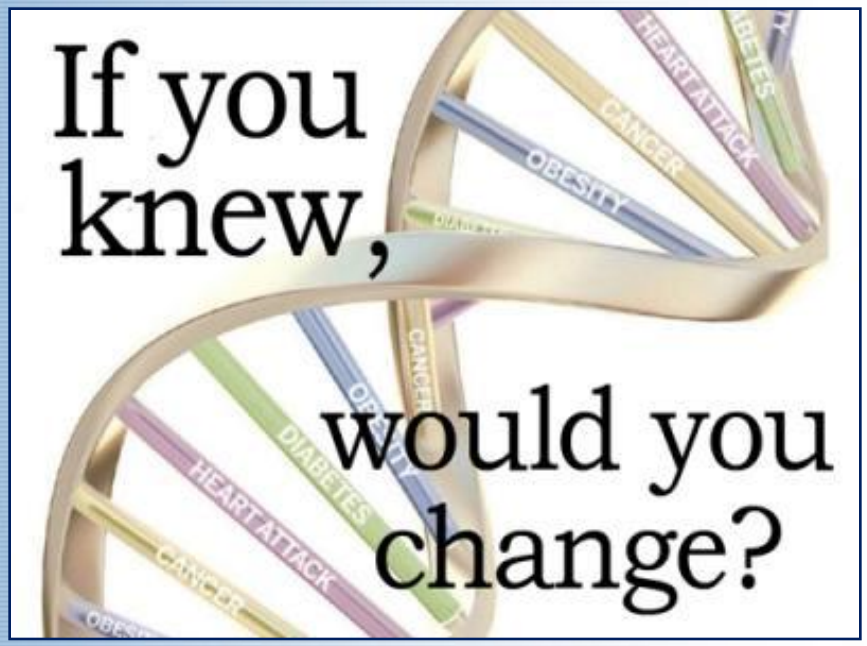
Lessons from my mother

- Show your work. (Registry)
- Be fair
  - Treat similar tests similarly.
  - GINA (Hurray!)
- Always tell the truth. (Claims)
- Avoid *omphaloscepsis.*

  We can opine on what we THINK people will think or do till the cows come home but we will be no closer to knowing the truth.

Personal Genomics

- Theoretical value
  - Improve individual health outcomes
  - Reduce health care costs



- Need evidence, evidence, evidence

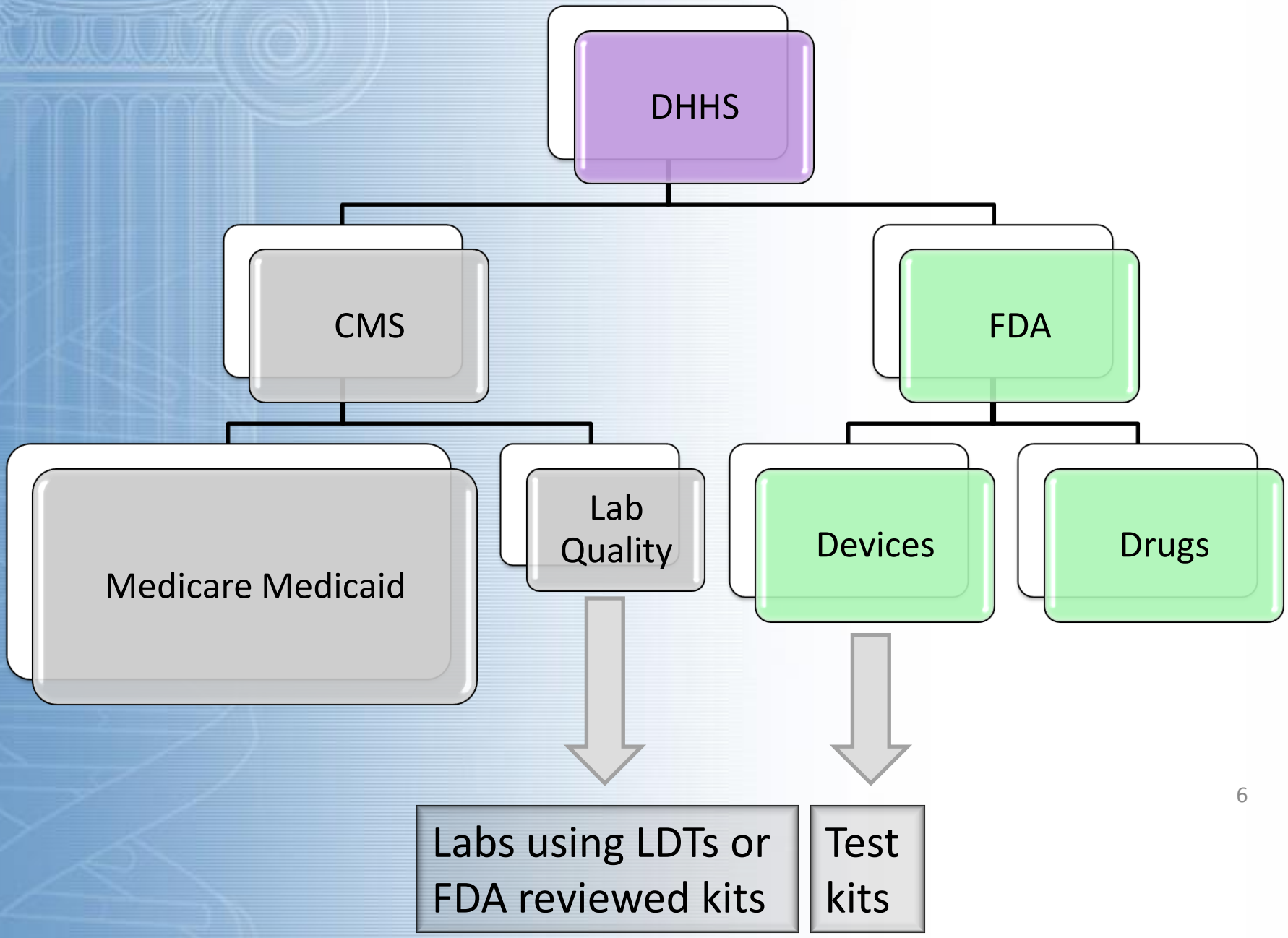
Key Prerequisites for Genetic Medicine

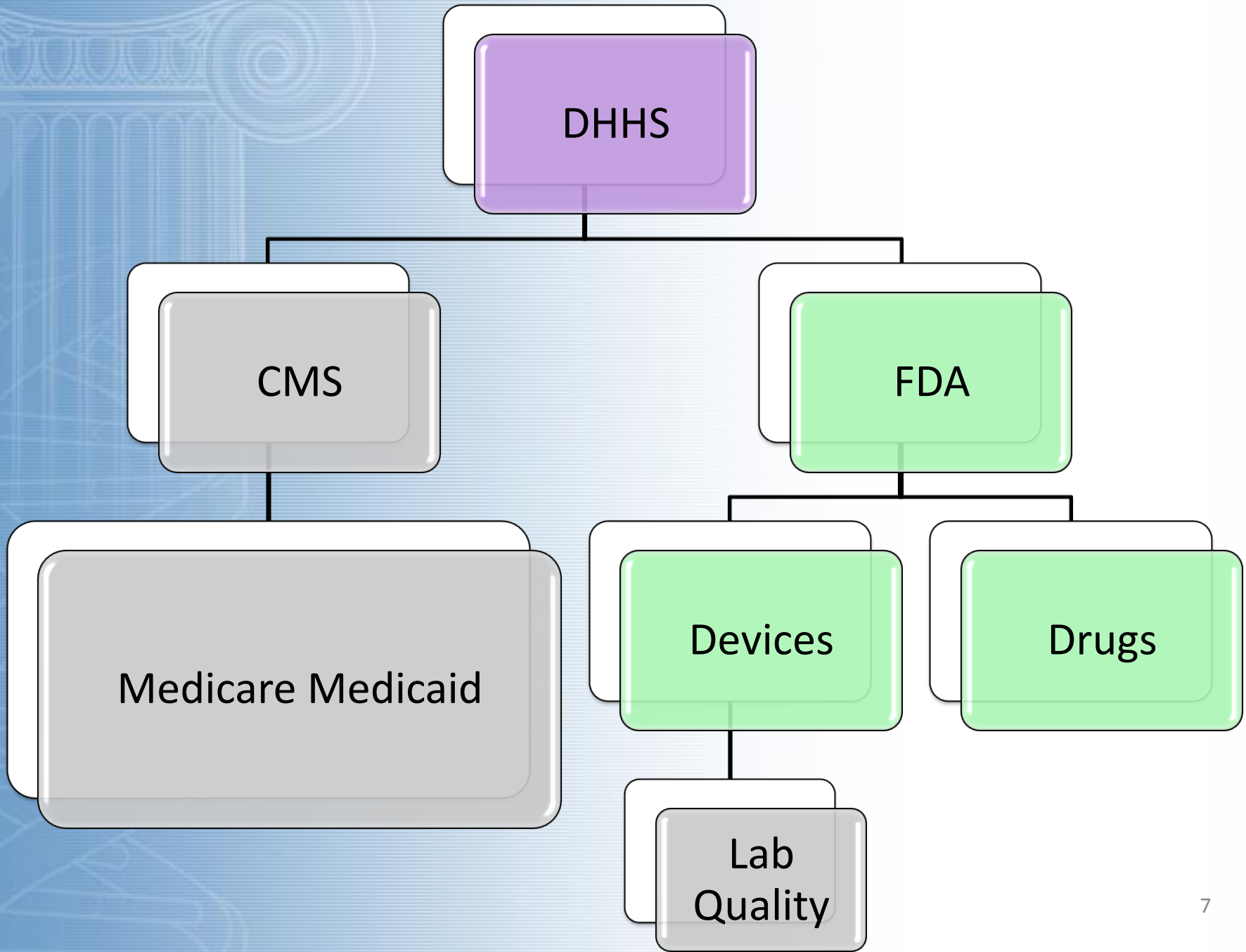
1. Robust, responsive, and responsible research enterprise
2. Improved guidelines development and adoption
3. Prepared patients and providers
4. Fair reimbursement for genetic services
5. Safeguards for genetic information
6. Safe and effective tests and interventions

Two Types of Tests

1. Laboratory developed tests (so-called homebrews)
2. Test “kits”

   - Level of regulatory oversight oddly disparate
   - Difference not apparent to patients and health care providers.


DHHS
CMS
FDA
Medicare Medicaid
Lab Quality
Devices
Drugs
Labs using LDTs or FDA reviewed kits
Test kits


DHHS
CMS
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Medicare Medicaid
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Drugs
Lab Quality

Problems with “Two Path” System

- Different standards based on mode of delivery (LDT v. Kit)
- Absence of public access to information
- Economic disincentive to FDA route
- Difference in level of validation opaque to physicians and patient
- Inadequate oversight of claims

Six Steps to Safe and Effective Genetic Testing

1. Level of oversight should be based on risk and not mode of manufacture.
2. Genetic tests should give the right answer nearly all the time.
3. Data on analytic and clinical validity and clinical utility should be publicly accessible.
4. High risk tests should be subject to independent review before entering market.
5. Pharmacogenetic data should be rapidly incorporated into the label.
6. Pharmacogenetic tests should be subject to post market surveillance.

In 1988 Congress found

- that patients both “expect such testing to be done properly” and “assume, quite reasonably, that their interests and the public health are being protected by appropriate government agencies.”

- a “seriously flawed system” for ensuring laboratory compliance and an “ineffective proficiency-testing system for evaluating the performance of laboratories.”

Sadly, still true today for genetic testing laboratories

Regulation of Clinical Laboratories in the United States

- Proficiency testing (PT)
  - "a method of externally validating the level of a laboratory's performance"
  - Congress stated that PT "should be the central element in determining a laboratory's competence, as it provides a measure of actual performance on laboratory test procedures rather than only gauging the potential for accurate outcomes."

Analytes that CMS requires PT

MICROBIOLOGY

Bacteriology
- *Aerobic/Anaerobic Culture & Identification*
- *Antibiotic Susceptibility Testing*
- *Direct Bacterial Antigen Detection*
- *Gram Stain*

Mycobacteriology
- *Acid Fast Stain*
- *Mycobacteriology Identification*
- *Mycobacteriology Susceptibility Testing*

Mycology
- *Culture and Identification*

Parasitology
- *Presence or Absence of Parasites*
- *Identification of Parasites*

Virology
- *Direct Viral Antigen Detection*
- *Viral Isolation and Identification*

DIAGNOSTIC IMMUNOLOGY

Syphilis Serology

General Immunology
- *Alpha-1 Antitrypsin*
- *Alpha Fetoprotein (tumor marker)*
- *Antinuclear Antibody*
- *Antistreptolysin O*
- *Anti-Human Immunodeficiency Virus (Anti-HIV)*
- *Complement C3*
- *Complement C4*
- *Hepatitis B Surface Antigen (HBsAg)*
- *Hepatitis B Core Antibody (Anti-HBc)*
- *Hepatitis Be Antigen (HBeAg)*
- *Immunoglobulins, total:*
  - *IgA*
  - *IgG*
  - *IgM*
  - *IgE*
- *Infectious Mononucleosis*
- *Rheumatoid Factor*
- *Rubella*

CHEMISTRY

Routine Chemistry
- *Alanine Aminotransferase (ALT or SGPT)*
- *Albumin*
- *Alkaline Phosphatase*
- *Amylase*
- *Aspartate Aminotransferase (AST or SGOT)*
- *Bilirubin, total*
- *Blood Gases:*
  - *pH*
  - *pCO2*
  - *pO2*
- *Calcium, total*
- *Chloride*
- *Cholesterol, total*
- *Cholesterol, HDL*
- *Creatine Kinase, total*
- *Creatine Kinase, Isoenzyme (CK-MB)*
- *Creatinine*
- *Glucose*
- *Iron, total*
- *Lactate Dehydrogenase (LDH), total*
- *LDH Isoenzymes (LDH1/LDH2)*
- *Magnesium*
- *Potassium*
- *Sodium*
- *Total Protein*
- *Triglycerides*
- *Urea Nitrogen*
- *Uric Acid*

Endocrinology
- *Cortisol*
- *Free Thyroxine*
- *Human Chorionic Gonadotropin*
- *T3 Uptake*
- *Triiodothyronine*
- *Thyroid Stimulating Hormone*
- *Thyroxine, total*

Toxicology
- *Blood Alcohol*
- *Blood Lead*
- *Carbamazepine*
- *Digoxin*
- *Ethosuximide*
- *Gentamicin*
- *Lithium*
- *Phenobarbital*
- *Phenytoin*
- *Primidone*
- *Procainamide and Metabolite*
- *Quinidine*
- *Theophylline*
- *Tobramycin*
- *Valproic acid*

HEMATOLOGY
- *Cell Identification*
- *WBC Differential*
- *Erythrocyte Count*
- *Hematocrit*
- *Hemoglobin*
- *Leukocyte Count*
- *Platelet Count*
- *Fibrinogen*
- *Partial Thromboplastin Time*
- *Prothrombin Time*

IMMUNOHEMATOLOGY
- *ABO Group*
- *D (Rho) Typing*
- *Unexpected Antibody Detection*
- *Compatibility Testing*
- *Antibody Identification*

- CMS has argued against new PT requirements citing absence of sufficient PT materials and programs.

- PT providers cite absence of demand sufficient to develop new materials and programs.

Interesting and terrifying factoids about PT

1. List of tests subject to PT created 20 years ago.
2. CMS took over a decade to create Pap smear PT standards
3. CMS took over a year to respond to a request for PT results that they claim are “publicly available.”
4. Questioned about the meaning of the numerous zero HIV PT scores and the action taken, CMS said they did not understand the data; they would look into it and get back to us. We are still waiting…..

CMS Regulation of Genetic Testing Laboratories

- No mandate to perform proficiency testing
- No evaluation of clinical validity
- Little public access to information
- No authority over claims and labels
- Buried in an agency with a different mission and expertise

FDA Regulation of Tests

- Test kits
  - Evidence of clinical validity for intended use(s) included in submission
  - Authority over manufacturer or distributor claims
  - Only a few human genetic tests have been approved by FDA as kits

- Laboratory-developed tests
  - Enforcement discretion
  - IVDMIA confusion
  - Ovasure oddity

U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services

Report of the Secretary's Advisory Committee on Genetics, Health, and Society

- PT requirement for all non-waived tests
- Development of a mandatory registry for lab-developed tests
- Risk-based oversight of lab-developed tests by FDA
- Enhancement of enforcement actions for non-compliance
- Clinical utility assessment
- Creation of electronic health records

Genentech
IN BUSINESS FOR LIFE

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LEGAL DEPARTMENT
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Division of Dockets Management
US Food and Drug Administration (FDA)
Department of Health and Human Services
5630 Fishers Lane
Room 1061
Rockville, MD 20852

December 5, 2008

Dear Sir or Madam:

Genentech submits the attached Citizen Petition under Sections 201, 301, 510, 513, 519, and 520 of the Food, Drug, and Cosmetic Act and 21 Code of Federal Regulations Section 10.30 to request the Commissioner of Food and Drugs require all *in vitro* diagnostic tests intended for use in drug or biologic therapeutic decision making be held to the same scientific and regulatory standards. These scientific and regulatory standards should apply regardless of whether the *in vitro* diagnostic tests are developed and sold by device manufacturers as diagnostic test "kits" or are developed in-house by laboratory-based companies for in-house testing ("laboratory-developed tests" or "LDTs").

Respectfully submitted,

Sean Johnston

Sean A. Johnston
Senior Vice President and General Counsel

cc: Michael O. Leavitt, Secretary of DHHS
Andrew C. von Eschenbach, MD, Commissioner of Food and Drugs
Gerald F. Masoudi, Chief Counsel, FDA
Janet Woodcock, MD, Director, Center for Drug Evaluation and Research, FDA
Daniel G. Schultz, MD, Director, Center for Devices and Radiological Health, FDA

Legislation

- Laboratory Test Improvement Act (Kennedy-Smith)
- Genomics and Personalized Medicine Act (Obama-Burr)

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PGx Drug Labeling

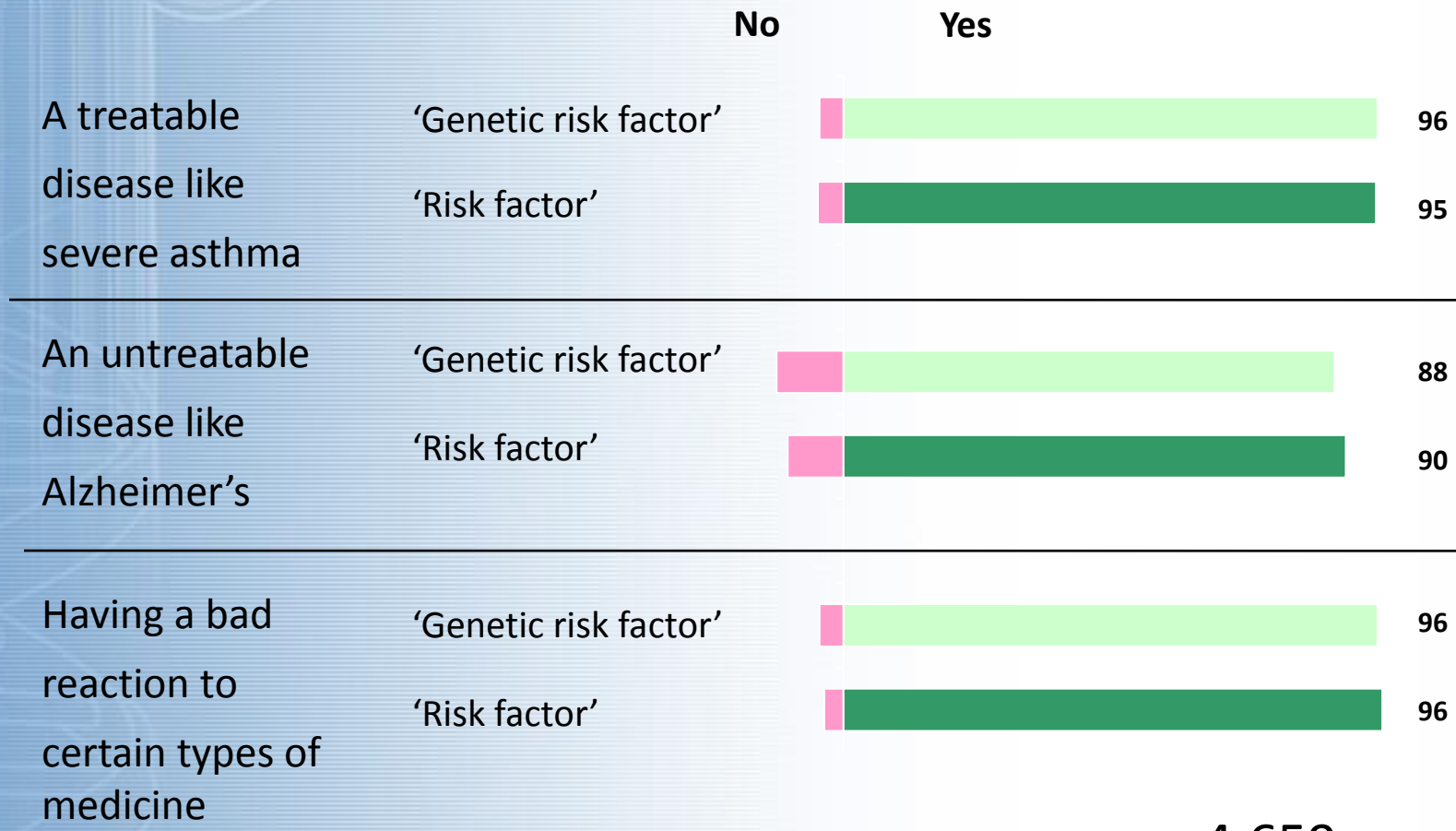
- Retrospective studies show that monoclonal antibodies to EGFR (Cetuximab and Panitumumab) do not work for folks with somatic K-RAS mutations.
- FDA now considering inclusion in the drug label.
- Would be nice to have high level of confidence in the test.

“Isn’t a large national cohort study a good idea?”

Dr. Greene, yesterday

- 80% of the general public think it is a good idea.
- 64% say they would participate.

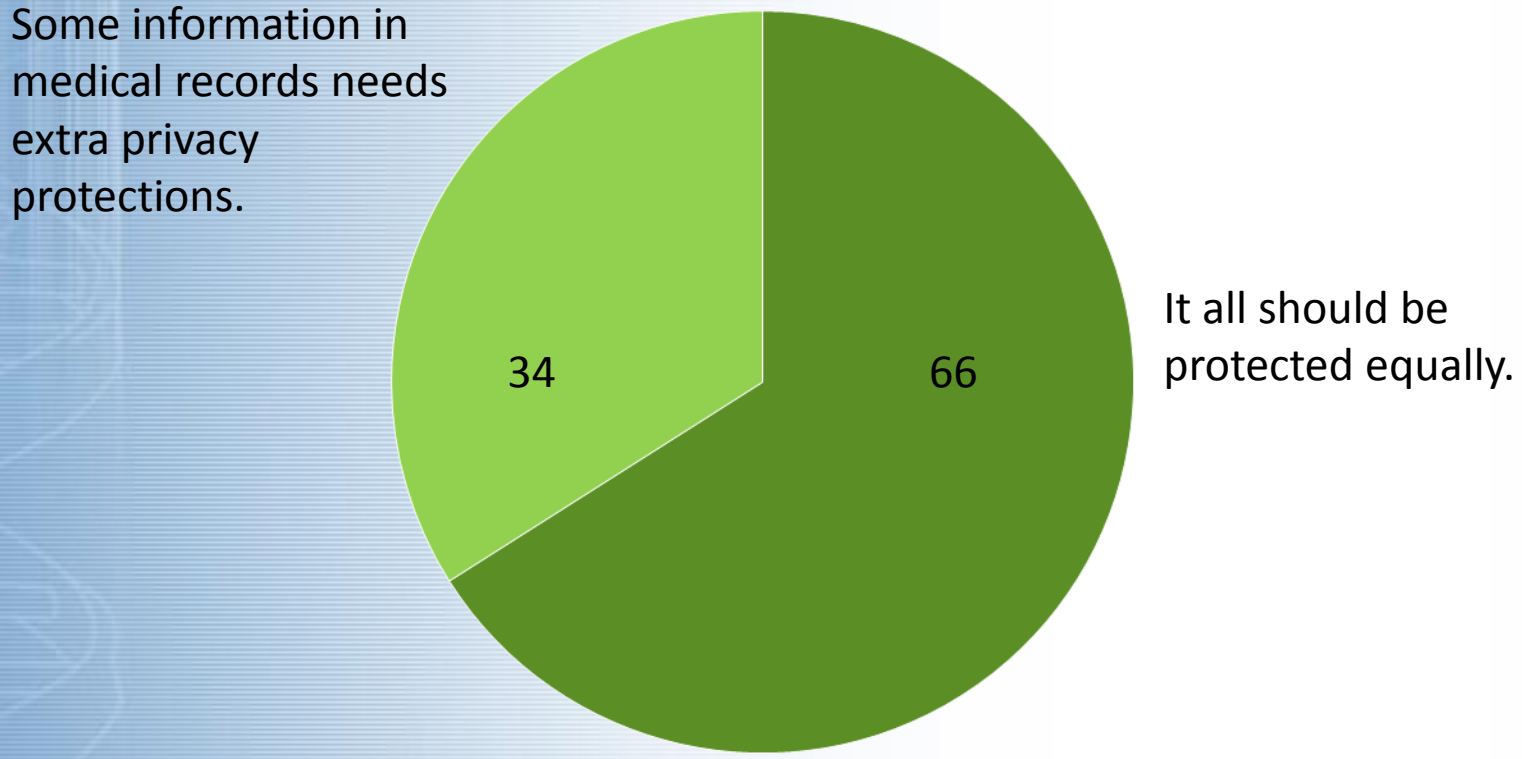
Would you want to know if researchers found that you [have a genetic risk factor for/ were at increased risk for]



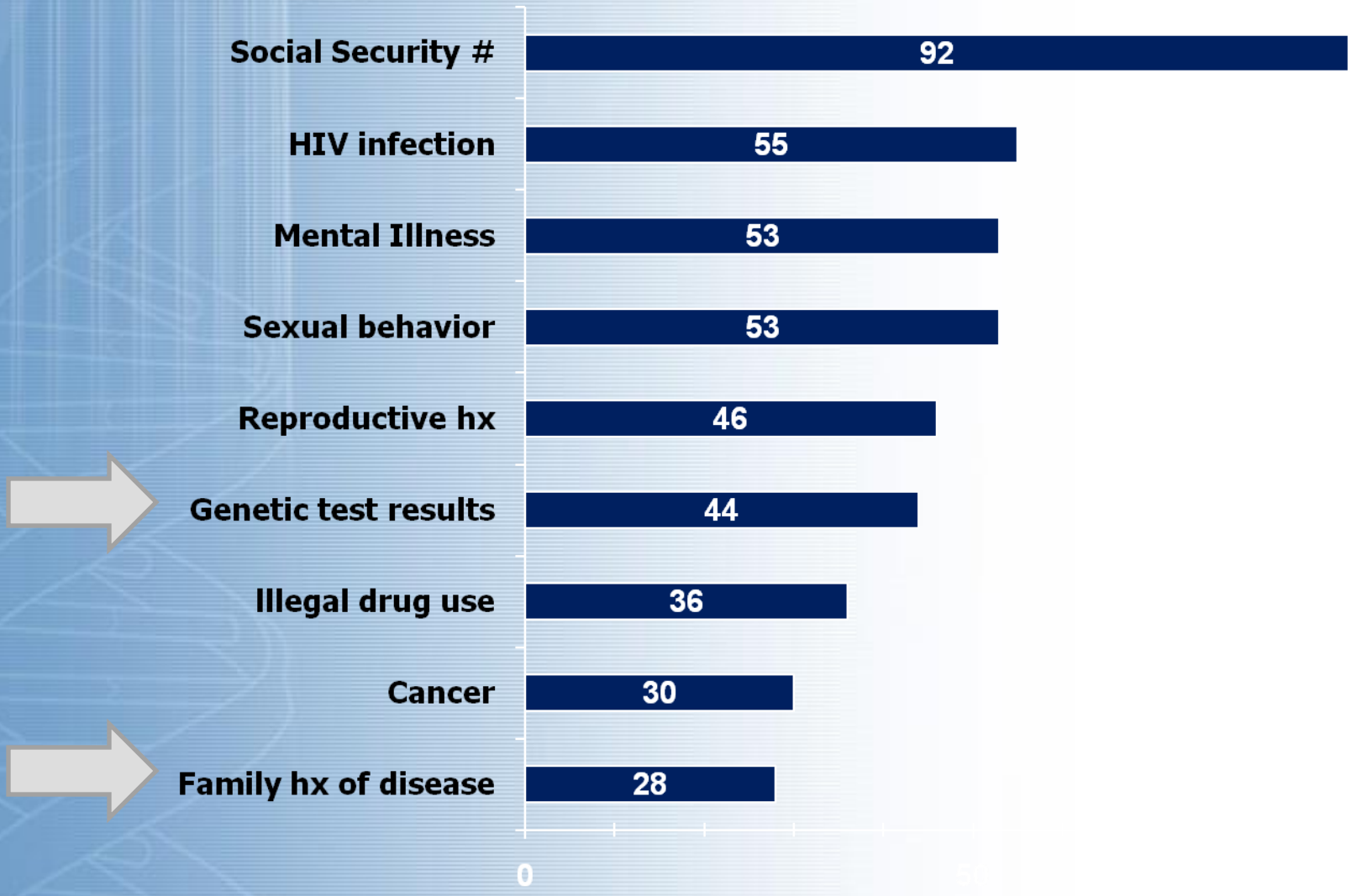
n=4,659

Kaufman et al., Genetics in Medicine, November 2008

Does some information on medical records need extra privacy protection?



What types of information in a medical record do you think need extra privacy protections? (n=1574)



Genetic Testing Policy Needs

Genetic Test Quality

- Mandatory proficiency testing
- Mandatory genetic test registry
- FDA oversight of hi-risk tests

Pharmacogenetic Labeling of Drugs

Truth in Genetic Testing Advertising

HIPAA modernization

GINA implementation

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