Clinical Laboratory Standard Setting

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Qualifications

- Chair, ACMG Lab Quality Assurance Committee
- Director, ACMG Board of Directors
- Member, CLSI Molecular Area Committee
- Member, ACMG/CAP Biochemical/Molecular Resource Committee
- Expert Panel Member, EGAPP
- Scientific Advisor, EurogenTest

- Profession: Clinical Molecular Geneticist
  - 19 years Clinical Molecular Genetic Laboratory Director

Professional Guidelines

- Professional guidelines set practice standards
- As the professional voice of the medical genetics community (advocating for providers and services), ACMG has several mechanisms for guideline development:
  - The Laboratory Quality Assurance Committee
    - Technical Guidelines for genetic lab testing
  - The Professional Practice and Guidelines Committee
    - Clinical Guidelines
  - ACMG Special Projects
    - Commissioned or grant funded

The American College of Medical Genetics (ACMG)

- **Policy statements**
  - Often a response to a specific issue/question
  - Often less than one page long
  - Example: BRCA-1 mutation in Ashkenazi Jewish women, statement on population screening
- **Practice guidelines**
  - Specifies what tests should be offered in what settings
  - Often does not specify exactly how testing is performed
  - Example: Fragile X syndrome diagnostic and carrier testing
- **Laboratory standards & guidelines**
  - Usually does not specify whether to test, or who to test
  - Focuses on ensuring quality testing and reporting
  - Example: Technical standards and guidelines for Fragile X

What are Clinical Laboratory Standards?

- **A1: Purpose of Guidelines These voluntary standards have been established as an educational resource to assist medical geneticists in providing accurate and reliable diagnostic genetic laboratory testing consistent with currently available technology and procedures in the areas of clinical cytogenetics, biochemical genetics and molecular diagnostics.**

The ACMG Laboratory Quality Assurance Committee as a Resource (1)

- The Medical Genetics community's authoritative body for laboratory genetic services:
  - Evaluates new technologies
  - Monitors accreditation requirements
  - Monitors laboratory proficiency testing
  - Interfaces with national groups and agencies
  - Develops standards and guidelines to address needs & assure high quality testing
    - Virtual laboratory manual, with on-going updates
    - Disease-specific guidelines
    - Model laboratory reports

The ACMG Laboratory QA Committee as a Resource (2)

The Medical Genetics community's authoritative body for laboratory genetic services (cont'd):

- Responds to patient and provider needs
- Carries out educational activities

- We believe that all health professionals will have a role in the genetic testing process and therefore need to be conversant with issues of:
  - Test quality
  - Communication of test results interpretation

- ACMG S&G serve as educational tools for those who:
  - Offer and order genetic tests
  - Discuss testing decisions and results with patients/families

Who Is Involved in Laboratory Standards Development?

- ACMG Quality Assurance Committee
  - Molecular Workgroup (9)
  - Cytogenetic Workgroup (7)
  - Biochemical Workgroup (4)
  - Biostatistician (1)
  - Selected experts in the field –topic specific

- ACMG-Commissioned *ad hoc* Committees funded for specific tasks
  - Pharmacogenetics Guidance Document
  - Newborn Screening

Lab QA Committee Members (2007)

Biochemical Genetics

Tina Cowan, PhD - Stanford, CA
Dieter Matern, PhD – Rochester, MN
Glenn Palomaki, BS - Gray, ME
Piero Rinaldo, MD, PhD - Rochester, MN
Chunli Yu, PhD – Atlanta, GA

Cytogenetics

Betty Hirsch, PhD - Minneapolis, MN
Jim Mascarello, PhD - Santa Fe, NM
Kathleen Rao, PhD - Chapel Hill, NC
P. Nagesh Rao, PhD - Los Angeles, CA
Debra Saxe, PhD - Atlanta, GA
Daynna Wolff , PhD -Charleston, SC

Molecular Genetics

Daniel Bellissimo, PhD - Milwaukee, WI
Wayne Grody, MD, PhD - Los Angeles
Madhuri Hegde, PhD – Atlanta, GA
Kathryn Kronquist, PhD – Denver, CO
Elaine Lyon, PhD – Salt Lake City, UT
Kristin Monaghan, PhD - Detroit, MI
Thomas Prior, PhD - Columbus, OH
Sue Richards, PhD- Portland, OR
Elaine Spector, PhD - Denver, CO

ACMG Executive Office

Mike Watson, PhD – Washington, DC
Judith Benkendorf, MS -DC

How do Standards Ensure Quality of Genetic Testing?

- Set standard of practice in field
- Used in development of laboratory inspection checklists as regulatory requirement for accreditation
- Used in developing proficiency testing challenges and test interpretation
- Educational resource for laboratories

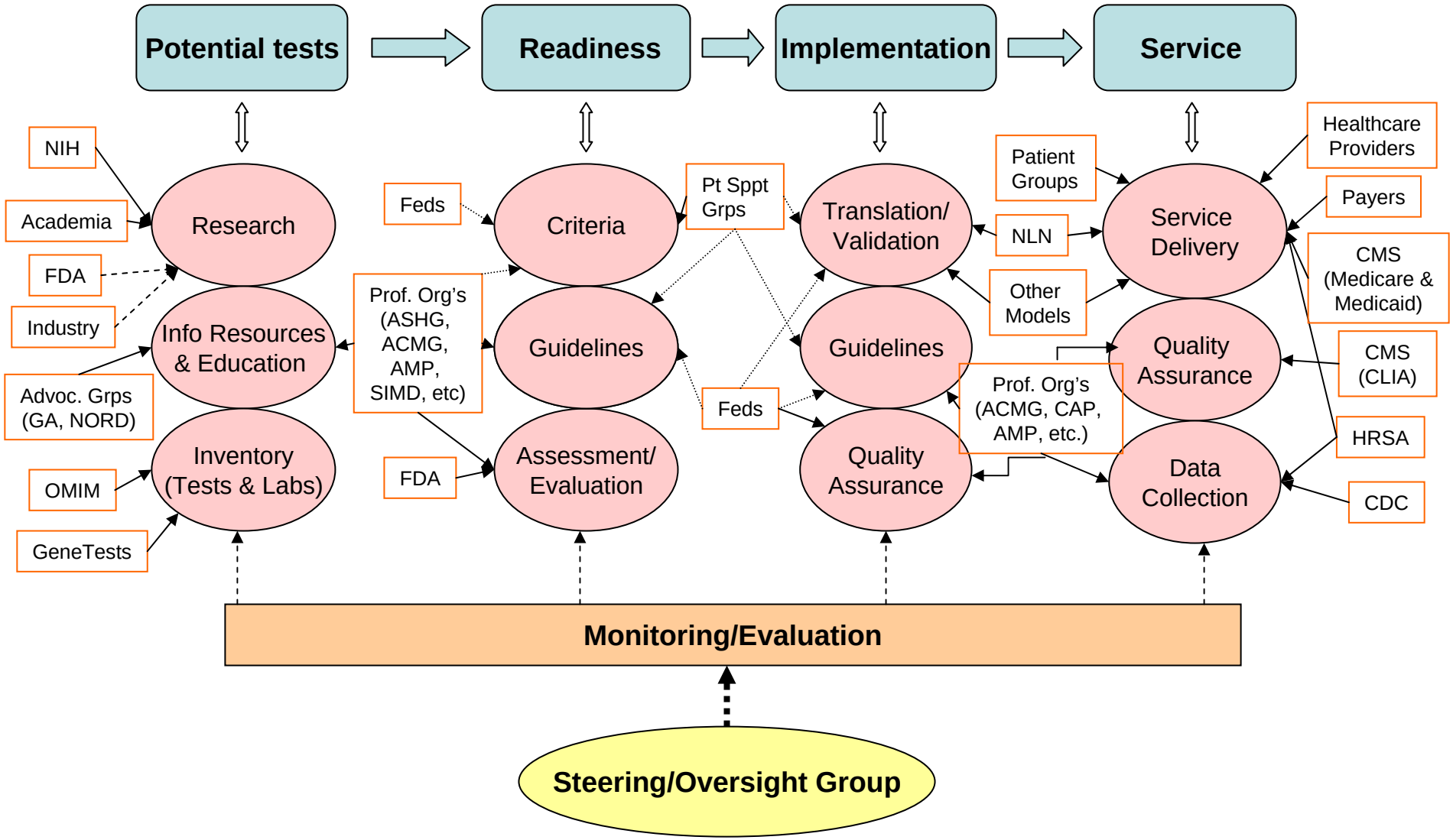
Rare Disease Testing: Interaction of Government & Private Sector

- CDC, NIH, and Professional organizations including ACMG: Meeting May 2004 "Promoting Quality Laboratory Testing for Rare Disease: Keys to Ensuring Quality Genetic Testing"
- First national meeting to address quality, availability, and accessibility of genetic testing for rare diseases

Sept 2005 Conference: Access to Quality Testing for Rare Diseases

- **Participants (200): patients/consumer advocacy groups, labs, payers, IVD industry, government agencies, researchers**
- **Purpose:**
  - **to raise awareness of need to improve availability, quality & accessibility of genetic testing for rare disorders**
  - **to develop models to enhance translation of genetic tests from research into clinical practice**

Draft Framework for Process to Enhance Genetic Testing for Rare Diseases



Note: Dashed lines indicate potential roles and involvement to be discussed. Solid lines indicate current/existing roles and involvement.

Example of a Laboratory Guideline

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ACMG Standards and Guidelines

Technical Standards and Guidelines: Molecular Genetic Testing for Ultra-Rare Disorders

Anne Maddalena, PhD[1], Sherri Bale, PhD[1], Soma Das, PhD[2], Wayne Grody, MD, PhD[3], Sue Richards, PhD[4], and the ACMG Laboratory Quality Assurance Committee

Key Words: *clinical genetic testing, sequencing, rare disorders, technical standards and guidelines*

Biochemical Genetics Disease-Specific Guidelines: Lab QA Committee

- Prenatal Screening for Open Neural Tube Defects - 2005
- Prenatal Screening for Down Syndrome (second trimester)-2005
- Second Timester Maternal Serum Screening for Fetal Open Neural Tube Defects & Aneuploidy -2005
- First trimester Down Syndrome Screening: Laboratory-based Nuchal Translucency
- Acylcarnitine Disorders

Molecular Genetic Disease-Specific Guidelines: Lab QA Committee

- Cystic Fibrosis Mutation Testing
- Venous Thromboembolism Testing (Factor V Leiden and Prothrombin 20210G>A)
- Fragile X Testing
- Huntington Disease Testing
- Molecular Genetic Testing for Ultra-Rare Disorders
- Ashkenazi Jewish Diseases
- Interpretation of Sequence Variants

Cytogenetic Testing Guidelines: Lab QA Committee

Based on Techniques and Tissue Types

- **Constitutional Chromosome Studies**
  - **Peripheral blood and solid tissue**
- **Acquired Chromosome Abnormalities**
- **Prenatal Diagnosis**
  - **Amniotic fluid, chorionic villi**
- **Fluorescence *in situ* Hybridation (FISH)**
  - **Metaphase, Interphase/nuclear, Multi-targeted**
- **Comparative Genomic Hybridization (CGH arrays)**
- **Solid Tumors**

ACMG QA Projects In Progress

- Quality Watch: A program for reporting and following up adverse events suspected to be caused by laboratory products and reagents, which impede accurate testing

- Other Specialized Guidelines in progress:
  - Maternal Cell Contamination (biochemical testing)
  - Ultra-Rare Disorders Testing (biochemical tests)
  - Informed Consent
  - Colorectal Cancer Testing
  - Gene Amplification

How is Standards Development Supported?

- ACMG Quality Assurance Committee is comprised of volunteer members who are not paid to develop guidelines or attend meetings
- Commissioned documents from ACMG are through grants, usually industry-funded
  - Cost is estimated at ~$100,000 per standard & guideline document to cover meetings, evidence-based review, and administrative writing costs
    - Example: Pharmacogenetics S&G
  - NBS S&G: ACMG estimates cost closer to $1M

How are Standards Developed?

- Identify a need.
- Seek approval from Lab QA and BOD to form workgroup
- Commission a leader from Lab QA who forms the workgroup of experts (~4-6 members)
- Over ~6 months of conference calls & emails a first draft is produced, circulated and reviewed with comments
- The revised draft is sent to the Lab QA subspecialty workgroup for review and comment (~1 month)
- The new revised draft is sent to full Lab QA committee for review (3-4 weeks) and comments.

How are Standards Developed? (2)

- A final revision is then discussed at the Lab QA meeting and voted on.
- If approved, it is sent to the BOD for review (2-3 weeks), and then voted on.
- If approved, it is posted on the ACMG website for member comment (2 months).
- All comments are addressed, incorporated into the document, and sent back to the BOD for final approval.
- If approved, it is included in the S&G Manual on ACMG website & sent to GIM for publication.
- After 3 years, it is up for review and revision.

How are Standards Enforced?

- **A3: Voluntary Adherence Adherence to these *Standards and Guidelines* is completely *voluntary* ……..**

  HOWEVER….

- **ACMG/CAP Proficiency Testing Program & CAP Laboratory Inspections are based on ACMG S&G**

How do Standards Relate to Regulatory Requirements?

- The ACMG S&G address CLIA requirements for laboratories as applied to genetic testing
  - ACMG S&G exceed CLIA minimum standards
- ACMG Lab QA modified S&G based on CLIAC recommendations
- ACMG Lab QA reviews NY State requirements
- ACMG Lab QA reviews S&G developed by our European and Australasian counterparts to strive for international harmony in clinical laboratories
  - Nomenclature standards
  - Reporting standards

How do Standard Setting Organizations Interact With and Involve Government?

- We respond as a group to government guidance statements, e.g. FDA on ASR rules; MUEs for CPT coding, etc.
- We include government representatives in our committee work of developing S&G
- We review & utilize ACCE documents and CDC evidence-based reviews in our decision-making process & guidelines development (EGAPP model)
- Example of the Ultra Rare Disorders S&G Document was in parallel with CDC efforts

How do Standards Keep Pace with Advances in Knowledge & Technology?

- **A7: Maintenance of Guidelines These *Standards and Guidelines* will be reviewed and updated periodically to assure their timeliness in this rapidly developing field.**
- **3 year review cycle requires affirmation, revision, or retirement**
- **Requires multiple workgroups in each genetic subspecialty to maintain updated review**
- **This is a big challenge with limited resources.**

FACTS for Reflection

- Human genome: ~35,000 genes
- New OMIM entries: 60-100 per month
- Current rare diseases: 6,000 – 7,000
- New rare diseases: ~20 per month (5/wk)
- Diseases for which clinical testing is available: 947
- New testing: <10 per month

Are There Gaps in Current Standards?

- **Absolutely!**
- **There are more genetic tests than S&G, and resources are limited.**
- **There is a need for more disease-specific S&G and new technology-driven guidelines.**
- **There is a gap in standard setting for testing of genes with exclusive IP of a single commercial group & for new tests marketed by Internet companies with direct to consumer marketing.**
- **ACMG QA currently does not use its limited resources to develop S&G on test monopolies.**
  - **ACMG/CAP Biochemical/Molecular Resource Committee is eliminating proficiency testing for exclusively licensed tests (SCAs, FRDA, etc.)**

Needs & Opportunities to Collaborate with Federal Government

- Funding for more Standards & Guidelines development through ACMG
- Engaging ACMG and other professional societies' memberships in national meetings to address issues of common interest, e.g. CDC model for rare disorders
- Providing funding for evidence-based reviews on more genetic disorders
- Providing funding for filling "gaps", such as RCTs that are required for establishing clinical validation prior to developing S&Gs

Do Laboratories Follow Standards & Guidelines?

CAP Molecular Surveys indicate that the vast majority of clinical molecular genetic laboratories are performing at a high level of excellence……..

Indicating that most labs do use the ACMG S&G

Resources

ACMG Standards and Guidelines for Clinical Genetics Laboratories

Our Virtual Laboratory Manual

http://www.acmg.net/Pages/ACMG_Activities/stds-2002/stdsmenu-n.htm

To Contact the Laboratory QA Committee

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ACMG

www.acmg.net

Thank You!

Questions?