Collaboration Education and Test Translation Program

www.cettprogram.org

Giovanna Spinella, M.D.
NIH ORD CETT Program Director

ICORD September, 2007

CLIA Rule

- CLIA RULE - "Sec.493.3 Applicability.=3D20
- (a) Basic rule. Except as specified in paragraph (b) of this section, a laboratory will be cited as out of compliance with section
- 353 of the Public Health Service Act unless it--
- (1) Has a current, unrevoked or unsuspended certificate of waiver, registration certificate, certificate of compliance, certificate for …..
- (2) Is CLIA-exempt. *(NY state and Washington state)*
- (b) Exception. These rules do not apply to components or functions of--
- (1) Any facility or component of a facility that only performs testing for forensic purposes;
- (2) Research laboratories that test human specimens **but do not report patient specific results for the diagnosis, prevention or treatment of any disease or impairment of, or the assessment of the health of individual patients;** or…"
- http://www.cms.hhs.gov/clia/default.asp?

Genetic Test Access

- 2004
- 33% - testing is available only from “research” labs
- 22% - clinical testing is available only outside US

- July 2007
- 20% - testing is available only from “research” labs
- 19% - clinical testing is available only outside US

Laboratories Listed in GeneTests

- 2004
- 40% - “Research only”
- 31% - Non US labs
- 40% - clinical testing in only 1 lab

- July 2007
- 47% - “Research only”
- 38% - Non US labs
- 28% - clinical testing in only 1 lab

Rare Disease Test Translation Major Participants

- Conference Organizers

  CDC, NIH ORD, Emory University

- Planning Committee

  Joe Boone (CDC)
  Bin Chen (CDC)
  Carol Greene (HHS)
  David Ledbetter (Emory)
  Giovanna Spinella (NIH)
  Mike Watson (ACMG)
  Joann Boughman (ASHG)
  Andy Faucett (CDC)
  Steve Groft (NIH)
  Michele Puryear (HRSA)
  Sharon Terry (Genetic Alliance)

- CDC Staff
- ASHG

Building the Momentum

- May 19–21, 2004 Atlanta, GA
  - Workgroup meeting of invited experts

  http://www.phppo.cdc.gov/dls/genetics/RareDiseaseConf.aspx
- March 17, 2005 ACMG Satellite
  - Workgroup meeting of invited experts (CETT idea)
- September 26–27, 2005 Washington, DC
  - Open national meeting
- October 6-7, 2006 Atlanta, GA
  - Workgroup meeting of invited experts with focus on Biochemical Genetics

National Laboratory Network for Rare Disease Genetic Testing

A family of laboratories for orphan disease diagnostics.

Six laboratories formed the NLN in May 2004 and agreed to share a commitment to ensure that quality, affordable genetic testing services are accessible to all.

NLN website:
www.rarediseasetesting.org

Rare Genetic Diseases CETT

www.cettprogram.org

Collaboration Education and Test Translation Program

ORD Program Director:	Giovanna Spinella, MD
Project Coordinator:	Andrew Faucett, MS
Scientific Advisor:	Suzanne Hart, PhD
Review Board Coordinator:	Roberta Pagon, MD
NCBI Liaison:	Lisa Forman, PhD
Biochemical Advisor:	William Gahl, MD, PhD

CETT Program Objectives

- To promote the development of new genetic tests for rare diseases.
- To facilitate the translation of genetic tests from research laboratories to clinical practices.

CETT Program Objectives

- To establish collaborations and provide education about each rare genetic disease; related genetic research & the clinical impact of testing.
- To support the collection and storage of genetic test result information in publicly accessible databases to leverage the information into new research and new treatment possibilities.

Guiding Philosophy

All parties benefit when:

- Quality of testing for rare disorders meets or **exceeds** existing standards

Guiding Philosophy

All parties benefit when:

- Clinical laboratories, researchers, clinicians, and disease specific advocacy groups collaborate
- High-quality educational materials explain what the test can and cannot tell you and how best to use the test

Applicants = Collaborative Group

- Required
  - Clinical (CLIA-certified) laboratory
  - Researcher (laboratory and/or clinician)
  - Disease specific advocacy group
- Recommended
  - Genetic Counselor
  - Clinical and laboratory research expert

CETT Program Update

- First applications accepted Feb-March 2006
- First Review Board evaluation in April 2006
- Facilitated application process
  - Constructive feedback
- Applications
  - Accepted monthly
  - Electronic submission
  - Reviewed in 2-3 month cycle

CETT Program Update

- Success Summary
  - August 2007 – 27 tests reviewed
  - 26 approved
  - 3 in submission now
  - 2 returned and re-submission encouraged
  - 1 resubmitted
- Test Development Summary
  - Sept 2007 – 16 tests available

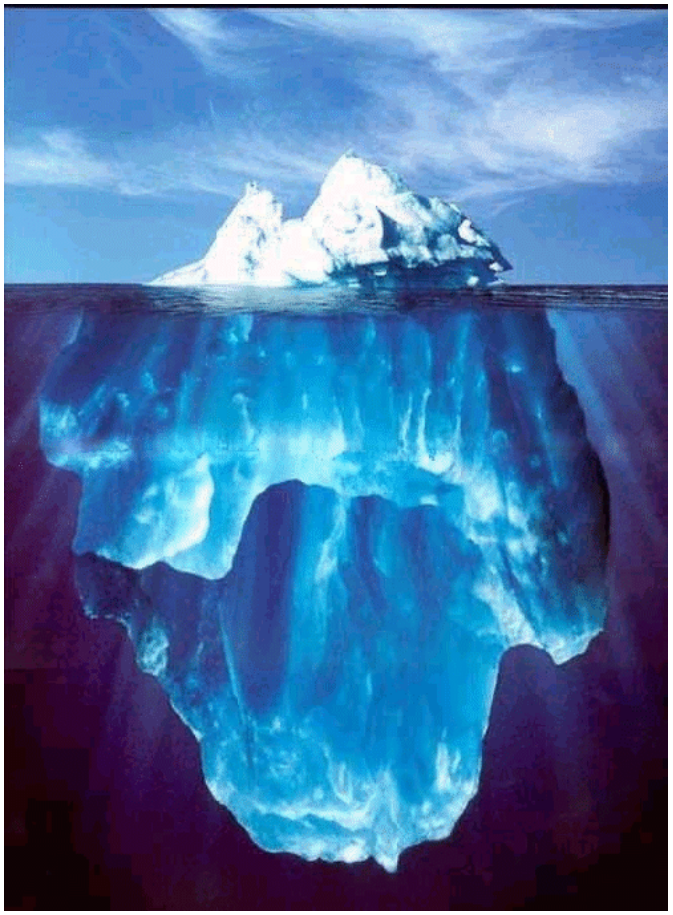
Program Cycle

- Review to Test Release
  - 1 month to 12 months
  - 5 month Average for released tests
- Anticipated Reviews
  - Averaging 2 per month

The CETT/NCBI Partnership

NCBI (NIH)

National Center for Biotechnology Information



- Help develop a useful data collection scheme and HIPPA compliant web based form
- Put data in a broader context to help advance knowledge about the disorder

The University of Chicago Genetic Services Laboratories
5841 S. Maryland Ave., Rm. L035, MC 0077, Chicago, Illinois 60637
Toll Free: (888) UC GENES (888) 824 3637
Local: (773) 834 0555 FAX: (773) 834 0556
ucgslabs@genetics.uchicago.edu www.genes.uchicago.edu
CLIA #: 14D0917593 CAP #: 18827-49

Collaboration, Education and Test Translation (CETT) Program:

Cornelia de Lange Syndrome

clinical questionnaire

Please include copy of form with sample

Submit to Lab

Print Form

Patient Name ____ ○ Male ○ Female **DOB** ____ **Today's Date** ____

Wt.: ○ lbs ○ Kg ____ **Ht.:** ○ in. ○ cm. ____ **Age at Onset:** ____ **Age Now:** ____ Submitting Dr. contact information ____

Ancestral Background:
(As reported by Patient. Please check as many as apply. Text boxes will expand as you type))

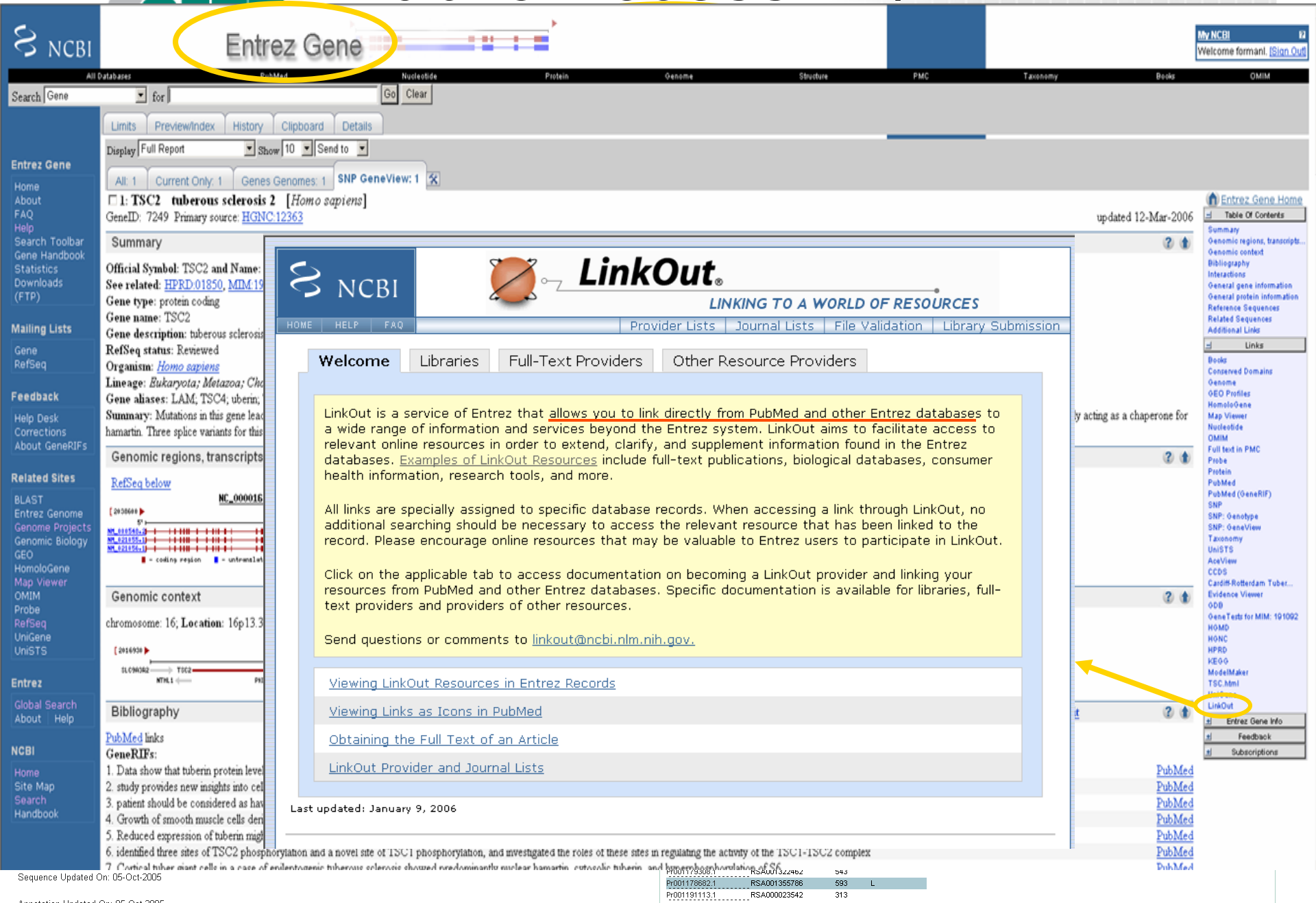
- ☐ Native American — Specify ____
- ○ African American ☐ Black ○ Not African Amer.
- ○ Latino or Hispanic ☐ Caucasian ○ Not Lat. or Hisp.
- ☐ Asian — Specify ____
- ☐ Native Hawaiian ☐ Other Pacific Islander
- ☐ Other Ethnicity — Specify ____

Features	Present:	Yes	No
Growth			
IUGR		○	○
Failure to Thrive		○	○
Gestational Age (wks)	____		
Birth Weight (gms)	____		
Birth Length (cm)	____		
Birth OFC (cm)	____		
Current OFC (CM)	____		
Craniofacial			
Microbrachycephaly		○	○
Synophrys/ arched eyebrows		○	○
Long, thick eyelashes		○	○
Low-Set ears		○	○

Features	Present:	Yes	No
Limb Abnormalities			
Upper extremity deformed		○	○
Describe	____		
Small Hands		○	○
Thumbs Proximal		○	○
5th finger clinodactyly		○	○
Limited elbow extension		○	○
Lower extremity involvement		○	○
Small feet		○	○
2-3 toe syndactyly		○	○
Gastrointestinal			
GER		○	○
Pyloric stenosis		○	○
Intestinal malrotation		○	○

- Data are de-identified and sent to NCBI.
  - Purpose: create opportunities that improve the clinical test interpretation by identifying genotype/ phenotype associations that can lead to targeted treatments for a disorder.
    - The more explicit the genotype information, the more likely such leveraging can occur

Public Access 24/7



Advocate Mentors

- Group of disease specific advocate leaders
- Resource to each collaborative group
- Assigned early in the process
- Option for “involved” genetic counselors to participate

Review Board

- 15 Members in year one
- Three teams of five members from:
  - Laboratory genetics
  - Medical genetics
  - Research
  - Primary care
  - Disease specific advocacy
- 18 Members – 3/07 – Add biochemical expertise

Review Board

- Vet guidelines by which applications are evaluated
- Evaluates quality of each application
- Provides constructive feedback for each application

Review Criteria

- Scientific Evidence
- Proposed Methodology
- Impact on Healthcare
- Laboratory Qualifications
- Data Collection and Sharing Plan
- Educational Materials
- Evidence of Collaboration – Empowered Roles
- Shared Development Costs

Tests Available as a Result of CETT

- Cornelia de Lange Syndrome – (U Chicago)
  - 2 genes – NIPBL & SMC1L1
- Joubert Syndrome (Prevention Genetics)
- Cherubism (Toronto Sick Children)
- X-linked Chondrodysplasia Punctata (U Chicago)
- Kallman Syndrome (Gene DX)
- Progressive Familial Intrahepatic Cholestasis (Baylor)
- Russell Silver (Emory)

Tests Available as a Result of CETT

- MPS VI (Emory)
- Niemann Pick A/B (Emory)
- X-Linked Periventricular nodular heterotopia
  - (Harvard U)
- Primary Ciliary Dyskinesia (UNC)
  - Targeted mutations – full sequencing under development
- Infantile Neuroaxonal dystrophy (Oregon HS)
- MADD (U of CO at Denver)

Tests Available Soon

Approved – In Development

- Arginase (UCLA)
- Allan Herndon Dudley - MCT8 (U Chicago)
- 9q34 deletion (Emory)
- Epimerase GALE (Emory)
- PXE (GeneDX)
- Familial Focal Segmental Glomerulosclerosis – NPHS2, ACTN4, TRPC6 – (Sick Kids)

More Tests Available Soon

Approved – In Development

- Arrhythmogenic Right Ventricular Cardiomyopathy – DSG2, DSP, PKP2 – (Sick Kids)
- X-linked Recessive Brachytelephalangic Chondrodysplasia Punctata – ARSE – (GeneDX)
- Bilateral Frontoparietal Polymicrogyria – GPR56 – (U Chicago)
- Autosomal Recessive Agammaglobulinemia – IGHM – (Correlagen)
- Urea Cycle Disorders – CPS1 & ASL – (Baylor)

Experience of CETT Program to Date

- Variability in Collaborative Group Composition
- Need for Educational Material Guidelines
- Laboratory Guidelines – CETT
  - VOUS (variants of unknown significance)
  - Reports
  - Turn-around time, control materials
  - Informed Consent
  - Role of Research / Clinical clarification for variants

Tools in Development

Developing CETT Standards- March 2007 Meeting

- Laboratory CETT Guidelines:

  VOUS, TAT, Pre-Implantation Genetic DX, Validation, Prenatal DX, Interpretation of Sequence Diff., Deletions and Duplications, Quality Control.

- Clinical Test Result Report Forms suggested framework/language
- Educational Materials Guidelines
- Pubic Databases and Rare Diseases Testing

The University of Chicago Genetic Services Laboratories

5841 S. Maryland Ave., Rm. L035, MC 0077, Chicago, Illinois 60637
Toll Free: (888) UC GENES (888) 824 3637
Local: (773) 834 0555 FAX: (773) 834 0556
ucgslabs@genetics.uchicago.edu www.genes.uchicago.edu
CLIA #: 14D0917593 CAP #: 18827-49

Genetic Testing for Cornelia de Lange Syndrome

Information for Patients and Families

What do I need to know about testing my child for Cornelia de Lange syndrome?

Cornelia de Lange syndrome (CdLS) is caused by a change in someone's DNA. People with CdLS are small for their age, have learning problems and look more like each other than their family members. This blood test may prove that your child has CdLS. However, half of the children with CdLS will have a negative result, so this test will not rule out CdLS. There is also a chance that the test will find something that we do not understand. Thus, we may need to test the child's parents to learn more. This information sheet will provide more details about CdLS and this testing. Please talk to a genetic counselor, if you have more questions about testing.

What is Cornelia de Lange syndrome?

Cornelia de Lange syndrome (CdLS) is a rare genetic condition. As with other syndromes, individuals with CdLS look alike. Common findings in these children include: small size at birth (often under five pounds), slow growth and small stature, and small head size (microcephaly). Typical facial features include thin eyebrows which frequently meet at midline (synophrys), long eyelashes, short upturned nose and thin, downturned lips.

Other frequent findings include extra body hair (hirsutism), small hands and feet, joining of the second and third toes, incurved fifth fingers, indigestion, seizures, heart defects, cleft palate, problems feeding, and learning problems. Limb differences, including missing limbs or portions of limbs, usually fingers, hands or forearms, are also found in some individuals. Not everyone with CdLS has all of the findings or is affected to the same degree.

What causes CdLS?

CdLS is caused by a change (mutation) in the *NIPBL* (Nipped-B-like) gene on chromosome 5. We each have two copies of the *NIPBL* gene. Half the individuals with CdLS have a change in one copy of the *NIPBL* gene. Genes are written instructions to make proteins. When there is a change in the instructions, the protein may not be made or may not work properly. Thus, the smaller amount of good protein from the *NIPBL* gene causes the features in CdLS. Research continues to look for other causes of CdLS.

Can my child be tested? Can I be tested? Can my family members be tested?

The first person to be tested in any family would be the individual thought to have CdLS. Testing for mutations in the CdLS gene is complex because it is a very large gene. It is like reading a very long book and looking for a single spelling mistake. You may read the whole book and miss the "typo," however when you do find it, then it is easy to test other family members (i.e. you know that the change is on page 875 in the second paragraph). Once a change is found in the person with CdLS, testing other family members, even during a pregnancy, is easy and fast because we know where to look. Testing is now available at The University of Chicago Genetics Services Laboratory.

Reasons for genetic testing for CdLS:

- confirm the diagnosis
- reassure that other family members are not affected
- provide information and resources for future pregnancies

GeneReviews: Author Template – Single Disease

(Customized template for author to enter text directly)

X-linked Dominant Chondrodysplasia Punctata 2

[Synonyms; Includes]

Authors: Richard Kelley, MD
Melissa A. Dempsey, MS, CGC

02/01/16

Summary

1. Rare disease tests can be successfully translated
2. Using a Review Board of experts is a model for test review
3. Collaboration between research, clinical and advocates is beneficial
4. Clinical laboratories continue to need:
   - Improved educational materials on testing
   - Improved laboratory reports

Andy Faucett, MS, CGC / afaucett@genetics.emory.edu

THANKS TO

Office of Rare Diseases (ORD)

Stephen Groft, Pharm D, Director

National Institutes of Health

www.cettprogram.org