

Attachment 1

Birth Defects Prevention Act of 1998

Public Law 105-168
105th Congress

An Act

To provide surveillance, research, and services aimed at prevention of birth defects,
and for other purposes.

Apr. 21, 1998
[S. 419]

*Be it enacted by the Senate and House of Representatives of
the United States of America in Congress assembled,*

SECTION 1. SHORT TITLE; FINDINGS.

(a) **SHORT TITLE.**—This Act may be cited as the “Birth Defects
Prevention Act of 1998”.

Birth Defects
Prevention Act of
1998.

42 USC 201 note.

(b) **FINDINGS.**—Congress makes the following findings:

42 USC 247b-4
note.

(1) Birth defects are the leading cause of infant mortality,
directly responsible for one out of every five infant deaths.

(2) Thousands of the 150,000 infants born with a serious
birth defect annually face a lifetime of chronic disability and
illness.

(3) Birth defects threaten the lives of infants of all racial
and ethnic backgrounds. However, some conditions pose excess
risks for certain populations. For example, compared to all
infants born in the United States, Hispanic-American infants
are more likely to be born with anencephaly spina bifida and
other neural tube defects and African-American infants are
more likely to be born with sickle-cell anemia.

(4) Birth defects can be caused by exposure to environ-
mental hazards, adverse health conditions during pregnancy,
or genetic mutations. Prevention efforts are slowed by lack
of information about the number and causes of birth defects.
Outbreaks of birth defects may go undetected because surveil-
lance and research efforts are underdeveloped and poorly
coordinated.

(5) Public awareness strategies, such as programs using
folic acid vitamin supplements to prevent spina bifida and
alcohol avoidance programs to prevent Fetal Alcohol Syndrome,
are essential to prevent the heartache and costs associated
with birth defects.

SEC. 2. PROGRAMS REGARDING BIRTH DEFECTS.

Section 317C of the Public Health Service Act (42 U.S.C. 247b-
4) is amended to read as follows:

“PROGRAMS REGARDING BIRTH DEFECTS

“SEC. 317C. (a) **IN GENERAL.**—The Secretary, acting through
the Director of the Centers for Disease Control and Prevention,
shall carry out programs—

“(1) to collect, analyze, and make available data on birth
defects (in a manner that facilitates compliance with subsection

(d)(2)), including data on the causes of such defects and on the incidence and prevalence of such defects;

“(2) to operate regional centers for the conduct of applied epidemiological research on the prevention of such defects; and

“(3) to provide information and education to the public on the prevention of such defects.

Public
information.

“(b) ADDITIONAL PROVISIONS REGARDING COLLECTION OF DATA.—

“(1) IN GENERAL.—In carrying out subsection (a)(1), the Secretary—

“(A) shall collect and analyze data by gender and by racial and ethnic group, including Hispanics, non-Hispanic whites, Blacks, Native Americans, Asian Americans, and Pacific Islanders;

“(B) shall collect data under subparagraph (A) from birth certificates, death certificates, hospital records, and such other sources as the Secretary determines to be appropriate; and

“(C) shall encourage States to establish or improve programs for the collection and analysis of epidemiological data on birth defects, and to make the data available.

Establishment.

“(2) NATIONAL CLEARINGHOUSE.—In carrying out subsection (a)(1), the Secretary shall establish and maintain a National Information Clearinghouse on Birth Defects to collect and disseminate to health professionals and the general public information on birth defects, including the prevention of such defects.

“(c) GRANTS AND CONTRACTS.—

“(1) IN GENERAL.—In carrying out subsection (a), the Secretary may make grants to and enter into contracts with public and nonprofit private entities.

“(2) SUPPLIES AND SERVICES IN LIEU OF AWARD FUNDS.—

“(A) Upon the request of a recipient of an award of a grant or contract under paragraph (1), the Secretary may, subject to subparagraph (B), provide supplies, equipment, and services for the purpose of aiding the recipient in carrying out the purposes for which the award is made and, for such purposes, may detail to the recipient any officer or employee of the Department of Health and Human Services.

“(B) With respect to a request described in subparagraph (A), the Secretary shall reduce the amount of payments under the award involved by an amount equal to the costs of detailing personnel and the fair market value of any supplies, equipment, or services provided by the Secretary. The Secretary shall, for the payment of expenses incurred in complying with such request, expend the amounts withheld.

“(3) APPLICATION FOR AWARD.—The Secretary may make an award of a grant or contract under paragraph (1) only if an application for the award is submitted to the Secretary and the application is in such form, is made in such manner, and contains such agreements, assurances, and information as the Secretary determines to be necessary to carry out the purposes for which the award is to be made.

“(d) BIENNIAL REPORT.—Not later than February 1 of fiscal year 1999 and of every second such year thereafter, the Secretary

shall submit to the Committee on Commerce of the House of Representatives, and the Committee on Labor and Human Resources of the Senate, a report that, with respect to the preceding 2 fiscal years—

“(1) contains information regarding the incidence and prevalence of birth defects and the extent to which birth defects have contributed to the incidence and prevalence of infant mortality;

“(2) contains information under paragraph (1) that is specific to various racial and ethnic groups (including Hispanics, non-Hispanic whites, Blacks, Native Americans, and Asian Americans);

“(3) contains an assessment of the extent to which various approaches of preventing birth defects have been effective;

“(4) describes the activities carried out under this section; and

“(5) contains any recommendations of the Secretary regarding this section.

“(e) **APPLICABILITY OF PRIVACY LAWS.**—The provisions of this section shall be subject to the requirements of section 552a of title 5, United States Code. All Federal laws relating to the privacy of information shall apply to the data and information that is collected under this section.

“(f) **AUTHORIZATION OF APPROPRIATIONS.**—For the purpose of carrying out this section, there are authorized to be appropriated \$30,000,000 for fiscal year 1999, \$40,000,000 for fiscal year 2000, and such sums as may be necessary for each of the fiscal years 2001 and 2002.”.

Approved April 21, 1998.

LEGISLATIVE HISTORY—S. 419:

CONGRESSIONAL RECORD:

Vol. 143 (1997): June 12, considered and passed Senate.

Vol. 144 (1998): Mar. 10, considered and passed House.

WEEKLY COMPILATION OF PRESIDENTIAL DOCUMENTS, Vol. 34 (1998):

Apr. 21, Presidential remarks.



Attachment 2
Certificate of Confidentiality



EXTENDED
CONFIDENTIALITY CERTIFICATE

Issued to

Employees of

Division of Birth Defects and Developmental Disabilities, National Center on Birth
Defects and Developmental Disabilities (NCBDDD), and Contractor Abt, Inc.
and Other Participants

conducting research known as

NATIONAL BIRTH DEFECTS PREVENTION STUDY

Contract No. (200-2007-22641)

The purpose of this research project is to collaborate in a population-based study to evaluate factors associated with the occurrence of birth defects and to test hypotheses for gene-environment interactions involved in the etiology of birth defects.

In accordance with the provisions of Section 301(d) of the Public Health Service Act (42 U.S.C. § 241(d)) this certificate is issued to protect the privacy of research subjects by withholding their identities from all persons not connected with the research.

Under authority vested in the Secretary of Health and Human Services under that section, all persons who

- (1) are employed by the NCBDDD, CDC, and their contractors and cooperating agencies; and
- (2) have, in the course of that employment, access to the information which would identify individuals who are the subjects of a research project entitled "National Birth Defects Prevention Study" are hereby authorized to protect the privacy of the individuals who are the subjects of that research by withholding their names and other identifying characteristics from all persons not connected with the conduct of that research, with the exceptions and limitations set forth below.

As provided in Section 301(d) of the Public Health Service Act (42 U.S.C. § 241(d)),

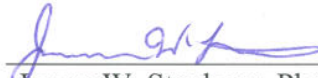
“Persons so authorized to protect the privacy of such individuals may not be compelled in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals.”

The following conditions apply to the protection provided under this certificate:

- (1) This certificate does not authorize the NCBDDD, CDC, or their contractors or cooperating agencies to refuse to reveal identifying information concerning research subjects if any of the following conditions exist:
 - (a) The subject (or, if he or she is legally incompetent, his or her guardian) consents in writing to disclosure of identifying information.
 - (b) Authorized personnel of the United States Department of Health and Human Services request such information for audit or program evaluation of the research project, or for investigation of the NCBDDD, CDC, or their contractors or cooperating agencies in carrying out the research project.
 - (c) Release is required by the Federal Food, Drug, and Cosmetic Act (21 U.S.C. §§ 301 et seq.) or regulations promulgated thereunder (Title 21, Code of Federal Regulations).
- (2) This certificate requires that there be no disclosures of identifying characteristics of research subjects in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings to compel disclosure of the identifying characteristics of research subjects, except as provided for in paragraph (1) above.
- (3) The confidentiality certificate does not govern the voluntary disclosure of identifying characteristics of research subjects.
- (4) This certificate does not represent an endorsement of the research project by the Department of Health and Human Services.
- (5) All research subjects in the project will be given a fair, clear explanation of the protection this certificate affords, and of the limitations and exceptions to the protection.

- (6) This certificate is effective upon issuance and will expire at the end of January 2014, or sooner if the holder is notified of cancellation in accordance with the procedures set out in 42 C.F.R. § 2a.8. The protection afforded by this certificate of confidentiality is permanent (including after death) for persons who participated as subjects in the research during any time the certificate was in effect.

Date: Jan 28, 2010



James W. Stephens, Ph.D.
Associate Director for Science, CDC

Attachment 3

A description of all birth defects surveillance systems in the US can be found at:
http://www.nbdpn.org/docs/2011_AR_ProgramDirectory.pdf

After the grantees have been identified the descriptions of the participating surveillance systems will be pulled from this directory and included in the list of attachments

Attachment 4

Letter of Authorization



Brenda Fitzgerald, MD, Commissioner

Nathan Deal, Governor

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December 1, 2011

Janet D. Cragan, MD, MPH
National Center on Birth Defects and Developmental Disabilities
Centers for Disease Control and Prevention
1600 Clifton Road, Mail Stop E-88
Atlanta, GA 30333

Dear Dr. Cragan:

This letter is in reference to current birth defects and fetal death surveillance activities being undertaken here in Georgia. The purpose of this letter is to set forth a partnership between the Georgia Department of Public Health (DPH) and the Centers for Disease Control and Prevention (CDC), National Center on Birth Defects and Developmental Disabilities (NCBDDD), and more specifically, the Metropolitan Atlanta Congenital Defects Program (MACDP), with respect to the collection of public health surveillance data for birth defects and fetal deaths.

Legal authority for the DPH to collect health information is provided in Chapter 31 of the Official Code of Georgia (O.C.G.A.). O.C.G.A. § 31-12-2 allows DPH "...to declare certain diseases, injuries, and conditions to be diseases requiring notice and to require the reporting thereof ... in a manner and at such times as may be prescribed." This authority also provides that "any person, including, but not limited to, practitioners of the healing arts, submitting in good faith reports or data...in compliance with the provisions of this Code section shall not be liable for any civil damages therefor." Georgia Code Chapter 31-10 and DPH Regulation 290-1-3 specifies the scope and authority of the Georgia vital records program, which requires the reporting of all fetal deaths.

Under these authorities, DPH has deemed birth defects (i.e., congenital defects, including fetal alcohol syndrome, developmental disabilities, and muscular dystrophy) and fetal deaths (i.e., stillbirths) to be notifiable conditions in Georgia. To track birth defects and fetal deaths in Georgia and learn about how they can be prevented and controlled, DPH supports and conducts public health surveillance for birth defects and fetal deaths in partnership with the Metropolitan Atlanta Congenital Defects Program (MACDP) in the Centers for Disease Control and Prevention (CDC), National Center on Birth Defects and Developmental Disabilities (NCBDDD). DPH herein requests the staff of MACDP to act with DPH in the collection of public health surveillance data related to birth defects and fetal deaths, as more fully described below.

As many types of birth defects are not usually detected at birth, simple examination of hospital records of children's births is not sufficient to provide adequate ascertainment of birth defects. Reports for individuals who have birth defects are needed from sources that include, but are not

December 1, 2011

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limited to, hospitals, clinics, private practitioners' offices, diagnostic imaging facilities, pregnancy termination centers, and laboratories. Reports are needed for children and products of conception with congenital defects and for women pregnant with fetuses affected by congenital defects. For effective surveillance, access is needed to the medical records of individuals known or likely to have congenital defects so that cases can be identified and pertinent information can be abstracted. Pertinent information includes personal identifiers, demographics, clinical signs and symptoms, detailed defect diagnoses, screening/diagnostic test results, medical care received, and types of treatment and intervention. Similarly, access is also needed to the medical records of women whose pregnancies resulted in a stillbirth and to all medical reports related to the evaluation of the fetus and placenta in the event of a stillbirth. Accordingly, pursuant to this letter, DPH has requested that the MACDP staff undertake the collection of this birth defect and fetal death surveillance data. Providers who enable MACDP staff access to medical records of their patients with birth defects or fetal deaths will be considered by DPH to be complying with the reporting requirement set forth in O.C.G.A. § 31-12-2 and Georgia Code Chapter 31-10 and DPH Regulation 290-1-3.

This letter, and the partnership between DPH and the MACDP staff to conduct birth defect and fetal death surveillance in Georgia, is valid through December 31, 2013. Please contact me if you have any questions.

Sincerely,



Cherie L. Drenzek, DVM, MS
State Epidemiologist

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Attachment 5

BD-STEPS Birth Defects Case Definitions

BD STEPS Birth Defects Case Definitions

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BD STEPS Birth Defects Case Definitions

1. Spina Bifida

BIRTH DEFECT & DEFINITION

- SPINA BIFIDA--herniation of the meninges and/or spinal cord tissue through a bony defect of spine closure

OTHER NAMES: spina bifida cystica, spina bifida aperta, myeloschisis, myelodysplasia, etc.

TYPES & DEFINITIONS

- MENINGOMYELOCELE/MYELOMENINGOCELE--90% of lesions, herniation of meninges and spinal cord tissue
- MENINGOCELE--herniation of meninges without spinal cord tissue
- RACHISCHISIS--spine defect without meninges covering the neural tissue
- LIPOMENINGOMYELOCELE/LIPOMENINGOCELE--lipomatous (fatty) tissue associated with a bony defect of the spine and herniation of meninges or spinal cord tissue, usually closed and located in the lumbosacral region
- MYELOCYSTOCELE--cystic lesion of the spinal cord central canal and herniation through a spinal defect
- OPEN LESION--neural tissue open to environment or covered by membrane only (90% of lesions)
- CLOSED LESION--neural tissue covered by normal skin
- LEVEL OF LESION--highest and lowest vertebrae--cervical (C), thoracic (T), lumbar (L), sacral (S)

ICD-9-CM CODES

- SPINA BIFIDA WITH HYDROCEPHALUS--741.0
- SPINA BIFIDA WITHOUT MENTION OF HYDROCEPHALUS--741.9

INCLUSIONS

- All cases including those cases prenatally diagnosed that do not have a postnatal examination to confirm the
- defect

EXCLUSIONS

- Spina bifida occulta
- Primary tethered cord
- Syringomyelia (hydromyelia)
- Diastematomyelia
- Diplomyelia
- Caudal lipomatous lesions not documented to involve neural tissue (updated 1/2009)

- Iniencephaly--a rare neural tube defect involving the occiput and inion, resulting in extreme retroflexion of the head variably combined with occipital encephalocele or rachischisis of the cervical and thoracic spine; iniencephaly always has a closed cranium; it is important to differentiate iniencephaly from cases of anencephaly with spinal retroflexion (updated 1/2009)

NBDPS CODES

- 741x0x: Meningomyelocele/myelomeningocele
- 741x1x: Meningocele
- 741x2x: Myelocele
- 741x3x: Myelocystocele
- 741x4x: Lipomeningomyelocele
- 741x5x: Lipomeningocele
- 741x6x: Rachischisis
- 741x8x: Other specified spina bifida
- 741x9x: Unspecified spina bifida
- 7410xx: Arnold Chiari malformation ± hydrocephalus, open lesion
- 7411xx: Arnold Chiari malformation ± hydrocephalus, closed lesion
- 7412xx: Arnold Chiari malformation ± hydrocephalus, unspecified open/closed lesion
- 7413xx: Hydrocephalus, other (aqueduct of Sylvius) or NOS, open lesion
- 7414xx: Hydrocephalus, other (aqueduct of Sylvius) or NOS, closed lesion
- 7415xx: Hydrocephalus, other (aqueduct of Sylvius) or NOS, unspecified open/closed lesion
- 7417xx: No mention hydrocephalus, open lesion
- 7418xx: No mention hydrocephalus, closed lesion
- 7419xx: No mention hydrocephalus, unspecified open/closed lesion
- 741xx1: Highest level, cervical
- 741xx2: Highest level, thoracic
- 741xx3: Highest level, lumbar
- 741xx4: Highest level, sacral
- 741xx9: Highest level, unspecified

2. Anophthalmia/microphthalmia

BIRTH DEFECT & DEFINITION

- ANOPHTHALMIA--total absence of the eye tissue or apparent absence of the globe in an orbit that otherwise contains normal adnexal structures
- MICROPHTHALMIA--reduction in the volume of the eye, usually characterized by corneal diameter less than 10 mm or anteroposterior globe diameter less than 20 mm

NOTE: these conditions may be seen with the ending "ia", "os" or "us"

TYPES & DEFINITIONS

- TRUE OR PRIMARY ANOPHTHALMIA--as above; occurs when there is complete failure of formation of the primary optic vesicle, usually bilateral; when unilateral, may have contralateral microphthalmia; verified only when histologic/microscopic exam shows that all ocular tissue is absent
- MICROPHTHALMIA--categories: colobomatous (uveal, iris, choroid and/or optic nerve) or noncolobomatous

OTHER NAMES: nanophthalmia = microphthalmic eye with normal intraocular structures and is a distinct genetic malformation

ICD-9-CM CODES

- ANOPHTHALMIA--743.00
- MICROPHTHALMIA--743.10-743.12

INCLUSIONS

- All cases must include diagnosis by an ophthalmologist or confirmation by surgical pathology or autopsy (updated 1/2009)

EXCLUSIONS

- "Small eyes" or "small palpebral fissures" unless there is confirmation of anophthalmia or microphthalmia
- Isolated microcornea with normal ocular size
- Ocular colobomas without anophthalmia or microphthalmia (updated 1/2009)
- Cryptophthalmos (updated 1/2009)

NBDPS CODES

- 743000-4: Anophthalmos
- 743100-4: Microphthalmos

3. Anotia/Microtia

BIRTH DEFECT & DEFINITION

- ANOTIA--total absence of the external ear and canal
- MICROTIA--malformation or hypoplasia of the auricle, ranging from measurably small external ear with minimal structural abnormality, to an ear with major structural alteration with absent or blind-ending canal

TYPES & DEFINITIONS

Microtia Classification System of Meurman (modified from Marks):

- TYPE I--generally small ear that retains most of the overall structure of the normal auricle--similar to lop/ cup
- defect, auditory meatus is usually patent and defects of the ossicular chain are infrequent
- TYPE II--moderately severe anomaly with longitudinal mass of cartilage with some resemblance to pinna
- (rudimentary auricle will be hook-shaped, have an S-shape or question mark appearance)
- TYPE III--ear is a rudiment of soft tissue and the auricle has no resemblance to the normal pinna
- TYPE IV--complete absence of all external ear structures, anotia

NOTE: types I - III will occasionally be accompanied by a preauricular tag(s)

ICD-9-CM CODES

- ANOTIA--744.01
- MICROTIA--744.23

NOTE: absence of the ear, congenital is included in the "other" code--744.09

INCLUSIONS

Standard

EXCLUSIONS

- Small ears NOS or small ears that retain most of the normal structure
- Type I microtia with or without abnormality of the external auditory canal
- Isolated atresia or stenosis of the external auditory canal
- Normal ears that are misplaced: low set, posteriorly rotated, etc. (updated 1/2009)
- "Decreased cartilage" reported as part of the estimate of gestational age (updated 1/2009)

NBDPS CODES

- 744010-4: Anotia
- 744210-4: Microtia

4-7. Conotruncal Heart Defects

BIRTH DEFECT & DEFINITION

- CONOTRUNCAL HEART DEFECTS (outflow tract anomalies)--anomalies of the outflow tract of the heart

TYPES & DEFINITIONS

- A. TRUNCUS ARTERIOSUS (TA)--single common arterial trunk instead of separate pulmonary artery and aorta, almost always associated with a malalignment-type VSD; there are subtypes 1, 2, 3 based on the pattern of truncal branching; no need to specify type
- B. DEXTRO-TRANSPOSITION OF GREAT ARTERIES (DTGA, DTGV)--transposed great arteries such that the pulmonary artery arises from the left ventricle and the aorta arises from the right ventricle
 - May be isolated or with other congenital heart defects (e.g., VSD, pulmonic stenosis)
 - If occurs with a VSD, do not code the VSD separately; use the code dTGA-VSD (745110)
 - If no VSD, use code for dTGA with intact ventricular septum (745100)
- C. TETRALOGY OF FALLOT (TOF, TET)--tetralogy = a malalignment-type VSD creates subvalvar pulmonic stenosis, overriding of the aorta, and right ventricular hypertrophy (= 4 defects in one code)
 - Do not code VSD and pulmonic stenosis separately
 - Absent and atretic pulmonary valve are distinctly different defects; thus, careful attention should be paid to the description and coding; **use TOF code 745200 and PV insufficiency code 746020 for TOF with absent pulmonary valve (effective 9/2002; updated 6/2005)**
 - "Pentalogy of Fallot" (TOF + ASD2) is an archaic term
- D. PULMONARY ATRESIA--atresia of the pulmonary artery; depending on subtype, is considered either in conotruncal defects or with obstructive defects
 - D1. PULMONARY ATRESIA WITH VSD (PA/VSD, TETRALOGY WITH PULMONARY ATRESIA)--absent connection from the right ventricle to the pulmonary artery and the aorta, usually with malalignment-type VSD; NBDPS code is 747310; alternative archaic terms are Truncus, type 4 or pseudotruncus
 - D2. PULMONARY ATRESIA WITH VSD (NOT TOF VARIANT)--use this code (746030) if PA/VSD is present, but anatomic details of the VSD/aorta are **not** described as "membranous/malalignment-type," or if the VSD is "muscular" (see obstructive heart defects)
 - D3. PULMONARY ATRESIA WITH INTACT VENTRICULAR SEPTUM (PA/IVS)--this is a distinctly different defect; code as 746000 (see obstructive heart defects)

ICD-9-CM CODES

- MALALIGNMENT (CONOVENTRICULAR, OUTLET) VENTRICULAR SEPTAL DEFECT--745.4
- DOUBLE-OUTLET RIGHT VENTRICLE--745.11
- TETRALOGY OF FALLOT--745.2

- PULMONARY ATRESIA WITH VSD, TETRALOGY OF FALLOT WITH PULMONARY ATRESIA--747.3 and 745.2
- TRUNCUS ARTERIOSUS--745.0
- DEXTRO-TRANSPOSITION OF GREAT ARTERIES--745.10
- INTERRUPTED AORTIC ARCH, TYPE B--747.11

INCLUSIONS

- Standard
- Include infants who are NEGATIVE or NOT TESTED for 22q11.2 deletion

EXCLUSIONS

- Exclude infants who are POSITIVE for 22q11.2 deletion
- Beginning with EDDs of 1/1/2006, all remaining isolated VSDs should be excluded, which encompasses perimembranous/membranous, malalignment/conoventricular, and inflow type; cases with VSDs which also have other eligible defects will continue to be included, as before, but the VSD should be marked as "eligible defect does not meet NBDPS criteria" (updated 1/2009)

NBDPS CODES

- 745000: Truncus arteriosus (TA)
- 745100: Dextro-transposition of great arteries with intact ventricular septum (D-TGA/D-TGV w/ IVS)
- 745110: Dextro-transposition of great arteries with ventricular septal defect (D-TGA/D-TGV w/ VSD)
- 745185: Double-outlet right ventricle with normally related great arteries (DORV-NGA)
- 745186: Double-outlet right ventricle with transposed great arteries (DORV-dTGA)
- 745188: Double-outlet right ventricle, OS (DORV, OS)
- 745189: Double-outlet right ventricle, NOS (DORV, NOS)
- 745200: Tetralogy of Fallot (TOF)
- 745487: Conoventricular septal defect, malalignment-type (subarterial) (VSDMAL) (no longer eligible as isolated defect)
- 747217: Interrupted aortic arch, type B (IAA, type B)
- 747310: Pulmonary atresia with VSD (tetralogy of Fallot with pulmonary atresia) (PA w/ VSD)

8-10. Obstructive Heart Defect

BIRTH DEFECT & DEFINITION

- OBSTRUCTIVE HEART DEFECTS--broad group of congenital heart defects in which there is obstruction to the flow of blood through either the left or right side of the heart or the great vessels

Right-Sided Obstructive Anomaly:

TRICUSPID ATRESIA (TA, TriAtresia, TrA)--atretic connection between the right atrium and the right ventricle, due to the absence or non-patency of the valve

- Be sure to code using the NBDPS tricuspid atresia code (746100) for atresia alone (not for stenosis)
- Tricuspid stenosis is not an NBDPS-eligible defect; in the original ICD9-BPA system, one code (7461) lumped both atresia and stenosis, which was a cause for confusion; in the presence of other eligible codes, use 746880 ("CHD, OS") for tricuspid stenosis (effective 2/2005; updated 6/2005)

Left-Sided Obstructive Anomaly:

COARCTATION OF THE AORTA (COA)--narrowing of the descending aorta, distal to the left subclavian; in most instances, the narrowing occurs close to the region where the ductus arteriosus inserts and is called juxtaductal coarctation

- Code separately, even in the presence of aortic stenosis or hypoplastic left heart syndrome (effective 2/2001)
- There are no exclusions based on severity (even a 'mild' coarctation is included), although it is helpful to include information about the severity (gradient) or type (ledge vs. long segment coarctation) of the lesion

HYPOPLASTIC LEFT HEART SYNDROME (HLHS)--extreme smallness of the left-sided heart structures (mitral valve and left ventricle) and aorta (including the aortic valve, ascending aorta, arch, and sometimes descending aorta [coarctation]); implies normally related great arteries

- Typical cases include mitral hypoplasia or atresia PLUS aortic hypoplasia or atresia, in the presence of a diminutive (non-apex forming) left ventricle
- In the typical case of HLHS, coarctation should be coded separately when present; mitral and aortic atresia or hypoplasia do not need separate coding if HLHS is coded
- In the presence of an unbalanced AV canal with right dominance, in which the left ventricle and aorta may be small, code the individual anomalies, but do **not** use the HLHS code
- A ventricular septal defect may be present and its size may influence the dimensions of the left ventricle (mitral atresia and intact septum are often associated with very small ventricle)

ICD-9-CM CODES

- AORTIC VALVE STENOSIS--746.3
- COARCTATION OF THE AORTA--747.10
- INTERRUPTED AORTIC ARCH, TYPE A--747.11
- HYPOPLASTIC LEFT HEART SYNDROME--746.7
- PULMONIC VALVE STENOSIS--746.02
- PULMONARY VALVE ATRESIA WITH INTACT VENTRICULAR SEPTUM--746.00

- TRICUSPID ATRESIA--746.1

INCLUSIONS

- Only valvar aortic and pulmonic stenoses, ASV (746300) and PSV (746010), are eligible for NBDPS; all other types of AS and PS (supravalvar, subvalvar, etc.) are ineligible and should not be given eligible codes (effective 9/2002; updated 6/2005)
- Some restrictions by severity of lesion are now cause for exclusion (see below)

EXCLUSIONS

- Beginning with EDDs on or after 1/1/2005, exclude valvar pulmonic stenosis when the peak gradient on echo or cardiac cath is less than 15 mmHg, or, in the absence of gradient information, those noted to be 'trivial', whiff, or mild; however, include **any** case in which the valve is described as abnormal (e.g., thickened, dysplastic, doming in systole)
- Coarctation of the aorta cases that are prenatally diagnosed but lack postnatal confirmation are excluded

NBDPS CODES

- 746300: Aortic stenosis, valvar (AVS)
- 747100: Coarctation of the aorta, preductal (proximal)
- 747110: Coarctation of the aorta, postductal (distal)
- 747120: Coarctation of the aorta, juxtaductal
- 747190: Coarctation of the aorta, NOS
- 747215: Interrupted aortic arch, NOS (IAA, NOS)
- 747216: Interrupted aortic arch, type A or type C (IAA, types A or C)
- 746700: Hypoplastic left heart syndrome (HLHS)
- 746010: Pulmonary stenosis, valvar (PSV)
- 746000: Pulmonary valve atresia/intact ventricular septum (PA/IVS)
- 746030: Pulmonary valve atresia with VSD (not tetralogy of Fallot variant) (PA w/ VSD, not TOF)
- 746100: Tricuspid atresia (TrA)

11. Anomalous Pulmonary Venous Return

BIRTH DEFECT & DEFINITION

- ANOMALOUS PULMONARY VENOUS RETURN (CONNECTION/DRAINAGE)--a condition in which a pulmonary vein or combination of pulmonary veins drains anomalously into the systemic venous circulation to the right heart or the body instead of into the left heart; often occurs with other cardiac defects

TYPES & DEFINITIONS

- TOTAL ANOMALOUS PULMONARY VENOUS RETURN (CONNECTION/DRAINAGE) (TAPVR/TAPVC/TAPVD)--failure of all pulmonary veins to connect to the left atrium

NOTE: pulmonary blood returns to the heart via supra-diaphragmatic or infra-diaphragmatic routes; these details are not needed for coding purposes

- PARTIAL ANOMALOUS PULMONARY VENOUS RETURN (CONNECTION/DRAINAGE) (PAPVR/PAPVC/PAPVD)--failure of 1,2,or 3 of the 4 pulmonary veins to connect to the left atrium; often associated with a sinus venosus type ASD

ICD-9-CM CODES

- TOTAL ANOMALOUS PULMONARY VENOUS RETURN--747.41
- PARTIAL ANOMALOUS PULMONARY VENOUS RETURN--747.42

INCLUSIONS

Standard

EXCLUSIONS

- Cases prenatally diagnosed that do not have a postnatal diagnostic examination to confirm the diagnosis

NBDPS CODES

- 747420: Total anomalous pulmonary venous return/connection/drainage (TAPVR)
- 747430: Partial anomalous pulmonary venous return/connection/drainage (PAPVR)

12. Cleft Lip +/- Palate

BIRTH DEFECT & DEFINITION

- CLEFT LIP +/- PALATE--incomplete closure of the lip; often accompanied by a maxillary alveolar (gum) defect and/or cleft palate ; maxillary alveolar defect may be a complete cleft that is continuous with the cleft palate, or it may be limited to a notch on the gum; cleft lip may be unilateral, bilateral, or median (distinguished from bilateral cleft lip by agenesis of premaxilla)

TYPES & DEFINITIONS

- COMPLETE CLEFT LIP--defect extends through the entirety of the lip and the nasal floor; may be unilateral or bilateral; usually associated with a more severe nasal deformation
- INCOMPLETE CLEFT LIP--defect of lip that does not extend into the nasal floor; may be unilateral or bilateral; there may be an incomplete cleft lip on one side and a complete cleft lip on the other side
- PSEUDOCLEFT LIP (**excluded from NBDPS**)--abnormal linear thickening or depressed groove of skin, or subtle scar-like pigmentary difference paralleling the philtral ridge on the affected side; may be associated with slight notch of the vermilion or a mild slouching of the alar cartilage

ICD-9-CM CODES

- CLEFT LIP--749.10-749.14
- CLEFT LIP WITH PALATE--749.20-749.25

INCLUSIONS

- Standard
- If cleft palate is associated with any type of cleft lip, it is coded as a cleft lip and palate, not cleft palate

EXCLUSIONS

- Pseudocleft lip; **microform cleft lip; forme fruste cleft lip (updated 1/2009)**
- Tessier type facial clefts
- Oblique facial clefts
- **Prenatal diagnosis without postnatal confirmation of the defect(s) (updated 1/2009)**

NBDPS CODES

- 749101-3: Cleft lip, unilateral
- 749110: Cleft lip, bilateral
- 749120: Cleft lip, central
- 749495: Cleft lip, NOS
- 749201-3: Cleft lip and palate, unilateral
- 749210: Cleft lip and palate, bilateral cleft lip
- 749220: Cleft lip and palate, central cleft lip
- 749290: Cleft lip and palate, NOS

13. Cleft Palate

BIRTH DEFECT & DEFINITION

- CLEFT PALATE--hole in roof of the mouth; incomplete fusion of the palatal shelves; may be limited to soft palate or also extend onto hard palate; if cleft palate is associated with cleft lip, it is coded as a cleft lip and palate

TYPES & DEFINITIONS

- PIERRE ROBIN ANOMALY (SEQUENCE)--combination of micrognathia, cleft palate, glossoptosis (tongue falls back into pharynx)
- SUBMUCOUS CLEFT PALATE (excluded from NBDPS)--defect of the soft palate with mucosa or a reduced, thin muscle layer bridging the midline; difficult to diagnose clinically in 1st year; often associated with a bifid uvula

ICD-9-CM CODES

- CLEFT PALATE--749.00-749.04

INCLUSIONS

Standard

EXCLUSIONS

- Submucous cleft palate
- Bifid or cleft uvula without overt cleft palate

NBDPS CODES

- 749001-3: Cleft hard palate, unilateral
- 749010: Cleft hard palate, bilateral
- 749020: Cleft hard palate, central
- 749030: Cleft hard palate, NOS
- 749041-3: Cleft soft palate, unilateral
- 749050: Cleft soft palate, bilateral
- 749060: Cleft soft palate, central
- 749070: Cleft soft palate, NOS
- 749090: Cleft palate, NOS

14. Esophageal Atresia +/- TE Fistula

BIRTH DEFECT & DEFINITION

- ESOPHAGEAL ATRESIA +/- TRACHEOESOPHAGEAL FISTULA (T-E FISTULA, TEF)--congenital complete discontinuity of the lumen of the esophagus resulting in a blind esophageal pouch occurring with or without an abnormal communication between the esophagus and trachea

TYPES & DEFINITIONS

- There are several classification schemas
- In 90% of cases the upper esophagus ends in a blind pouch and the lower segment forms a fistula with the trachea

ICD-9-CM CODES

- ESOPHAGEAL ATRESIA, TRACHEOESOPHAGEAL FISTULA--750.3

INCLUSIONS

Standard

EXCLUSIONS

- TE fistula without esophageal atresia
- Esophageal stenosis
- Trachea atresia
- Tracheoesophageal cleft

NBDPS CODES

- 750300: Esophageal atresia without TE fistula
- 750310: Esophageal atresia with TE fistula

15. Limb Deficiency, Transverse

BIRTH DEFECT & DEFINITION

- TRANSVERSE LIMB DEFICIENCY--complete or partial absence of distal structures of a limb in a transverse plane at the point where the deficiency begins with proximal structures essentially intact

OTHER NAMES: congenital amputation

TYPES & DEFINITIONS

- AMELIA--complete absence of a limb
- HEMI- OR MEROMELIA--partial absence of a limb (rather nonspecific; can also be used for longitudinal defects)
- TRANSVERSE TERMINAL DEFICIENCY--absence of distal structures with proximal structures essentially intact (used for deficiencies below the elbow)
- APHALANGIA--absence of phalanges
- ADACTYLY--absence of digits
- OLIGODACTYLY--fewer than 5 digits
- ACHEIRIA--absence of a hand

ICD-9-CM CODES

- UPPER LIMB TRANSVERSE DEFICIENCY--755.21
- UPPER LIMB LONGITUDINAL DEFICIENCY OF PHALANGE(S)--755.29
- LOWER LIMB TRANSVERSE DEFICIENCY--755.31
- LOWER LIMB LONGITUDINAL DEFICIENCY OF PHALANGE(S)--755.39

INCLUSIONS

- Standard
- Isolated missing digits, except isolated missing thumb

EXCLUSIONS

- Unspecified limb deficiency
- Generalized limb shortening including chondrodysplasias
- Nail hypoplasia
- **Brachydactylies type A-E (updated 1/2009)**
- **Lower extremity deficiencies with sirenomelia sequence (updated 1/2009)**

NBDPS CODES

- 755200-4: Transverse deficiency or amputation of the arm, NOS
- 755205-9: Total absence of the arm
- 755240-4: Absence of the forearm and hand
- 755245-9: Absence of the hand or fingers
- 755300-4: Transverse deficiency or amputation of the leg, NOS
- 755305-9: Total absence of the leg
- 755340-4: Absence of the lower leg and foot
- 755345-9: Absence of foot or toes

16. Diaphragmatic Hernia

BIRTH DEFECT & DEFINITION

- DIAPHRAGMATIC DEFECTS (HERNIA)--incomplete formation of the diaphragm in through which some portion of the abdominal contents herniates into the thoracic cavity

OTHER NAMES: congenital diaphragmatic hernia (CDH), absence, agenesis, or aplasia of diaphragm, hemidiaphragm

TYPES & DEFINITIONS

- POSTEROLATERAL HERNIA = BOCHDALEK HERNIA--defect involving the posterior and/or lateral portions of the diaphragm
- AGENESIS--apparent absence of an entire side of diaphragm; represents a large Bochdalek hernia
- ANTERIOR HERNIA = MORGAGNI HERNIA (aka Retrosternal, Parasternal, Morgagni-Larrey hernia)
- LARGE ANTERIOR HERNIA = SEPTUM TRANSVERSUM HERNIA--type of defect found in Pentalogy of Cantrell
- PARAESOPHAGEAL HERNIA--defect in the diaphragm surrounding the esophagus
- OTHER--includes, for example, central diaphragm defects, anterolateral defects, and unusual/atypical defects
- HERNIA SAC--approximately 15% of CDH have a sac, which is a localized thinning or out-pouching of the diaphragm; a sac is **not** a type of hernia

ICD-9-CM CODES

- DIAPHRAGMATIC HERNIA--756.6

INCLUSIONS

- Standard
- Prenatally diagnosed cases should be included only if bowel was documented in the chest by prenatal ultrasound

EXCLUSIONS

- Eventration of the diaphragm--not a true herniation, but an upward displacement of abdominal contents into an out-pouched diaphragm resulting from weakness or absence of diaphragmatic musculature
- Hiatal hernia
- CCAM (cystic adenomatoid malformation of the lung)

NBDPS CODES

- 756600-4: Diaphragmatic hernia, NOS
- 756605: Diaphragmatic hernia, esophageal
- 756610-4: Diaphragmatic hernia, Bochdalek
- 756615-9: Diaphragmatic hernia, Morgagni

17. Gastroschisis

BIRTH DEFECT & DEFINITION

- GASTROSCHISIS--congenital fissure of the anterior abdominal wall, lateral to the umbilicus, usually to the right, with a small bridge of skin separating the defect from the umbilicus; accompanied by herniation of the small, and part of the large, intestines, and occasionally other abdominal organs, into the amniotic cavity, and lacking a protective membrane

TYPES & DEFINITIONS

- LIMB-BODY WALL COMPLEX--disruption complex involving lateral body wall defect, limb reduction defect, neural tube defects, heart and other anomalies

ICD-9-CM CODES

- GASTROSCHISIS--756.79

INCLUSIONS

- Standard
- Prenatally diagnosed cases if high resolution ultrasound was done and the umbilicus was visualized

EXCLUSIONS

Standard

NBDPS CODES

- 756710: Gastroschisis

Attachment 6
Introductory Letter

This document was produced for the National Birth Defects Prevention Study;
a similar document will be created for BD-STEPS.

Date

<Subject's Name>
<Address>
<City, State Zipcode>

Dear Ms. <Last Name>:

The National Centers for Disease Control and Prevention and the <Center>, along with <seven> other states, are trying to understand why one out of every 33 babies are born with birth defects. To do this, we need to speak with women who delivered a baby without a birth defect as well as <mothers whose babies had birth defects/ women who had a pregnancy affected by a birth defect > as part of the National Birth Defects Prevention Study. We would like to invite you to join us in this important project.

If you agree to participate, you will be asked to complete a telephone interview that takes about an hour. The interview can be done in one call or in several shorter calls at a time that is convenient for you. We will ask you questions about your health, diet, and lifestyle during your recent pregnancy. Any information that could identify you will be kept private.

When the telephone interview is finished, you will receive a kit in the mail containing a soft <brush similar to a small toothbrush>. We are asking parents to collect cheek cells from themselves <and their infants> by rubbing the inside of the cheek with the soft <brush >. This sample will provide cell material for valuable genetic research. If you do not want to provide cheek cells, we would still like you to complete the telephone interview.

We will call you within two weeks to arrange the telephone interview. If you would rather call us to schedule an interview, please call our toll free number at <1-888-743-7324>.

We have enclosed a pamphlet with answers to the questions women commonly ask about the study and a Fact Sheet about your rights as a research subject. If you'd like more information, contact <Dr. Margaret Honein> at <(404) 498-4315>. Also enclosed is a \$20 money order to thank you for your time. This money order is yours to keep whether or not you participate in the study. After the interview, a cheek cell kit will be sent with an additional \$20 money order. And if you complete the entire study (interview plus the cheek cell sample), we will send you a third \$20 money order when we receive your cheek cell sample to compensate you for your time.

Thousands of women are taking part in this national study that is being conducted in eight states. We hope you will help us with this important research so that more women can have healthy babies. Thank you for considering this request.

Sincerely,

<Dr. Jennita Reefhuis>
<Address>

Enclosures

Attachment 7
Human Subjects Fact Sheet

This document was produced for the National Birth Defects Prevention Study;
a similar document will be created for BD-STEPS.

Rights of Research Subjects

National Birth Defects Prevention Study Rights of Research Subjects Fact Sheet

As a potential participant in this research study, you have the right to:

- * Be informed of the nature and purpose of the study.
- * Be given an explanation of the procedures to be followed in the study.
- * Be given a description of any discomforts and risks reasonably to be expected from the study procedures.
- * Be given an explanation of any benefits you can reasonably expect from participation.
- * Be informed of medical treatment, if any, available to you during and after the study if complications should arise.
- * Be given an opportunity to ask any questions concerning the study or procedures involved.
- * Be informed that you may withdraw from the study at anytime without penalty.
- * Be given the opportunity to decide to participate or not without the use of any force or undue influence on your decision.

All information that we gather in this study will be kept private. This is because the study has been given a Certificate of Confidentiality by the Centers for Disease Control and Prevention. This means anything you tell us will not have to be given out to anyone, even if a court orders us to do so, unless you say it's okay. We may share information about you with other researchers but that information will not identify you or anyone else in the study. You should also understand that study investigators are not prevented from reporting information obtained from you to authorities in order to prevent serious harm to yourself or others.

The National Birth Defects Prevention Study Question and Answer brochure will give you more information about how your privacy is protected in this study. If you have questions about your rights as a subject in this research study, please call the Office of the Deputy Associate Director for Science for CDC at 1-800-584-8814, leave a message including your name, phone number, and refer to protocol #2087, and someone will call you back as soon as possible.

Derechos de los Sujetos de Investigaciones Científicas

Estudio Nacional para la Prevención de los Defectos de Nacimiento Derechos de los Sujetos de Investigaciones Científicas Hoja Informativa

Como un posible participante de este estudio científico, usted tiene derecho a:

- * Recibir información sobre la naturaleza y el propósito del estudio.
- * Recibir una explicación acerca de los procedimientos que se seguirán en el estudio.
- * Recibir una explicación de cualquier incomodidad o riesgo que razonablemente se pueda esperar de los métodos usados en el estudio.
- * Recibir una explicación acerca de cualquier beneficio que razonablemente usted pueda esperar recibir por su participación en este estudio.
- * Recibir información sobre los diversos tratamientos médicos, si existen, que usted pudiera aprovechar durante y después del estudio, en caso de que se presentarán complicaciones imprevistas.
- * Tener la oportunidad de hacer cualquier pregunta, en respecto al estudio o a los procedimientos del mismo.
- * Recibir información sobre su derecho de retirar su participación del estudio, a cualquier momento, sin ninguna consecuencia adversa.
- * Tener la oportunidad de dar su consentimiento, o de negarse a dar su consentimiento, para participar en el estudio, sin que en su decisión se haya usado ningún método forzoso, fraude, engaños, obligación, coerción o cualquier otro tipo de influencia indebida.

Toda información personal que acumulamos durante el estudio se mantendrá estrictamente privada. Esta estipulación es necesaria, puesto que este estudio lleva la Certificación de Confidencialidad de los Centros Nacionales para el Control y Prevención de las Enfermedades. Esto quiere decir que nada de lo que usted diga puede pasar a manos de otra persona, aun en el caso de haber una orden de la corte que pida esta información, a no ser que usted haya dado primero su autorización. En cambio, a los investigadores sí se les permite que compartan información entre ellos mismos acerca de su caso, pero esa información no le identifica por nombre a usted ni a ningún otro participante. Sin embargo, usted debe entender que los investigadores no son prevenidos de denunciar la información obtenida de usted a las autoridades para prevenir un daño serio a usted misma o a los otros.

El folleto titulado "Estudio Nacional para la Prevención de los Defectos de Nacimiento - Preguntas y Respuestas", le dará mejor explicaciones sobre cómo este estudio protege su confidencialidad. Si tiene alguna pregunta sobre sus derechos como participante en este estudio de investigación, favor de llamar a la Oficina del Director Asociado del Diputado de la Ciencia para la CDC al 1-800-584-8814, deje su mensaje incluyendo su nombre y teléfono, y refiérase al protocolo #2087, y alguien le devolverá su llamada lo más pronto posible.

Attachment 8
Calendar

This document was produced for the National Birth Defects Prevention Study;
a similar document will be created for BD-STEPS.

2006

2007

January (enero)

Su	Mo	Tu	We	Th	Fr	Sa
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31				

February (febrero)

Su	Mo	Tu	We	Th	Fr	Sa
			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28				

January (enero)

Su	Mo	Tu	We	Th	Fr	Sa
	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30	31			

February (febrero)

Su	Mo	Tu	We	Th	Fr	Sa
				1	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22	23	24
25	26	27	28			

March (marzo)

Su	Mo	Tu	We	Th	Fr	Sa
			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30	31	

April (abril)

Su	Mo	Tu	We	Th	Fr	Sa
						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30						

March (marzo)

Su	Mo	Tu	We	Th	Fr	Sa
				1	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22	23	24
25	26	27	28	29	30	31

April (abril)

Su	Mo	Tu	We	Th	Fr	Sa
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30					

May (mayo)

Su	Mo	Tu	We	Th	Fr	Sa
	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30	31			

June (junio)

Su	Mo	Tu	We	Th	Fr	Sa
				1	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22	23	24
25	26	27	28	29	30	

May (mayo)

Su	Mo	Tu	We	Th	Fr	Sa
	1	2	3	4	5	
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30	31		

June (junio)

Su	Mo	Tu	We	Th	Fr	Sa
					1	2
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17	18	19	20	21	22	23
24	25	26	27	28	29	30

July (julio)

Su	Mo	Tu	We	Th	Fr	Sa
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23	24	25	26	27	28	29
30	31					

August (agosto)

Su	Mo	Tu	We	Th	Fr	Sa
	1	2	3	4	5	
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30	31		

July (julio)

Su	Mo	Tu	We	Th	Fr	Sa
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31				

August (agosto)

Su	Mo	Tu	We	Th	Fr	Sa
			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30	31	

September (septiembre)

Su	Mo	Tu	We	Th	Fr	Sa
					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30

October (octubre)

Su	Mo	Tu	We	Th	Fr	Sa
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31				

September (septiembre)

Su	Mo	Tu	We	Th	Fr	Sa
						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30						

October (octubre)

Su	Mo	Tu	We	Th	Fr	Sa
	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30	31			

November (noviembre)

Su	Mo	Tu	We	Th	Fr	Sa
			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30		

December (diciembre)

Su	Mo	Tu	We	Th	Fr	Sa
					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30
31						

November (noviembre)

Su	Mo	Tu	We	Th	Fr	Sa
				1	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22	23	24
25	26	27	28	29	30	

December (diciembre)

Su	Mo	Tu	We	Th	Fr	Sa
						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30	31					

2008

2009

January (enero)

Su	Mo	Tu	We	Th	Fr	Sa
		1	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30	31		

February (febrero)

Su	Mo	Tu	We	Th	Fr	Sa
					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	

January (enero)

Su	Mo	Tu	We	Th	Fr	Sa
					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30
31						

February (febrero)

Su	Mo	Tu	We	Th	Fr	Sa
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28

March (marzo)

Su	Mo	Tu	We	Th	Fr	Sa
						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30	31					

April (abril)

Su	Mo	Tu	We	Th	Fr	Sa
			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30		

March (marzo)

Su	Mo	Tu	We	Th	Fr	Sa
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31				

April (abril)

Su	Mo	Tu	We	Th	Fr	Sa
				1	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22	23	24
25	26	27	28	29	30	

May (mayo)

Su	Mo	Tu	We	Th	Fr	Sa
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31						

June (junio)

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May (mayo)

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June (junio)

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July (julio)

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August (agosto)

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July (julio)

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August (agosto)

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September (septiembre)

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October (octubre)

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September (septiembre)

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October (octubre)

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November (noviembre)

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December (diciembre)

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November (noviembre)

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December (diciembre)

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30	31					

Attachment 9
Q and A Brochure

This document was produced for the National Birth Defects Prevention Study;
a similar document will be created for BD-STEPS.

Questions You May Have...

How did you get my name?

Part of our ongoing work to find causes of birth defects includes studying them when they occur. State law allows us to monitor cases of birth defects. This is how we identified most women in the study. Women whose babies do not have birth defects were selected randomly from women who gave birth in the same year.

What does the study involve?

The study has two parts: 1) a telephone interview at a time convenient for you, and 2) a collection of cheek cells from immediate family members.

How will the study benefit my family?

Study results will not directly benefit you or your family. However, many women feel good about helping to find causes of birth defects.

What do I get for participating?

We have enclosed \$20 with the introductory letter to thank you for your time and inconvenience. The money is yours to keep whether or not you participate in the study. We will send another \$20 with the cheek cell kit. And if you complete both parts of the study, you will get a third \$20 when we receive your cheek cell samples.

Do I have to participate?

No. There will be no harmful effects if you refuse. Your decision will not affect health care services or other benefits you or your family may receive.

What will I be asked in the interview?

The interview covers a wide range of topics about you and the father. These include your:

- recent pregnancy and the 3 months before you became pregnant
- past pregnancies
- health and diet
- prescription and non-prescription drugs taken
- family background and lifestyle
- work and hobbies

The interviewers ask everyone the same questions in the same way. Sometimes we ask you to answer in your own words; other times, we will give you several possible responses to choose from.

Questions You May Have (continued)...

Can you not get this information from my doctor or my hospital records?

No. Most doctors do not routinely ask about the topics we are studying. You are the only one who can supply the information we need.

What if I do not want to answer?

You may skip any questions you wish.

What if I can not remember?

It is OK to say so. We want you to answer as accurately and honestly as possible.

How did you decide what topics to study? Are these things known to cause birth defects?

We do not know what causes or does not cause most birth defects. The purpose of the study is to find this out. Many topics were chosen because parents frequently have questions about them.

Contact Information

We hope you will participate in our study. The information you can give us is crucial. We believe this type of study holds the best promise for solving the mystery of birth defects.

For more information, please contact:

Tineka Yowe-Conley
National Center on Birth Defects and
Developmental Disabilities
Centers for Disease Control and Prevention
1600 Clifton Road, MS E86
Atlanta, GA 30333
Phone: 404-498-4315
E-mail: nbdps@cdc.gov

National Birth Defects Prevention Study

Q&A Questions & Answers

About the Study...

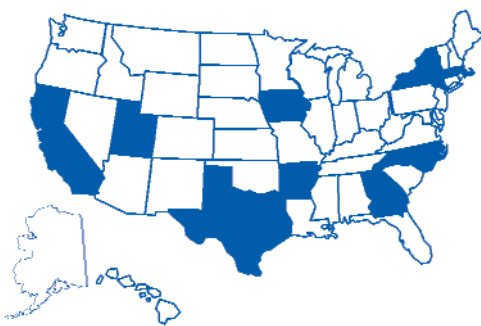
Why are you studying birth defects?

People are often surprised to learn that birth defects are common, found in 1 in 33 newborns. Most of the time, doctors and scientists do not know what caused them. This study will move us closer to understanding the causes of birth defects and ways to prevent them.

What is the National Birth Defects Prevention Study?

A nationwide effort to find causes of birth defects.

- Interviews are conducted by 9 birth defects programs called "Centers for Birth Defects Research and Prevention." They are located in Arkansas, California, Georgia, Iowa, Massachusetts, New York, North Carolina, Texas, and Utah.



- About 2,500 women are interviewed each year.
- Many different types of birth defects are being studied. About 1,800 women interviewed yearly will have had children or pregnancies affected by birth defects.
- About 700 of those interviewed yearly are mothers of infants with no birth defects.
- Women interviewed will be sent a cheek cell collection kit to help us compare genetic factors with information given during the interview.
- The study is funded by the Centers for Disease Control and Prevention.

About the Study (continued)...

Why are you interviewing women?

There is no way to recreate the many events and exposures that happen during pregnancy in a lab - only women can give us this information.

Why do you need information about genes?

The cheek cell samples provide critical genetic information. The interview provides critical information about factors in the environment that may affect birth defects. This study will help us find out how the two interact.

About the Findings...

How do you interpret the results?

- We ask the same questions to all women, whether or not their pregnancies were affected by birth defects.
- We then compare responses between groups.
- We do not look at individual answers; we only consider groups. We calculate averages and other statistics for our analyses.
- We combine data from all Centers to perform statistical tests.
- We study genetic material from cheek cells to see if certain forms of genes are more likely to be seen when birth defects occur.

What will the results show?

The study looks at a large group of women. This means findings will apply to "the average woman" rather than any specific individual. There are many possible results. We may uncover:

- Risk factors, things that contribute to birth defects.
- Protective factors, things that lower the chances of having a baby with birth defects.
- Neutral factors, things that neither raise nor lower risk.

About the Findings (continued)...

Can you give an example of a risk factor?

Cigarette smoking is a risk factor for developing lung cancer. This means that those with lung cancer are more likely to be smokers. While not all smokers develop lung cancer and not all persons with lung cancer are smokers, we know that not smoking helps prevent lung cancer.

Likewise, the same is true for findings from this birth defects study. Having one or more risk factors does not prove what caused birth defects in a particular case. But avoiding those risk factors, if possible, may help prevent future birth defects.

What will you do with the study findings?

We publish findings in medical journals. Because birth defects are of great interest, findings are often covered in the news as well. They may also be used in health education materials. We will also publish findings in a yearly newsletter that we send to women who took part in the study. Remember, all our findings pertain to groups of women; no one will be able to identify you from our reports or publications.

Your privacy will be protected in the following ways:

- Your answers and any results of genetic tests will not be seen by anyone outside the study.
- Your identity is secret. We will never use your name, the father's name, or your child's name in any report or publication.
- Information about you will not be given to anyone outside the study, including insurance companies or other government agencies, even if requested by a court of law.
- Records are kept under lock and key. Identifying information is removed from computer files, which are password protected.

To Participate...

An interviewer will call you in about 2 weeks to set up a convenient time for the phone interview. She will make sure that you understand the most important points about the study, its disadvantages and benefits. These are:

- This is a national study to discover clues about what causes birth defects. It is being conducted in 9 states. It has 2 parts: a telephone interview and a cheek cell collection.
- The interview takes an hour or so. It can be split into several segments to best suit your schedule. It covers a broad range of topics.
- Cheek cell collection consists of rubbing a soft brush inside the cheek. This procedure causes little to no discomfort. The kit will be sent to you in the mail.
- Some women interviewed find it emotionally difficult to discuss their pregnancies. There is no other likely disadvantage.
- Taking part in the study will not benefit you or your family directly. However, the findings may help others prevent birth defects in the future.
- You can choose not to participate. This decision will not affect the care or services that you or your family receives.
- You can choose not to answer any specific questions. You are free to stop the interview at any time.
- You can choose not to provide cheek cell samples.
- All your answers and results of genetic tests are confidential. Your identity will remain private.

Attachment 10
Intro Phone Scripts

This document was produced for the National Birth Defects Prevention Study;
a similar document will be created for BD-STEPS.

National Birth Defects Prevention Study

Atlanta

**Introductory Telephone Script
and Informed Consent**

**Mother of Living Case Child or
Living Control Child**

Hello, may I speak with <**First and Last Name of Mother**>? My name is <**Interviewer**> and I am calling for the <**Atlanta**> National Birth Defects Prevention Study. Recently we mailed a letter to you asking you to participate in the research study. Did you receive this letter?

[IF SUBJECT ASKS WHERE YOU ARE CALLING FROM OR WHO ABT IS, STATE: “I am calling for the <Centers for Disease Control> from Abt Associates in Hadley, MA. Abt is a public health research organization.”]

IF NO: We are enrolling families in <Atlanta>, hoping to discover clues about what causes birth defects. To do this, we are interviewing mothers of healthy infants as well as mothers whose babies had birth defects. You were selected from women who recently had babies. The study involves a telephone interview about your health, diet, and lifestyle. We are interested in having you participate in the study, but first need to send you a letter describing the study. May I get your current address to send you the letter?

NO [SKIP TO UNDECIDED SUBJECT SCRIPTS]

YES [RECORD ADDRESS.] Thank you. Your participation will help us understand more about the causes of birth defects and their prevention.

**IF YES: RESPOND TO SUBJECT’S QUESTIONS; ASK IF SHE HAS QUESTIONS.
READ INFORMED CONSENT TELEPHONE SCRIPT:**

This is an interview study to discover clues about what causes birth defects. Interviews are being conducted as part of the National Birth Defects Prevention Study.

The interview takes an hour or so (*but we can do it in short sections*). It covers a broad range of questions about:

- Your pregnancies,
- Your health, including prescription and non-prescription drugs you may have taken,
- Your diet,
- Your family background,
- Your work and hobbies,
- Your lifestyle, and
- Your baby’s father.

Some of the questions ask about sensitive issues such as recreational drug use, sexually transmitted diseases, and induced abortions. Some women interviewed find it emotionally difficult to discuss their pregnancies. There is no other likely risk.

Taking part in the study will not benefit you or your family directly; however, the findings may help others in the future to prevent birth defects.

We enclosed a question and answer brochure with the letter we sent you. Do you have any more questions?

ANSWER QUESTIONS.

We are interviewing mothers of healthy infants as well as mothers whose babies had birth defects. Some children were selected through a surveillance (tracking) program called the <Metropolitan Atlanta Congenital Defects Program> that has been run by the <Centers for Disease Control> for the past <30> years. (State laws give us permission to review medical records when birth defects are present. This is how we identified most mothers in the study.) Mothers whose babies don't have birth defects were selected randomly from women who gave birth in the same year.

Thousands of women are taking part in this national study. Three hundred mothers of infants diagnosed with birth defects and one hundred mothers of healthy infants will be interviewed each year for a total of five years in <Atlanta>. Nationwide, 16,000 women will be surveyed. Interviews are being conducted in Atlanta and five states.

Confidentiality and Certificate of Confidentiality: [REFER TO HUMAN SUBJECTS FACT SHEET.]

All information that we gather in this study will be kept private. This is assured by a Certificate of Confidentiality that protects your legal rights under the Public Health Service Act (*under section 301[d] of the Public Service Act 42 U.S.C. 241[d]*). The Certificate of Confidentiality prevents study staff from being forced under a court order or other legal action to identify you or anyone else in this study. This protection lasts forever (even after death) for any persons who were subjects in the research during any time the certificate was in effect. However, you should understand that the investigators are not prevented from reporting information obtained from you to authorities in order to prevent serious harm to yourself or others. Records may be reviewed by officials checking on the quality of the research. Information about you may be shared with other participating sites when and if it has been approved by research review committees. However, the shared data will not contain any information that could identify you or any other individual. This information will be used only for the study of birth defects. If you would like a copy of the Certificate of Confidentiality for this study, you may call Ms. Carolyn Sullivan or Ms. Kimberly Newsome at **1-404-498-4315**, and a copy will be sent to you.

Voluntary Participation in Interview and Cheek Cell Kit: The study has two parts – the (1) telephone interview and (2) optional cheek cell kit. Participation in all parts of this study is voluntary. You can do the interview but decide not to do the cheek cell kit. You are free to withdraw from any or all parts of this study at any time. At any time in the future, you may have your interview or cheek cell samples destroyed or removed from the study (by calling Ms. Kimberly Newsome at **1-404-498-4315**).

Incentive for Interview: We enclosed a **\$20 money order with your letter** to thank you for your time (for the interview).

Voluntary Cheek Cell Kit (Buccal Cells): The Cheek Cell Kit is entirely voluntary (optional). It will help us understand the genetics of birth defects. After the interview, we will mail a kit to you with small, soft brushes to collect cell samples from the inside of the mouth for yourself, your child, and your child's father. (The brush is similar to a tiny toothbrush.) We will **enclose \$20 per family in the kit** to provide for any inconvenience. You can decide whether to take part in this part of the study after you receive the kit. The kit will include directions and all necessary materials to collect the samples. (Cheek cell samples will be stored without your names.) We will also send an additional **(third) \$20 money order** after you return the cheek cell samples to compensate you for the time required to complete the entire study.

For More Information: If you'd like more information about the study, please contact Ms. Kimberly Newsome at **1-404-498-4315**. If you have questions about your rights as a subject in this research study, please call the Office of the Deputy Associate Director for Science for CDC at **1-800-584-8814** (*for CDC*). Leave a message including your name, phone number, and refer to Protocol #2087, and someone will call you back as soon as possible.

You can choose not to participate. There will be no bad effects from this decision; it will not affect the care or services you or your family receives.

You can choose not to answer any specific questions. You are free to stop the interview at any time.

All your answers are confidential. Your identity will remain private. The information you provide may be shared with other birth defects researchers, but without any information that could identify you.

If you have any concerns about the study or how it is conducted, you may contact <Ms. Kimberly Newsome> at <1-404-498-4315>. If you have questions about your rights as a subject in this research study, please call the Office of the Deputy Associate Director for Science for CDC at 1-800-584-8814 (for CDC). Leave a message including your name, phone number, and refer to Protocol #2087, and someone will call you back as soon as possible.

To make sure I'm doing the best job I can, my supervisor may record and listen as I ask the questions. (If you do agree to be interviewed, will it be OK for my supervisor to listen or record the interview?)

Do you wish to continue/be interviewed?

OR: When would be a convenient time to conduct the telephone interview?

PROBES:

- We can start now and see how far we get.
- We can do the interview in short sections such as 10 or 15-minute sessions, if that would be more convenient.
- I can set an appointment with you to call back at a convenient time.

IF YES:

RECORD DATE AND TIME (INCLUDE TIME ZONE) OF APPOINTMENT.

VERIFY PHONE NUMBER: I need to verify your telephone number where you can be reached for the interview.

CONFIRM: We have scheduled your appointment on <DAY, DATE> at <TIME>. Would you please call us at our toll-free number <1-888-743-7324> if you need to change your appointment.

Thank you for agreeing to participate in the National Birth Defects Prevention Study.

IF NO: We would like to know for what reason or reasons you have decided not to participate.

[RECORD REASONS. REFER TO UNDECIDED SUBJECT SCRIPTS.]

Thank you for your time in talking with me about this study.

National Birth Defects Prevention Study

Atlanta

**Introductory Telephone Script
and Informed Consent**

**Mother of Stillborn or Deceased Child, or
Therapeutic Abortion (TAB)**

Hello, may I speak with <First and Last Name of Mother>? My name is <Interviewer> and I am calling for the Atlanta National Birth Defects Prevention Study. Recently we mailed a letter to you asking you to participate in the research study. Did you receive this letter?

[IF SUBJECT ASKS WHERE YOU ARE CALLING FROM OR WHO ABT IS, STATE: "I am calling for the <Centers for Disease Control> from Abt Associates in Hadley, MA. Abt is a public health research organization."]

IF NO: We are enrolling families in <Atlanta>, hoping to discover clues about what causes birth defects. You were selected from women who recently had a pregnancy affected by a birth defect. Your pregnancy was identified through a surveillance (tracking) program called the <Metropolitan Atlanta Congenital Defects Program> that has been run by the <Centers for Disease Control> for the past <30> years. We are sorry about your loss and extend our sympathy to you. We understand that it may be difficult for you to think and talk about your experience. However, we are interested in factors that may help prevent birth defects and pregnancy problems. (The study involves a telephone interview about your health, diet, and lifestyle.) We are interested in having you participate in the study, but first need to send you a letter describing the study. May I get your current address to send you the letter?

NO [SKIP TO UNDECIDED SUBJECT SCRIPTS]

YES [RECORD ADDRESS.] Thank you. Your participation will help us understand more about the causes of birth defects and their prevention.

**IF YES: RESPOND TO SUBJECT'S QUESTIONS; ASK IF SHE HAS QUESTIONS.
READ INFORMED CONSENT TELEPHONE SCRIPT:**

This is an interview study to discover clues about what causes birth defects. Interviews are being conducted as part of the National Birth Defects Prevention Study.

The interview takes an hour or so (*but we can do it in short sections*). It covers a broad range of questions about:

- Your pregnancies,
- Your health, including prescription and non-prescription drugs you may have taken,
- Your diet,
- Your family background,
- Your work and hobbies,
- Your lifestyle, and
- Your baby's father.

Some of the questions ask about sensitive issues such as recreational drug use, sexually transmitted diseases, and induced abortions.

Some women interviewed find it emotionally difficult to discuss their pregnancies. There is no other likely risk.

Taking part in the study will not benefit you or your family directly; however, the findings may help others in the future to prevent birth defects.

We enclosed a question and answer brochure with the letter we sent you. Do you have any more questions?

ANSWER QUESTIONS.

We are interviewing mothers of healthy infants as well as women who had a pregnancy affected by a birth defect. You were selected from women who recently had a pregnancy affected by a birth defect. Your pregnancy was identified through a surveillance (tracking) program called the <Metropolitan Atlanta Congenital Defects Program> that has been run by the <Centers for Disease Control> for the past <30> years. (State laws give us permission to review medical records when birth defects are present. This is how we identified most women in the study.) Women whose babies don't have birth defects were selected randomly from women who gave birth in the same year.

Thousands of women are taking part in this national study. Three hundred mothers of infants diagnosed with birth defects and one hundred mothers of healthy infants will be interviewed each year for a total of five years in <Atlanta>. Nationwide, 16,000 women will be surveyed. Interviews are being conducted in Atlanta and five states.

Confidentiality and Certificate of Confidentiality: [REFER TO HUMAN SUBJECTS FACT SHEET.]

All information that we gather in this study will be kept private. This is assured by a Certificate of Confidentiality that protects your legal rights under the Public Health Service Act (*under section 301[d] of the Public Service Act 42 U.S.C. 241[d]*). The Certificate of Confidentiality prevents study staff from being forced under a court order or other legal action to identify you or anyone else in this study. This protection lasts forever (even after death) for any persons who were subjects in the research during any time the certificate was in effect. However, you should understand that the investigators are not prevented from reporting information obtained from you to authorities in order to prevent serious harm to yourself or others. Records may be reviewed by officials checking on the quality of the research. Information about you may be shared with other participating sites when and if it has been approved by research review committees. However, the shared data will not contain any information that could identify you or any other individual. This information will be used only for the study of birth defects. If you would like a copy of the Certificate of Confidentiality for this study, you may call Ms. Carolyn Sullivan or Ms. Kimberly Newsome at **1-404-498-4315**, and a copy will be sent to you.

Voluntary Participation in Interview and Cheek Cell Kit: The study has two parts – the (1) telephone interview and (2) optional cheek cell kit. Participation in all parts of this study is voluntary. You can do the interview but decide not to do the cheek cell kit. You are free to withdraw from any or all parts of this study at any time. At any time in the future, you may have your interview or cheek cell samples destroyed or removed from the study (by calling Ms. Kimberly Newsome at **1-404-498-4315**).

Incentive for Interview: We enclosed a **\$20 money order** to thank you for your time (for the interview).

Voluntary Cheek Cell Kit (Buccal Cells): The Cheek Cell Kit is entirely voluntary (optional). It will help us understand the genetics of birth defects. After the interview, we will mail a kit to you with small, soft brushes to collect cell samples from the inside of your mouth. (The brush is similar to a tiny toothbrush.) We will **enclose \$20 per family in the kit** to provide for any inconvenience. You can decide whether to take part in this part of the study after you receive the kit. The kit will include directions and all necessary materials to collect the samples. (Cheek cell samples will be stored without names.) We will also send an additional **(third) \$20 money order** after you return the cheek cell samples to compensate you for the time required to complete the entire study.

For More Information: If you'd like more information about the study, please contact Ms. Kimberly Newsome at **1-404-498-4315**. If you have questions about your rights as a subject in this research study, please call the Office of the Deputy Associate Director for Science for CDC at **1-800-584-8814** (*for CDC*). Leave a message including your name, phone number, and refer to Protocol #2087, and someone will call you back as soon as possible.

You can choose not to participate. There will be no bad effects from this decision; it will not affect the care or services you or your family receives.

You can choose not to answer any specific questions. You are free to stop the interview at any time.

All your answers are confidential. Your identity will remain private. The information you provide may be shared with other birth defects researchers, but without any information that could identify you.

If you have any concerns about the study or how it is conducted, you may contact <Ms. Kimberly Newsome> at <1-404-498-4315>. If you have questions about your rights as a subject in this research study, please call the Office of the Deputy Associate Director for Science for CDC at 1-800-584-8814 (for CDC). Leave a message including your name, phone number, and refer to Protocol #2087, and someone will call you back as soon as possible.

To make sure I'm doing the best job I can, my supervisor may record and listen as I ask the questions. (If you do agree to be interviewed, will it be OK for my supervisor to listen or record the interview?)

Do you wish to continue/be interviewed?

OR: When would be a convenient time to conduct the telephone interview?

PROBES:

- We can start now and see how far we get.
- We can do the interview in short sections such as 10 or 15-minute sessions, if that would be more convenient.
- I can set an appointment with you to call back at a convenient time.

IF YES:

RECORD DATE AND TIME (INCLUDE TIME ZONE) OF APPOINTMENT.

VERIFY PHONE NUMBER: I need to verify your telephone number where you can be reached for the interview.

CONFIRM: We have scheduled your appointment on <DAY, DATE> at <TIME>. Would you please call us at our toll-free number <1-888-743-7324> if you need to change your appointment.

Thank you for agreeing to participate in the National Birth Defects Prevention Study.

IF NO: We would like to know for what reason or reasons you have decided not to participate.

[RECORD REASONS. REFER TO UNDECIDED SUBJECT SCRIPTS.]

Thank you for your time in talking with me about this study.

National Birth Defects Prevention Study
Atlanta
Introductory Telephone Script
and Informed Consent

**Mother: Affected Pregnancy
with Unknown Outcome**

Hello, may I speak with <First and Last Name of Mother>? My name is <Interviewer> and I am calling for the Atlanta National Birth Defects Prevention Study. Recently we mailed a letter to you asking you to participate in the research study. Did you receive this letter?

[IF SUBJECT ASKS WHERE YOU ARE CALLING FROM OR WHO ABT IS, STATE: "I am calling for the <Centers for Disease Control> from Abt Associates in Hadley, MA. Abt is a public health research organization."]

IF NO: We are enrolling families in <Atlanta>, hoping to discover clues about what causes birth defects. You were selected from women who recently had a pregnancy affected by a birth defect. Your pregnancy was identified through a surveillance (tracking) program called the <Metropolitan Atlanta Congenital Defects Program> that has been run by the <Centers for Disease Control> for the past <30> years. We understand that it may be difficult for you to think and talk about your pregnancy. However, we are interested in factors that may help prevent birth defects and pregnancy problems. (The study involves a telephone interview about your health, diet, and lifestyle.) We are interested in having you participate in the study, but first need to send you a letter describing the study. May I get your current address to send you the letter?

NO [SKIP TO UNDECIDED SUBJECT SCRIPTS]

YES [RECORD ADDRESS.] Thank you. Your participation will help us understand more about the causes of birth defects and their prevention.

**IF YES: RESPOND TO SUBJECT'S QUESTIONS; ASK IF SHE HAS QUESTIONS.
READ INFORMED CONSENT TELEPHONE SCRIPT:**

This is an interview study to discover clues about what causes birth defects. Interviews are being conducted as part of the National Birth Defects Prevention Study.

The interview takes an hour or so (*but we can do it in short sections*). It covers a broad range of questions about:

- Your pregnancies,
- Your health, including prescription and non-prescription drugs you may have taken,
- Your diet,
- Your family background,
- Your work and hobbies,
- Your lifestyle, and
- Your baby's father.

Some of the questions ask about sensitive issues such as recreational drug use, sexually transmitted diseases, and induced abortions.

Some women interviewed find it emotionally difficult to discuss their pregnancies. There is no other likely risk.

Taking part in the study will not benefit you or your family directly; however, the findings may help others in the future to prevent birth defects.

We enclosed a question and answer brochure with the letter we sent you. Do you have any more questions?

ANSWER QUESTIONS.

We are interviewing mothers of healthy infants as well as women who had a pregnancy affected by a birth defect. You were selected from women who recently had a pregnancy affected by a birth defect. Your pregnancy was identified through a surveillance (tracking) program called the <Metropolitan Atlanta Congenital Defects Program> that has been run by the <Centers for Disease Control> for the past <30> years. (State laws give us permission to review medical records when birth defects are present. This is how we identified most women in the study.) Women whose babies don't have birth defects were selected randomly from women who gave birth in the same year.

Thousands of women are taking part in this national study. Three hundred mothers of infants diagnosed with birth defects and one hundred mothers of healthy infants will be interviewed each year for a total of five years in <Atlanta>. Nationwide, 16,000 women will be surveyed. Interviews are being conducted in Atlanta and five states.

Confidentiality and Certificate of Confidentiality: [REFER TO HUMAN SUBJECTS FACT SHEET.]

All information that we gather in this study will be kept private. This is assured by a Certificate of Confidentiality that protects your legal rights under the Public Health Service Act (*under section 301[d] of the Public Service Act 42 U.S.C. 241[d]*). The Certificate of Confidentiality prevents study staff from being forced under a court order or other legal action to identify you or anyone else in this study. This protection lasts forever (even after death) for any persons who were subjects in the research during any time the certificate was in effect. However, you should understand that the investigators are not prevented from reporting information obtained from you to authorities in order to prevent serious harm to yourself or others. Records may be reviewed by officials checking on the quality of the research. Information about you may be shared with other participating sites when and if it has been approved by research review committees. However, the shared data will not contain any information that could identify you or any other individual. This information will be used only for the study of birth defects. If you would like a copy of the Certificate of Confidentiality for this study, you may call Ms. Carolyn Sullivan or Ms. Kimberly Newsome at **1-404-498-4315**, and a copy will be sent to you.

Voluntary Participation in Interview and Cheek Cell Kit: The study has two parts – the (1) telephone interview and (2) optional cheek cell kit. Participation in all parts of this study is voluntary. You can do the interview but decide not to do the cheek cell kit. You are free to withdraw from any or all parts of this study at any time. At any time in the future, you may have your interview or cheek cell samples destroyed or removed from the study (by calling Ms. Kimberly Newsome at **1-404-498-4315**).

Incentive for Interview: We enclosed a **\$20 money order** to thank you for your time (for the interview).

Voluntary Cheek Cell Kit (Buccal Cells): The Cheek Cell Kit is entirely voluntary (optional). It will help us understand the genetics of birth defects. After the interview, we will mail a kit to you with small, soft brushes to collect cell samples from the inside of your mouth. (The brush is similar to a tiny toothbrush.) We will **enclose \$20 per family in the kit** to provide for any inconvenience. You can decide whether to take part in this part of the study after you receive the kit. The kit will include directions and all necessary materials to collect the samples. (Cheek cell samples will be stored without names.) We will also send an additional **(third) \$20 money order** after you return the cheek cell samples to compensate you for the time required to complete the entire study.

For More Information: If you'd like more information about the study, please contact Ms. Kimberly Newsome at **1-404-498-4315**. If you have questions about your rights as a subject in this research study, please call the Office of the Deputy Associate Director for Science for CDC at **1-800-584-8814** (*for CDC*). Leave a message including your name, phone number, and refer to Protocol #2087, and someone will call you back as soon as possible.

You can choose not to participate. There will be no bad effects from this decision; it will not affect the care or services you or your family receives.

You can choose not to answer any specific questions. You are free to stop the interview at any time.

All your answers are confidential. Your identity will remain private. The information you provide may be shared with other birth defects researchers, but without any information that could identify you.

If you have any concerns about the study or how it is conducted, you may contact <Ms. Kimberly Newsome> at <1-404-498-4315>. If you have questions about your rights as a subject in this research study, please call the Office of the Deputy Associate Director for Science for CDC at 1-800-584-8814 (for CDC). Leave a message including your name, phone number, and refer to Protocol #2087, and someone will call you back as soon as possible.

To make sure I'm doing the best job I can, my supervisor may record and listen as I ask the questions. (If you do agree to be interviewed, will it be OK for my supervisor to listen or record the interview?)

Do you wish to continue/be interviewed?

OR: When would be a convenient time to conduct the telephone interview?

PROBES:

- We can start now and see how far we get.
- We can do the interview in short sections such as 10 or 15-minute sessions, if that would be more convenient.
- I can set an appointment with you to call back at a convenient time.

IF YES:

RECORD DATE AND TIME (INCLUDE TIME ZONE) OF APPOINTMENT.

VERIFY PHONE NUMBER: I need to verify your telephone number where you can be reached for the interview.

CONFIRM: We have scheduled your appointment on <DAY, DATE> at <TIME>. Would you please call us at our toll-free number <1-888-743-7324> if you need to change your appointment.

Thank you for agreeing to participate in the National Birth Defects Prevention Study.

IF NO: We would like to know for what reason or reasons you have decided not to participate.

[RECORD REASONS. REFER TO UNDECIDED SUBJECT SCRIPTS.]

Thank you for your time in talking with me about this study.

National Birth Defects Prevention Study

Atlanta

Revised Short Telephone Script:
Interview Already Scheduled

[SHORT VERSION OF SCRIPT FOR WOMEN WHO ALREADY CONSENTED AT THE TIME THE INTERVIEW WAS SCHEDULED – FULL CONSENT SCRIPT WAS PREVIOUSLY READ TO SUBJECT. THE INTERVIEW BEGINS WITH THIS REMINDER.]

Hello, may I speak with <**First and Last Name of Mother**>? My name is <**Interviewer**> and I am calling for the <**Atlanta**> National Birth Defects Prevention Study. Recently, you scheduled an interview for this time. Is this still a convenient time to conduct the interview?

[IF SUBJECT ASKS WHERE YOU ARE CALLING FROM OR WHO ABT IS, STATE: “I am calling for the <Centers for Disease Control> from Abt Associates in Hadley, MA. Abt is a public health research organization.”]

IF NO: When would be a more convenient time for me to call you to conduct the interview?
RECORD DATE AND TIME (INCLUDE TIME ZONE) OF NEW APPOINTMENT.

VERIFY PHONE NUMBER: I need to verify your telephone number where you can be reached for the interview.
CONFIRM: We have scheduled your appointment on <DAY, DATE> at <TIME>. Would you please call us at our toll-free number <**1-888-743-7324**> if you need to change your appointment.

Thank you. We look forward to talking with you later.

IF YES:

Thank you for agreeing to participate. I want to remind you that:

- All your answers are confidential.
- You can choose not to answer any specific questions.
- You are free to stop the interview at any time without losing any benefits.

IF NOT PREVIOUSLY ASKED: My supervisor may listen in from time to time to make sure I’m doing the best job I can. Will it be o.k. for my supervisor to listen?

IF YES: VERIFY NAME AND/OR BIRTHDATE OF CHILD. PROCEED WITH INTERVIEW.

IF NO: SET UP “NO MONITORING SIGNAL OR SIGN” FOR SUPERVISOR.
THEN VERIFY NAME AND/OR BIRTHDATE OF CHILD. PROCEED WITH INTERVIEW.

Attachment 11
Outline of the BD-STEPS CATI

This is a draft version of the sections of the Computer Assisted Telephone Interview instrument.

DRAFT

Centers for Birth Defects Research and Prevention Birth Defects Study To Evaluate Pregnancy exposureS (BD-STEPS) Computer-Assisted Telephone Interview

Topics

ESTABLISHING DATES
MULTIPLE BIRTHS
PREGNANCY HISTORY
FAMILY HISTORY OF BIRTH DEFECTS
FERTILITY
DIABETES
HEART DISEASE
THYROID DISEASE
ASTHMA
AUTOIMMUNE DISEASE
TRANSPLANT RECEIPT
CANCER
DEPRESSION / ANXIETY
GENITOURINARY INFECTIONS
FEVERS
MEDICATION / HERBALS
STRESS
PHYSICAL ACTIVITY
OBESITY
SMOKING
ALCOHOL
RESIDENCE HISTORY
MATERNAL OCCUPATION
RACE / ACCULTURATION

11/13/2012

DRAFT – Do not disseminate

EDUCATION

INCOME

INSURANCE STATUS

DENTAL PROCEDURES

ON-LINE MODULES

- Maternal occupation
- Family history of birth defects
- Over-the-counter medication use

CONSENT FOR MEDICAL RECORD REVIEW

- Fertility assistance
- Dental procedures

DRAFT

Attachment 12
Thank you Letter

This document was produced for the National Birth Defects Prevention Study;
a similar document will be created for BD-STEPS.

*The National Birth Defects Prevention Study – Protocol , Attachment 27
Thank You Letter Interview Only (Living/English)
Revised 1/5/07(contact info only)*

11/13/2012

«First_Name» «Middle_Name» «Last_Name»
«Address»
«City», «State» «zip»

Dear Ms. «Last_Name»:

On behalf of the Centers for Birth Defects Research and Prevention, we want to thank you for allowing us to interview you for The National Birth Defects Prevention Study

As we mentioned, it is our hope that by gathering information from a larger number of mothers, we may be able to learn more about the subject of birth defects. Your cooperation has been most valuable to us, and hopefully, will also be of value to other mothers and children in the future.

Please feel free to call us if you have any questions which were not answered. In addition, we hope that we may feel free to contact you again, if, as we progress in our work, any new questions arise.

We have enclosed a copy of the National Birth Defects Prevention Study newsletter. This newsletter is published yearly and updates participants on the progress of the study. In order to receive future issues of this newsletter, please notify us when you have a change of address.

Thank you again for being so helpful.

Sincerely yours,

Jennita Reefhuis, PhD
Principal Investigator
National Center on Birth Defects and Developmental Disabilities
Centers for Disease Control and Prevention
1600 Clifton Road
Mailstop E-86
Atlanta, GA 30333

Enclosure

Attachment 13
NBDPS Newsletter

NBDPS News is a periodic newsletter of the CDC- funded Centers for Birth Defects Research and Prevention.

The purpose of this newsletter is to inform the public of the Centers' activities and current news about birth defects.

NBDPS Update

The National Birth Defects Prevention Study (NBDPS) continues to search for causes of birth defects. We have talked to more than 37,000 women from 10 states. They include those who have had pregnancies affected by birth defects and those who have babies without birth defects. We also have received cheek cell kits from more than 23,000 families.

Over the years, our work has provided data to study risk factors for birth defects. Currently, NBDPS researchers have about 300 project ideas. In 2010 and 2011, 57 papers were published in medical and health journals using data from the NBDPS. The results of some of these papers will be discussed in this newsletter.

We thank the many families who have taken part in this study. The information they have shared will bring us closer to finding the causes of birth defects.

Recent Findings From the NBDPS

Medication Use During Pregnancy

Using medicine during pregnancy is common. So, it is important to learn how this might affect a mother and her baby. More knowledge will help women and their doctors make better choices about treatments during pregnancy.

Using data from the NBDPS and other sources, researchers have been able to look at medication use over time. They have used these data to see what kinds of medications women were taking during pregnancy. They found that medication use during pregnancy has gone up over the last 30 years. During the first trimester of pregnancy, 70%–80% of women said they took at least one medicine. About 50% of women said they took at least one prescription medicine during that time. This shows the need for continued research on the risks or safety of using these medicines during pregnancy.



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Recent Findings 1

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Informing and Helping Families..... 4

Genetic Methods in the NBDPS 5

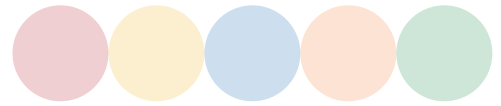
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Mitchell AA, Gilboa SM, Werler MM, Kelley KE, Louik C, Hernandez-Diaz S and the National Birth Defects Prevention Study. Medication use during pregnancy, with particular focus on prescription drugs: 1976–2008. Am J Obstet Gynecol. 2011 Jul;205(1):51.e1-8.

Recent Findings from the NBDPS (continued)



Researchers did not find a link between acetaminophen use and any specific type of birth defect.

Medicine To Ease Morning Sickness and Risk of Birth Defects

Morning sickness, including nausea and vomiting, is common during pregnancy. Certain medicines can be used to treat morning sickness. We wanted to better understand how these medicines might affect a mother and her baby.

Nearly 70% of women in the study reported morning sickness during the first trimester. Of these women, about 15% took a medicine to ease their symptoms. The NBDPS researchers found that most of the medicines did not increase the risk for many of the birth defects that were studied. But for some birth defects, including hypospadias and cleft palate, there might have been some association. More studies are needed to further explore any possible links.

Anderka M, Mitchell AA, Louik C, Werler MM, Hernandez-Diaz S, Rasmussen SA, and the National Birth Defects Prevention Study. Medications used to treat nausea and vomiting of pregnancy and the risk of selected birth defects. *Birth Defects Res A Clin Mol Teratol.* 2012 Jan;94(1):22-30.

Treatment With Prescription Painkillers (Opioids) and Birth Defects

Doctors often treat severe pain with prescription painkillers called opioids. Small amounts also can be found in

some over-the-counter cough medicines. Unfortunately, we do not have a lot of information about the effects of prescription painkillers on a pregnant woman and her unborn baby. We were able to look at this issue using NBDPS data.

Treatment with these types of painkillers just before or during early pregnancy was reported by 2% to 3% of the women in the NBDPS. Codeine and hydrocodone (sold as Vicodin®) were the most commonly used. Some birth defects, including spina bifida (a birth defect of the baby's spine) and certain heart defects, were linked with use of a prescription painkiller in our study. Previous studies found a similar link between codeine and heart defects. Our study was the first to find painkiller use related to other birth defects. When making treatment choices, women and their doctors should think about the benefits and risks of prescription painkillers.

Broussard CS, Rasmussen SA, Reefhuis J, Friedman JM, Jann MW, Riehle-Colarusso T, et al. Maternal treatment with opioid analgesics and risk for birth defects. *Am J Obstet Gynecol.* 2011 Apr;204(4):314.e1-11.

Clomiphene Citrate and Birth Defects

Clomiphene citrate, sold as Clomid® or Serophene®, is a drug used to help women who have trouble getting pregnant. It is one of the most common medicines used for infertility. As such, it is important to understand any possible risks connected with using it.

NBDPS researchers found that using this medicine was more common among mothers of babies born with certain birth defects. These include craniosynostosis, some heart defects, and some other birth defects. Some of these links were seen for the first time. That is why more research is needed to learn if the risks came from using clomiphene citrate or from the reason the couple had trouble getting pregnant.

Reefhuis J, Honein MA, Schieve LA, Rasmussen SA and the National Birth Defects Prevention Study. Use of clomiphene citrate and birth defects, National Birth Defects Prevention Study, 1997-2005. *Hum Reprod.* 2011 Feb;26(2):451-7.

Birth Defects and Acetaminophen Use

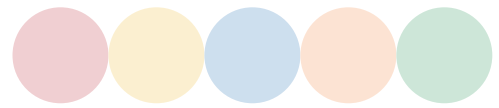
Acetaminophen, sold as Tylenol®, is an over-the-counter medicine used to treat mild pain or to lower a fever. Often, it is found in cold or flu medications and prescription painkillers. Pregnant women often use it.

This study looked at acetaminophen use during early pregnancy (first 3 months). About 47% of mothers of babies with a birth defect and about 45% of mothers of babies without a birth defect said that they used it during the first trimester. Researchers did not find a link between acetaminophen use and any specific type of birth defect. They did find that acetaminophen used to lower a fever during pregnancy might have lowered the risk for certain birth defects.

Feldkamp ML, Meyer RE, Krikov S, Botto LD. Acetaminophen use in pregnancy and risk of birth defects: findings from the National Birth Defects Prevention Study. *Obstet Gynecol.* 2010 Jan;115(1):109-15.



Recent Findings from the NBDPS (continued)



Smoking and Neural Tube Defects

Smoking cigarettes during pregnancy can lead to harmful effects for the baby. These include being born too small or too early. We looked at the effect of smoking on birth defects of the baby's brain (anencephaly) and spinal cord (spina bifida). We also looked at the effects of secondhand smoke during pregnancy.

When compared to nonsmokers, pregnant women who were around secondhand smoke were more likely to have a baby with a spina bifida or anencephaly.

Suarez L, Ramadhani T, Felkner M, Canfield MA, Brender JD, Romitti PA, et al. Maternal smoking, passive tobacco smoke, and neural tube defects. *Birth Defects Res A Clin Mol Teratol.* 2011 Jan;91(1):29-33.

Genital Tract Infections and Birth Defects

Genital tract infections are common during pregnancy. Some studies have shown these infections during pregnancy can lead to adverse outcomes, including babies being born too early. We used NBDPS data to find out if these kinds of infections were linked to birth defects.

We found that genital tract infections were associated with an increased risk for some birth defects, including cleft lip and cleft palate. Some of these increased risks had not been seen before. Therefore, more studies are needed to confirm these findings.

Carter TC, Olney RS, Mitchell AA, Romitti PA, Bell EM, Druschel CM, and the National Birth Defects Prevention Study. Maternal self-reported genital tract infections during pregnancy and the risk of selected birth defects. *Birth Defects Res A Clin Mol Teratol.* 2011 Feb;91(2):108-16.

Caffeine and Selected Birth Defects

Caffeine is found in different foods and drinks, including coffee, tea, chocolate, and soft drinks. Many women consume caffeine during pregnancy (about two of every three women). Often, we are

asked about caffeine use and birth outcomes. To address this issue, we used NBDPS data to find out if using caffeine during pregnancy increased the risks for birth defects. Overall, the findings were reassuring and did not show an increase in risk for the birth defects we studied.

Browne ML, Hoyt AT, Feldkamp ML, Rasmussen SA, Marshall EG, Druschel CM, et al. Maternal caffeine intake and risk of selected birth defects in the National Birth Defects Prevention Study. *Birth Defects Res A Clin Mol Teratol.* 2011 Feb;91(2):93-101.



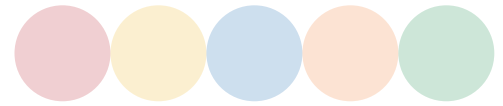
About 3% of women in the United States have diabetes and over 30% are obese. Obesity and diabetes before pregnancy are risk factors for birth defects.

Looking At Physical Activity

Obesity and diabetes are common among women in the United States. About 3% of women in the United States have diabetes and over 30% are obese. Obesity and diabetes before pregnancy are risk factors for birth defects. Physical activity can have many positive health effects, such as a lower risk of type 2 diabetes and weight loss. But, we do not know much about physical activity and birth defects. Earlier studies have reported mixed results. Some studies have suggested that heavy lifting or a lot of time spent standing might be related to birth defect risk, while others did not find these results. Several studies have suggested that physical activity might lower the risk for some birth defects.

The NBDPS allows us to study this important relationship. The first step in looking at this issue was to decide the types of questions to ask and how to ask them. We wanted to know not only about the level of physical activity, but also the different ways that one can be active. This can include activities done during free time or household work. In October 2010, we added a revised version of the short International Physical Activity Questionnaire to the NBDPS.

Looking At Physical Activity (continued)



The NBDPS interview now asks women about their physical activity in the 3 months before pregnancy. We look at moderate and vigorous activities. Moderate activities cause breathing to be somewhat harder than normal. They can include gardening, actively playing with children, carrying light loads, or bicycling at a regular pace. Vigorous activities cause breathing much harder than normal. These include heavy lifting or fast bicycling. The questions added to the NBDPS were:

- Number of days per week engaged in moderate and vigorous activities
- Type and duration of activities on those days

Women also are asked about walking, during work, at home, and during travel. Finally, they are asked about the time they spend sitting, such as during visits with friends, reading, working at a desk, or watching television.

We are excited to have started asking these questions. It will take some time to gather enough data. Once we do, we plan to study the effects of physical activity on the risk for birth defects. We also plan to study how physical activity might change the relationship between diabetes and obesity and birth defects.



Informing and Helping Families



Every. Life. Inspires.

family's story. Julie wanted the video to include the experiences of other parents raising children with spina bifida. She also wanted to answer the questions she was asked and the questions parents might have been reluctant to ask. The purpose of the video is to give families hope, encouragement, and advice from others who have gone through what they are going through.

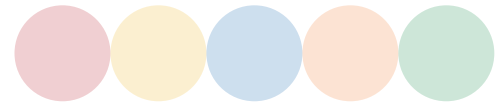
As Julie created the video, she met the McGinley family, who would be having twin boys. One boy, Eli, had spina bifida. The family allowed the birth to be videotaped for Julie's project. Eli lived for only 5 days. The video was completed, thanks to donations from family and friends. The video is known as Project ELI (Every Life Inspires). Project ELI is not meant to take the place of medical information, but rather to be a source to help families. Julie has made the video available on DVD for health care providers and their staff members. The Project ELI video is available at <http://www.communityconnectionsar.org/services-programs/project-eli>.

Having a child is a special time in a parent's life. However, when a parent is told that his or her child has a birth defect, that special time can fill with worry. Parents and family members who get a diagnosis of a birth defect can have many questions and concerns.

Julie Mayberry, who works with the Arkansas Folic Acid Coalition, has made a video that addresses some of these concerns. Julie's daughter, Katie, was born with spina bifida. She decided to speak out about her



Genetic Methods in the NBDPS



In the NBDPS, families are asked to collect cheek cell samples. Many wonder how we use these samples to help find the causes of birth defects. Studies have suggested that birth defects are caused by both genetic (inherited) and nongenetic (environmental and lifestyle) factors. To see if that is true, we collect information about each mother's lifestyle, diet, health, and environment before and during her pregnancy. We also collect cheek cell samples to look at each family's genetic material (DNA).

Cheek Cell Collection

Cheek cells contain DNA. NBDPS laboratories remove DNA from the cheek cells and measure the amount of DNA. During this process, we use a coded number to identify the DNA samples to protect each participant's identity. Samples have no names or other personal identifying information directly connected with them. Each study site stores the key to each sample's code in a secure location. Only a limited number of study staff has access to that information. Protecting each participant's identity is very important.

We get information from families who have children with birth defects (case families) and from families who have children with no birth defects (control families). Data from case and control families are compared with each other. For example, we compare information we collect during the interview about a medicine mothers took while they were pregnant. We also compare information from their DNA samples to tell us how quickly or slowly the mothers' bodies are able to break down and remove the medicine. The differences we see between case and control families might tell us that both the medicine and the DNA are involved in causing birth defects.

Improving the NBDPS

We are always looking for ways to make our study better. As a group, birth defects are common and affect 1 of every 33 babies born in the United States. However, individual birth defects are much less common and it takes many years to collect enough DNA samples and environmental information to complete meaningful studies. While we wait for more families to participate, we have

completed focus group discussions with mothers in Georgia who had already participated in the study. During the discussions, we asked mothers why they wanted to be part of the study; whether they wanted to be part of just the interview or wanted to provide DNA; and what challenges they faced when collecting DNA. We also asked them how they felt about the study materials; the best ways to contact them; and about different kinds of DNA collection methods. We are very excited about the ideas the mothers gave us, and the changes we have been able to make based on this information. We have updated the study folders and other materials we send to families. We also have created a website (www.nbdps.org) that has a lot of information to help answer questions about the study, or about birth defects in general. It contains resources in one location for families. It also contains a short video on how to collect cheek cell samples.

And, it is never too late to send in cheek cell samples. DNA does not change over time, so cheek cells can be collected years after birth and still be extremely helpful. Families who have participated in the NBDPS interview, but have not yet provided cheek cell samples are able to do this at any time. They can contact the study staff in their state to request a kit to collect cheek cells.

In the future, we plan to use new methods for genetic studies. These new methods will let researchers look at many pieces of each person's DNA or all of their DNA to see if there are changes that might be involved in causing birth defects.

As you can see, there are many exciting opportunities for new studies. We thank the many families who have shared information with us about their lifestyle, diet, health, and environment before and during pregnancy; cheek cell samples; or both. These efforts will help us find answers to what causes birth defects. We hope to help prevent future birth defects by sharing the results of our study with women and their physicians.

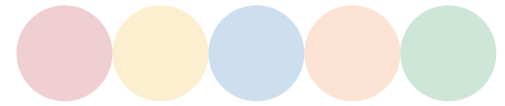
If you would like to share ideas for improving cheek cell collection or any other parts of the study, please email us at nbdps@cdc.gov. We are happy to hear about your experiences and to answer any questions or concerns you might have.



DNA strand

It is never too late to send in cheek cell samples. DNA does not change over time, so cheek cells can be collected years after birth and still be extremely helpful.

NBDPS Honors and Awards



Dr. Feldkamp, Caton and Holmes Received Awards for Their Work



Marcia Feldkamp, PhD, PA, MSPH

Dr. Feldkamp was awarded the F. Clark Fraser New Investigator Award by the Teratology Society. Dr. Feldkamp is the principal investigator of the Utah Center. She is also Director of the Utah Birth Defect Network. She was honored for her work on gastroschisis, a birth defect where the intestines protrude outside the body through a hole beside the belly button. The award honors those who have built a career in birth defects research within 10 years of graduating. Dr. Feldkamp is committed to the study of birth defects. She works to move research findings into prevention action. Her goal is to increase the number of babies born healthy. Congratulations, Dr. Feldkamp!



Alissa Caton, PhD

Dr. Caton received an award for her article "Antihypertensive Medication Use During Pregnancy and the Risk of Cardiovascular Malformations." Dr. Caton works with the New York State Department of Health. Her article looked at the use of medicine to treat high blood pressure during pregnancy. She found that treatment with medicine or having high blood pressure during pregnancy might increase the risk of having a baby born with certain heart defects. The journal Hypertension selected the article as a top original paper published in 2009 in the population science group. Congratulations, Dr. Caton!



Lewis B. Holmes, MD

Dr. Holmes was awarded the 2012 Godfrey P. Oakley, Jr. Award by the National Birth Defects Prevention Network, Inc. This award is given to an individual who has advanced the field of birth defects. Dr. Holmes is one of the principal investigators with the Massachusetts Center. He has made many major contributions to the field of genetics, teratology, and the epidemiology of birth defects. Congratulations, Dr. Holmes!

Iowa Registry Earns State Leadership Award

The Iowa Birth Defects Registry (IBDR) received a national award for its work in collecting quality data and for its prevention efforts. Dr. Paul Romitti, the principle investigator of the Iowa Center, directs the IBDR. This State Leadership Award is given each year by the National Birth Defects Prevention Network.



Arkansas Center Receives Education & Prevention Award

The Arkansas program was given a national award for its education and prevention work. The award honors the outstanding activities of an agency to promote public awareness of birth defects. It recognizes the Arkansas Center's work on folic acid education, newborn screening for critical heart defects, and birth defects prevention.



Resource Corner

We provide several resources that might be of interest. The Centers are not responsible for the content found on these websites.



Physical Activity

The **March of Dimes** website has recommendations about safe exercises and how women can remain active during pregnancy: http://www.marchofdimes.com/pregnancy/physicalactivity_indepth.html.

The **Office on Women's Health** at the U.S. Department of Health and Human Services runs a website that offers advice to women regarding exercise and how to stay healthy and safe during pregnancy: <http://www.womenshealth.gov/pregnancy/you-are-pregnant/staying-healthy-safe.cfm>.

The **Centers for Disease Control and Prevention (CDC)** provides guidelines for healthy exercise during and after pregnancy: <http://www.cdc.gov/physicalactivity/everyone/guidelines/pregnancy.html>.



Heart Defects

The KidsHealth website from **Nemours Foundation** gives a basic overview of some of the warning signs that a child may have a congenital heart defect and describes some of the more common heart defects: http://kidshealth.org/parent/medical/heart/if_heart_defect.html.

The **National Heart, Lung, and Blood Institute** website contains information for parents and children living with congenital heart defects and provides links to clinical trials that study congenital heart defects: <http://www.nhlbi.nih.gov/health/health-topics/topics/chd/livingwith.html>.

The **American Heart Association** has information about congenital heart defects, such as risks, care, treatment, tools and resources: http://www.heart.org/HEARTORG/Conditions/CongenitalHeartDefects/Congenital-Heart-Defects_UCM_001090_SubHomePage.jsp.

The **Cincinnati Children's Hospital** has a wealth of information available in the Heart Institute Encyclopedia, including information on health topics such as cardiac anomalies and congenital heart defects: <http://www.cincinnatichildrens.org/patients/child/encyclopedia/default/>.

The **Royal Children's Hospital (RCH) of Melbourne** has detailed information on heart defects. On the home page, select "Departments & Services," then "Cardiology." On the cardiology department page, a list of common heart defects is given. You can click on each one for more in-depth information for a specific heart defect: <http://www.rch.org.au>.

Genetics

The **Dolan DNA Learning Center** website provides numerous resources on fragile X syndrome, phenylketonuria (PKU), Tay-Sachs disease, and other genetic disorders, including video clips of parents and children describing what it is like to have such diseases: <http://www.ygyh.org/index.htm>.

The **March of Dimes** website contains information on the causes and diagnosis of chromosomal abnormalities and offers links to support groups for families of affected babies: http://www.marchofdimes.com/baby/birthdefects_chromosomal.html.

Directory of the Centers for Birth Defects Research and Prevention National Birth Defects Prevention Study Sites

ARKANSAS

Charlotte Hobbs
University of Arkansas for Medical Sciences
Arkansas Children's Hospital
Telephone: (501) 364-5001; (877) 662-4567 (toll-free)
E-mail: hobbscharlotte@uams.edu
Internet: <http://arbirthdefectsresearch.uams.edu>

CALIFORNIA

Gary Shaw, DrPH
Stanford University
Telephone: (650) 721-5746
E-mail: gmschow@stanford.edu
Internet: <http://www.cdph.ca.gov/programs/cbdmp/Pages/default.aspx>

Directory of the Centers for Birth Defects Research and Prevention

National Birth Defects Prevention Study Sites (continued)

GEORGIA/CDC

Jennita Reefhuis, PhD
Sarah Tinker, PhD
Centers for Disease Control and Prevention
Telephone: (404) 498-4315
E-mail: nbdps@cdc.gov
Internet: <http://www.cdc.gov/ncbddd>

IOWA

Paul Romitti, PhD
University of Iowa
Telephone: (888) 850-8534 (toll-free)
E-mail: NBDPS@uiowa.edu
Internet: <http://www.public-health.uiowa.edu/ircid>

MASSACHUSETTS

Marlene Anderka, ScD, MPH
Massachusetts Department of Public Health
Telephone: (888) 302-2101 (toll-free)
E-mail: marlene.anderka@state.ma.us
Internet: <http://www.mass.gov/birthdefectscenter>

NEW YORK

Charlotte Druschel, MD, MPH
New York State Department of Health
Telephone: (518) 402-7990; (888) 296-8192 (toll-free)
E-mail: cmd05@health.state.ny.us
Internet: <http://www.health.state.ny.us/nysdoh/cmrcmr/home.htm>

NORTH CAROLINA

Andrew Olshan, PhD
University of North Carolina, Chapel Hill
Robert Meyer, PhD
North Carolina Dept. of Health & Human Services
Telephone: (877) 204-5994 (toll-free)
E-mail: alison_woomert@unc.edu
Internet: <http://www.schs.state.nc.us/SCHS/bdmp>

TEXAS

Mark Canfield, PhD
Peter Langlois, PhD
Texas Department of State Health Services
Telephone: (512) 458-7232; (888) 844-4633 (toll-free)
E-mail: mark.canfield@dshs.state.tx.us
Internet: <http://www.dshs.state.tx.us/birthdefects>

UTAH

Marcia Feldkamp, PhD, PA
Lorenzo Botto, MD
Utah Department of Health
Telephone: (866) 818-7096 (toll-free)
E-mail: ubdn@utah.gov
Internet: <http://www.health.utah.gov/birthdefect>

share your stories

If you want to share your experience about the NBDPS, please contact your Center listed in the directory.

Newsletter Ideas and Mailing:

Please contact your Center listed in the directory if you:

- No longer wish to receive this newsletter,
- Need to update your mailing address, or
- Would like to receive this newsletter via e-mail.

Also, please let us know if you have topic ideas for future issues.



Attachment 14
Informed Consent for Cheek Cell

This document was produced for the National Birth Defects Prevention Study;
a similar document will be created for BD-STEPS.

Informed Consent for Cheek Cell Samples

TITLE OF STUDY: National Birth Defects Prevention Study

RESEARCHERS:

National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, and the Centers for Birth Defects Research and Prevention

PURPOSE:

Major birth defects occur in about three out of every 100 babies. The cause is unknown for most of these babies. Birth defects can be prevented only if these causes are understood. The Centers for Disease Control and Prevention (CDC) is doing a research study of babies who do and do not have birth defects to try to understand their causes. To help us to understand environmental and other causes of birth defects, you have already provided us with information through a questionnaire. To help us to understand more about the genetics of birth defects, we are collecting samples from the inside of the cheek from the child, and his/her mother and father.

PROCEDURES:

If you decide to take part in this study, we would like you to give us samples of cells from the inside of the cheek from the child, mother, and father. Samples are collected by brushing the inside of the cheek with a soft brush for 30 seconds. These samples will be used to study genes, which may play a role in why some babies have birth defects. They will only be used to study birth defects and for no other purpose. We have no plans to ever destroy these samples. In some cases, we cannot get reliable information from a sample. This doesn't happen very often. There can be a variety of reasons why this happens. Some possible reasons are too little material in the sample, the sample got contaminated during shipping or processing, or other reasons. If this happens, we will contact you and ask if you are willing to send another sample.

RISKS:

The possible physical risk of this procedure is for temporary, minor discomfort to the inside of the mouth. To protect your confidentiality, no names or other personal information will be attached to the samples.

BENEFITS:

There is no personal benefit to you for taking part in this study. The major benefit is that this study may result in a better understanding of the causes of birth defects. This information will be helpful to all individuals of childbearing age, or who may have children someday. We will share what we learn with other health professionals through medical publications. None of these publications will include information that could identify you or your child in any way.

CONFIDENTIALITY:

All information that we gather in this study will be kept private. This is assured under Section 301(d) of the Public Health Service Act (42 U.S.C. 241(d)). The Certificate of Confidentiality prevents study staff from being forced under a court order or other legal action to identify you or

anyone else in this study. Records may be reviewed by officials checking on the quality of the research. This protection lasts forever (even after death) for any persons who were subjects in the research during any time the certificate was in effect. However, you should understand that the investigators are not prevented from reporting information obtained from you to authorities in order to prevent serious harm to yourself or others. Cheek cell samples will be stored without your names but are linkable. Information about you may be shared with other participating sites and other researchers when and if it has been approved by research review committees. The shared data will not contain any information that could identify any individual. This information will be used only for the study of birth defects. If you would like a copy of the Certificate of Confidentiality for this project, please call Ms. Kimberly Newsome at (404) 498-4315 and it will be provided to you.

COSTS/COMPENSATION:

Parents who agree to provide cheek cell samples on themselves and their child will receive \$20.00 per family with the kit to provide for any expense or inconvenience. Each family will receive an additional \$20 when the kit is returned. CDC does not normally pay for medical treatment in the unlikely event of injury as a result of taking part in this study.

RIGHT TO REFUSE OR WITHDRAW:

Participation in all parts of this study is voluntary. You and your child are free to not take part in the study and you are free to withdraw from any or all parts of this study at any time without penalty or loss of benefits to you. If at any time in the future, you would like to have your interview information or cheek cell samples destroyed or removed from the study, please call Ms. Kimberly Newsome or Ms. Carolyn Sullivan at (404) 498-4315.

LABORATORY RESULTS:

The studies that will be done on these samples are not meant to test your medical status. Since all studies will be done in research labs, we do not plan to return to you the results of the studies. Research labs do not have the same quality control standards as clinical labs. Research labs may also use less expensive techniques, which can make the tests less reliable than those from a clinical lab. However, a few of these studies may have clinical importance. For any tests that have clinical importance, we will publish summarized results in the study newsletter. This newsletter is sent to all participants. If you have questions about whether any genetic tests would be useful to you, we recommend that you consult your health care provider.

CONTROL and OWNERSHIP OF BIOLOGIC MATERIALS:

Some of the cheek cell samples will be studied shortly after they are collected. Most of the cheek cell samples will be stored in a specimen bank for studies in the future. Study researchers will have control over the stored samples unless you request that your sample be removed from storage.

COMMERCIAL VALUE OF BIOLOGIC MATERIALS:

We will not use the cheek cell samples collected from you for commercial purposes.

PARTICIPANT CONSENT:

I have read this consent form or had its contents explained to me. All of my questions have been satisfactorily answered.

SIGNATURES

Print Infant's name: _____

Parent: I have read this consent form or had its contents explained to me. All of my questions have been satisfactorily answered. I voluntarily agree to provide a cheek cell sample for my child.

Parent's Signature: _____
(Sign here if a sample is being sent from your child -- either parent may sign.)
Date: _____

Mother: I have read this consent form or had its contents explained to me. All of my questions have been satisfactorily answered. I voluntarily agree to provide a cheek cell sample.

Mother's Signature: _____
(Sign here if a sample is being sent from the mother.)
Date: _____

Signature of Parent/Legal Guardian of mother if mother is a minor:

Father: I have read this consent form or had its contents explained to me. All of my questions have been satisfactorily answered. I voluntarily agree to provide a cheek cell sample.

Father's Signature: _____
(Sign here if a sample is being sent from the father.)
Date: _____

Signature of Parent/Legal Guardian of father if father is a minor:

If you have any questions, please contact:

Kimberly Newsome
National Center on Birth Defects and Developmental Disabilities, CDC
(404) 498-4315

If you have questions about your rights as a subject in this research study, please call the Office of the Deputy Associate Director for Science for CDC at 1-800-584-8814, leave a message including your name, phone number, and refer to protocol #2087, and someone will call you back as soon as possible.

Attachment 15
Certificate of Confidentiality Request



Memorandum

Date January 5, 1999

From Project Officer, National Birth Defects Prevention Study
BDGDB, DBDDD, NCEH (F45)

Subject Application for a 301(d) Certificate of Confidentiality for 8 Sites Conducting The
National Birth Defects Prevention Study

To Carolyn Russell, Director, MASO MS E-11

Please accept this request for a Certificate of Confidentiality for the National Birth Defects Prevention Study (NBDPS) currently being carried out by eight Centers for Birth Defects Research and Prevention ("the Centers"). The NBDPS allows the Centers (located in Arkansas, Atlanta, California, Iowa, New Jersey, New York, Massachusetts, and Texas) to collaborate in a population-based study to improve our understanding of factors which influence the occurrence of birth defects. This will be the largest epidemiological study of birth defects to date.

Each State has the legal authority to ascertain birth defect cases and a random sample of controls. Cases are ascertained within each state's ongoing surveillance program. The study has three main components: 1) parental interviews (NBDPS Attachment 8); 2) improved birth defects classification based on the clinical review of abstracted medical data (NBDPS Attachment 6); and 3) biologic specimens for use in evaluating genetic and biologic markers of exposure and susceptibility (NBDPS Attachments 9 and 12). Each year for the next five years, each of the eight project sites will contribute 400 interviews per year (300 cases and 100 controls). Thus, an estimated 16,000 interviews will be conducted through this collaborative effort, including births from October 1, 1997 to September 30, 2002.

Because this project supports one of the key missions of NCEH's Division of Birth Defects and Developmental Disabilities, funding is quite likely to continue indefinitely; therefore we are requesting a Certificate for a five year period. Protection with a 301(d) Certificate of Confidentiality is sought because this study involves research of a sensitive nature, including the collection of the following: a) information relating to the use of alcohol, drugs, or other addictive products; b) information that, if released, could reasonably be damaging to an individual's financial standing, employability, or reputation within the community; c) information that would normally be recorded in a patient's medical record, and the disclosure of which could reasonably lead to social stigmatization or discrimination.

The specific sensitive information collected during this study which warrants a 301(d)

Certificate of Confidentiality includes: maternal health conditions (diseases, congenital abnormalities, injuries; examinations, medications, and therapies; pregnancy history); family history (biologic versus adoptive parentage; health information about family members); lifestyle (tobacco use, alcohol use, illegal drug use); employment history (occupation, employer name, chemical exposures) (NBDPS Attachment 8). The NBDPS does not collect reports or conduct tests for reportable communicable diseases.

The NBDPS is based on the previous experience of the Birth Defects Risk Factor Surveillance Program (BDRFSP), which was initiated at CDC and had 308(d) confidentiality assurance protection. It was expanded in 1993 through cooperative agreements with California and Iowa. The NBDPS is a project funded in part by the CDC National Center for Environmental Health. Current funding runs until 2002 and is expected to continue for additional years. The activities of this project are both intramural and extramural, consisting of one CDC/contractor-operated site in Atlanta, Georgia and seven CDC-funded cooperative agreements in seven other states. The seven cooperative agreement holders are: Arkansas Children's Hospital Research Institute (U50/CCU613236); March of Dimes/California Birth Defects Program (U50/CCU913241); University of Iowa (U50/CCU713238); Massachusetts Department of Public Health (U50/CCU113247); New Jersey Department of Health (U50/CCU213243); Health Research Institute (New York) (U50/CCU213244); Texas Department of Health (U50/CCU613232).

Because all sites (except the CDC's Atlanta site) were funded by cooperative agreements, it was determined by the CDC OGC and Confidentiality Officer that a 301(d) Confidentiality Certificate was the appropriate confidentiality protection. A letter from each of the Centers initiating this request is attached [NBDPS Attachment 29]. NCEH has delayed finalizing the application until CDC IRB approval was imminent. Final revised documents were submitted in late December, and final CDC IRB approval is expected very soon. (Although the letters originated earlier this year, we have been in communication with the Centers about the certificate, and each site continues to feel this confidentiality protection would be valuable.)

The data to be covered by 301(d) confidentiality certificate protection include the interviews, clinical data, and results of testing on biological samples collected for the National Birth Defects Prevention Study. Each site operates a state surveillance program established by law that was operational prior to the Centers study. Surveillance data already in the possession of the sites is not to be included under the certificate.

The NBDPS Protocol is Attached in full. The protocol has been reviewed by the each site's IRB and each site has received individual IRB approval (NBDPS Attachment 30). Each Center is in compliance with protection of human subjects regulation (45 CFR Part 46). All Centers have agreed to submit requests for modification of the written informed consent forms to their IRB when CDC IRB and confidentiality approval is obtained. It is anticipated that individual IRBs may require minor revisions.

Each Center has developed consent forms using the standard developed for the study. However, if a Certificate of Confidentiality is granted, the following statement will be included in the introductory telephone script, informed consent documents and letters to participants:

“The interview data, clinical data and results of testing on biological samples that we gather for this study will be kept private. This is assured under Section 301(d) of the Public Health Service Act (42 U.S.C. 241(d)). The Certificate of Confidentiality prevents study staff from being forced under a court order or other legal action to identify you or anyone else in this study. Records may be reviewed by officials checking on the quality of the research. This protection lasts forever (even after death) for any persons who were subjects in the research during any time the certificate was in effect. Information about you may be shared with other researchers when and if it has been approved by research review committees.”

The consent forms stipulate that genetic test results will not routinely be provided to participants; however, if a specific request is made, a listing of health professionals qualified to interpret the results will be provided, and the subject will be asked to designate one of these individuals to receive their results and advise them concerning interpretation.

Identifiable data will be retained by the individual state institutions and unidentifiable pooled data from all project sites will be maintained at CDC. Selected data sharing among participating institutions may occur, as permitted by the 301(d) Certificate of Confidentiality. The grantee institutions will determine the length of retention of identifiable data they hold. Individual Centers wish to have the option of sharing identifiable data with other collaborators; collaborators are defined as researchers having a bona fide relationship with the individual Center. In addition to having a bona fide relationship with the Center, the collaborator must be sponsored by the Principle Investigator of the Center.

In addition to the funding each Center receives to conduct the National Birth Defects Prevention Study, each Center receives funding to conduct local studies that are initiated by the Center and approved by their IRB. The same type of sensitive information requiring confidentiality protection will be involved in these local projects. An example of such a study is the Texas Center study of obesity and nutrition among Hispanic mothers of infants with and without neural tube defects. Data from these local studies will not be shared among the Centers and are intended for local use only. If a Center wants these local studies to be covered by the Certificate they will present the study protocol to the CDC Confidentiality Review Group for approval before implementation.

CDC does not wish to mandate how the individual Centers use their own data. If the institution's local IRB approves the sharing of identifiable data gathered within that site's research project, we request that neither CDC confidentiality review or IRB review will be required. The applicants understand and agree to the following conditions which will be stated in the Certificate:

a) The Certificate does not authorize the holder, its employees, or contractors to refuse to disclose information in the course of an audit or program evaluation of the research by authorized personnel of the U.S. Department of Health and Human Services --situations where identifiable records may be reviewed or copied by Federal investigators, but where the research subjects are not the targets of the inquiry and where their identities are irrelevant to the inquiry.

b) The Certificate cannot be used to prevent disclosure if the subject (or the subject's guardian if he/she is legally incompetent) consents in writing to disclosure of identifying information.

If you have questions regarding this application, please call me at 770-488-7171.

Larry D. Edmonds, M.S.P.H.

Attachments:

National Birth Defects Prevention Study Protocol

Copy of the letter from these institutions initiating this request (NBDPS Attachment 29)

NBDPS telephone interview (NBDPS Attachment 8)

IRB approvals from individual study sites (NBDPS Attachment 30)

Letters of introduction to participants (NBDPS Attachment 18)

Written Informed Consent Documents - CDC prototype (NBDPS Attachment 10)

Attachment 16
FAQ Cheek Cell Collection

This document was produced for the National Birth Defects Prevention Study;
a similar document will be created for BD-STEPS.

Frequently Asked Questions About Cheek Cell Brushes

What happens to the cheek cell brushes?

Your brushes are sent to a central lab where the genetic material is removed from the brushes and checked for usability. Samples are then labeled with a code number and stored until researchers are ready to use them. Most samples are okay, but sometimes the lab may find out there is not enough material to study. In these rare cases we may ask for a second sample of your cheek cells.

What kinds of tests will be done?

The goal of our study is to understand the causes of birth defects. Some genes are already thought to be important in the causes of birth defects. We study these genes to learn how changes in them could lead to a birth defect. Other genes that have not yet been looked at in birth defects studies will also be tested. Many of the gene studies will need large numbers of families. Often, genetic material will be stored for many years before we have enough families for studies to be done.

Will I receive my results?

No, you will not receive individual test results. Instead, we will send a newsletter that contains important study results to all who participate. This newsletter will inform families of any major findings, especially if the results of a study might be useful for family members who are interested in genetic testing. Families can then talk with their doctor or genetic counselor to help them decide whether the gene test could be helpful to them.

Why can't my results be sent to me?

There are several reasons why your test results are not sent to you.

First, the tests done on your samples are for research. This means our study will look for connections between birth defects and genes. Before these connections can be useful, the tests need to be repeated in other labs using samples from other families. Until this is done, we cannot be sure these connections mean anything to individual families.

Second, in most cases, birth defects are caused by a combination of genes and other factors, such as exposures to certain medicines or chemicals in the environment. Because of this, we will learn about the causes of birth defects by examining data from both telephone interviews and gene tests. In most cases, the results from one gene test will not be meaningful without knowing other information.

Third, while our tests are done carefully, they do not meet the strict standards required for medical tests. Since these standards might not have been met, we will not send individual test results.

Will a cold or illness affect the samples?

No, being sick won't affect the quality of the cheek samples. You can collect a sample even when a person is sick.

Will collecting the samples hurt?

No. It will cause little to no discomfort for you or your family members.

What if I collect the samples, then forget to mail them for a while?

We will get better results if the samples get to us soon after they are collected. If your samples do not get mailed within a week, you can ask for another kit to collect new samples.

What if everyone can't give the samples at the same time?

It will be best if you collect all the samples at about the same time and then mail them. But if this is not possible, you can mail what you have. If you have other samples to send at a later time, you may ask for another mailing envelope.

What if I no longer want to be part of the study?

You may ask to be removed from the National Birth Defects Prevention Study at any time. Please call Tineka Yowe-Conley at 404-498-4315 if you want to be removed from the study. After receiving this request, we will destroy your cheek cell samples.

Who can I call if I have more questions?

You can call Tineka Yowe-Conley at 404-498-4315.



Thank you again for participating in this important study of birth defects!

Preguntas frecuentes sobre la toma de muestras de células bucales

¿Qué se hace con las muestras de células bucales?

Sus muestras de células bucales son enviadas a un laboratorio central donde se les saca el material genético y se determina si este material tiene alguna utilidad. A las muestras se les coloca una etiqueta con un código y se guardan hasta que los investigadores estén listos para usarlas. La mayoría de las muestras son adecuadas, sin embargo, a veces el laboratorio determina que no tienen suficiente material para su estudio. En estos casos esporádicos, es probable que le pidamos que se tome otras muestras.

¿Qué tipos de pruebas se harán?

La meta de nuestro estudio es entender las causas de los defectos congénitos. Se piensa que algunos genes desempeñan un papel importante en las causas de algunos defectos congénitos. Nosotros estudiamos estos genes a fin de determinar si un cambio en ellos pudiera provocar algún defecto congénito. También se estudiarán otros genes que todavía no han sido incluidos en los estudios de los defectos congénitos. Para llevar a cabo muchos de los estudios genéticos, se requerirá una gran cantidad de familias. A menudo el material genético será guardado por muchos años antes de que tengamos suficientes familias para realizar los estudios.

¿Me darán los resultados de los estudios?

No se entregarán resultados individuales, pero sí enviaremos a todos los participantes un boletín con los resultados importantes del estudio. Mediante este boletín informaremos a las familias sobre cualquier descubrimiento importante que se haya hecho, especialmente si los resultados del estudio pudieran ser útiles a aquellos miembros de la familia interesados en las pruebas genéticas. Las familias podrán entonces hablar con su médico o con un consejero genético para que las ayude a decidir si las pruebas genéticas les servirán de algo.

¿Por qué no pueden enviarme los resultados?

Existen varias razones por las cuales no se le puede enviar los resultados.

En primer lugar, las pruebas que se realizan con sus muestras son parte de la investigación. Esto significa que el estudio buscará identificar las relaciones entre los defectos congénitos y los genes. Antes de que estas conexiones tengan alguna utilidad, deben repetirse las pruebas en otros laboratorios con muestras de otras familias. Hasta que se haga esto, no podremos saber con seguridad si estas conexiones significan algo para cada familia.

En segundo lugar, en la mayoría de los casos, los defectos congénitos son provocados por una combinación de genes y otros factores, tales como la exposición a medicinas o sustancias químicas

ambientales. Por lo tanto, para conocer las causas de los defectos congénitos, necesitaremos examinar tanto los datos de las entrevistas telefónicas como los de las pruebas genéticas. En la mayoría de los casos, los resultados de una prueba genética no significarán nada a menos que tengamos otra información.

En tercer lugar, si bien realizamos las pruebas con mucho cuidado, éstas no cumplen con las normas estrictas necesarias para las pruebas médicas. Debido a que probablemente no se haya cumplido con estas normas, no enviaremos resultados individuales a nadie.

¿Duele la toma de las muestras?

No. Ni usted ni sus familiares sentirán prácticamente ninguna molestia.

¿Se verán afectadas las muestras si tengo gripe u otra enfermedad?

No. Estar enfermo no afectará la calidad de las muestras bucales. Se puede tomar una muestra de una persona aun cuando esté enferma.

¿Qué pasa si me tomo las muestras y luego se me olvida enviárselas a ustedes por un tiempo?

Los resultados serán mejores si las muestras nos llegan lo más pronto posible después de haberlas tomado. Si las muestras no son enviadas dentro de la semana siguiente a su toma, usted puede solicitar otro kit para tomar otras muestras.

¿Qué pasa si no todos pueden enviar las muestras al mismo tiempo?

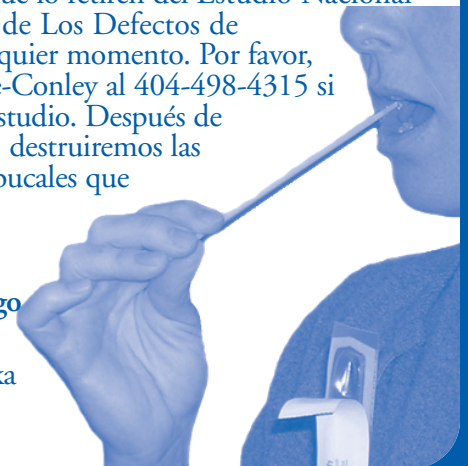
Lo mejor sería que todos tomaran las muestras y nos las enviaran más o menos al mismo tiempo. Pero si esto no es posible, usted puede enviarnos las que tenga. Si tiene otras muestras que enviar más adelante, puede solicitar otro sobre de correo para que nos las envíe.

¿Qué pasa si ya no quiero seguir participando en el estudio?

Usted puede pedir que lo retiren del Estudio Nacional Para La Prevención de Los Defectos de Nacimiento en cualquier momento. Por favor, llame a Tineka Yowe-Conley al 404-498-4315 si quiere retirarse del estudio. Después de recibir esta solicitud, destruiremos las muestras de células bucales que nos haya enviado.

¿Con quién puedo comunicarme si tengo más preguntas?

Puede llamar a Tineka Yowe-Conley al 404-498-4315.



¡Gracias nuevamente por participar en este importante estudio sobre los defectos congénitos!

Attachment 17
Thank You Letter with \$20

This document was produced for the National Birth Defects Prevention Study;
a similar document will be created for BD-STEPS.

*The National Birth Defects Prevention Study – Protocol #2087, Attachment 27
Thank You Letter Buccal Return (Living/English)
Revised 1/5/07 (contact info only)*

11/13/2012

«First_Name» «Middle_Name» «Last_Name»
«Address»
«City», «State» «zip»

Dear Ms. «Last_Name»:

On behalf of the Centers for Birth Defects Research and Prevention, we want to thank you again for allowing us to interview you and for completing the cheek cell kit for The National Birth Defects Prevention Study.

As we mentioned, it is our hope that by gathering information from a larger number of women, we may be able to learn more about the subject of birth defects. Your cooperation has been most valuable to us, and hopefully, will also be of value to other mothers and children in the future. Enclosed is a \$20 money order to compensate you for your time.

Please feel free to call us if you have any questions which were not answered. In addition, we hope that we may feel free to contact you again, if, as we progress in our work, any new questions arise.

Thank you again for being so helpful.

Sincerely yours,

Jennita Reefhuis, PhD
Principal Investigator
National Center on Birth Defects and Developmental Disabilities
Centers for Disease Control and Prevention
1600 Clifton Road
Mailstop E-86
Atlanta, GA 30333

Attachment 18A
Buccal Recollect Phone Scripts

This document was produced for the National Birth Defects Prevention Study;
a similar document will be created for BD-STEPS.

National Birth Defects Prevention Study – Atlanta

Buccal Recollection Script

Hello, may I speak with <**First and Last Name of Mother**>? My name is <**Interviewer**> and I am calling for the <**Atlanta**> National Birth Defects Prevention Study. Recently you completed the study by mailing us cheek cell samples from <your family / yourself / your child / your child's father>.

We did some initial tests on study samples and we were unable to get reliable information from your sample. This doesn't happen very often. And there can be variety of reasons why this happens. Some possible reasons are too little material in the sample, the sample got contaminated during shipping or processing, and other reasons.

We would like to mail you a new cheek cell packet to you so we can analyze your samples again. Would it be alright for us to send you another packet <for you/your baby/and baby's father>?

IF YES: Thank you! We appreciate your help with this important part of the study. The cheek cells are an important part of the study and will help identify genetic risk factors for birth defects. You should receive the kit in approximately ___ days. Please read and sign the consent form included in the packet and return it as soon as possible. You will receive a \$20 money order with the packet. When you return your packet to us, you will receive an additional \$20 money order.

IF NO: We understand. Thank you for the help that you have given by completing the interview and providing your samples in the previous kit(s).

ANSWER QUESTIONS:

QUESTION: What happened to my sample?

ANSWER: There can be several reasons why the sample did not work such as too little material in the sample or the sample got contaminated during shipping or processing.

QUESTION: Why do you need a resample in my particular situation? What was wrong with my samples? Did I do something wrong in collecting the samples before? Did you lose my samples?

ANSWER: I do not have information about the specific reason why a new sample is needed in your case. For reasons of confidentiality, the lab does not give us any specific information on this. However, we do know that samples that take longer in the mail or are mailed when the temperatures are hotter are more likely to need to be repeated.

QUESTION: What do I get for doing this again?

ANSWER: We will include a \$20 money order in the cheek cell packet. You will receive an additional \$20 money order once we receive it.

QUESTION: Is there something wrong with me, <my baby> or <the baby's father>?

ANSWER: We have not yet done any testing on the samples to look for risk factors for birth defects. We first process the sample to make sure there is enough DNA to do these tests. After we looked at your sample we realized we needed to request a new sample from you <and your family/your baby/the baby's father>.

QUESTION: Were all of the samples bad? Will we need to re-collect from all of us or just for the bad sample?

ANSWER: The lab does not tell us if one or all of the samples had too little DNA or if there is any other problem. They only tell us which families need to be recontacted and asked for new samples. <In most cases, the lab has more difficulty getting enough DNA from the baby samples. This happens because it is harder to collect a good sample from a baby. Sometimes, babies have a lot of spit that can make the sample harder to process.>

QUESTION: If <NIOB's> father participated in the first collection, but is not available to participate in a recollection, do you still want the recollection from me and my baby?

ANSWER: Yes, please. Each cheek cell sample increases our chances of finding genetic factors that may increase the risk of birth defects.

QUESTION: What will happen to the bad samples? Will they be destroyed, and when will they be destroyed?

ANSWER: We plan to keep all samples collected for the study. If at any time in the future, you would like to have your interview information or cheek cell samples destroyed or removed from the study, please call Ms. Kimberly Newsome or Ms. Carolyn Sullivan at (404) 498-4315.

QUESTION: Why is it so important to do the cheek cell sample again? Why do you need these samples?

ANSWER: Each cheek cell sample increases our chances of finding genetic factors that may increase the risk of birth defects.

If you have additional questions or would like more information, please call Ms. Kimberly Newsome, NBDPS Study Coordinator, at 404-498-4315.

Attachment 18B
Buccal Recollect Letter

This document was produced for the National Birth Defects Prevention Study;
a similar document will be created for BD-STEPS.

<Date>

<Name>

<Address 1>

<Address 2>

Dear <Participant>,

Thank you for participating in the National Birth Defects Prevention Study. As part of the study, you sent us cheek cell samples. The cheek cells are an important part of the study and will help identify genetic risk factors for birth defects.

We did some initial tests on the study samples and we were unable to get reliable information from your sample. This doesn't happen very often. And there can be variety of reasons why this happens. Some possible reasons are too little material in the sample, the sample got contaminated during shipping or processing, and other reasons.

We are writing to request that you send us a second sample so that we can analyze your sample again. As you previously read in the study consent form, your participation is voluntary, and you may withdraw your samples at any time. Please read the enclosed "Informed Consent for Cheek Cell Samples." If you choose to submit a second sample, please sign the consent form and return it with the completed cheek cell kit in the enclosed postage paid envelope. A money order for \$20 has been included for your time and effort involved in collecting another set of samples. You will also receive a second \$20 money order when we receive your kit.

We apologize for the inconvenience that this may cause you. We will be glad to talk with you about the need for these new samples. We can be reached at (404) 498-4315, or toll-free at (888) 743-7324. Thank you very much for your consideration.

Sincerely,

Jennita Reefhuis, PhD

Principal Investigator

National Center on Birth Defects and

Developmental Disabilities

Centers for Disease Control and Prevention

1600 Clifton Road

Mailstop E-86

Atlanta, GA 30333

Attachment 19
Data Sharing Guidelines

This document was produced for the National Birth Defects Prevention Study;
a similar document will be created for BD-STEPS.

**ANALYSIS AND PUBLICATION GUIDELINES
FOR THE NATIONAL BIRTH DEFECTS PREVENTION STUDY (NBDPS) CONDUCTED BY THE
CENTERS FOR BIRTH DEFECTS RESEARCH AND PREVENTION (CBDRP)**

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ANALYSIS AND PUBLICATION GUIDELINES FOR THE NATIONAL BIRTH DEFECTS PREVENTION STUDY (NBDPS) CONDUCTED BY THE CENTERS FOR BIRTH DEFECTS RESEARCH AND PREVENTION (CBDPRP)

The Data Sharing Committee

I. GOALS and PURPOSE

The purpose of this committee is:

1. To assure and expedite orderly and timely presentation to the scientific community of all pertinent data resulting from the collaborative NBDPS;
2. To promote accurate and scientifically sound presentations and papers from the NBDPS and its collaborating investigators;
3. To assure that all participating investigators have the opportunity to be involved in data analysis and the preparation of NBDPS papers and presentations;
4. To assure that press releases, interviews, presentations, and publications are accurate and objective, and do not compromise the collaborative study and the acceptance of its results;
5. To establish guidelines for authorship, acknowledgements, and funding citations for any presentations and publications of the NBDPS; and
6. To maintain a record of proposed and published papers and presentations from the NBDPS study.

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II. SCOPE OF THE GUIDELINES

This policy covers papers, abstracts, and presentations that involve unpublished data collected by the NBDPS and compiled at the Centers for Disease Control and Prevention (CDC) from the ten participating study sites [AR, CA, GA, IA, MA, NC, NJ (inactive), NY, TX, and UT]. The data covered by these guidelines include all interview, clinical, and biologic data associated with this study. It does not apply to data collected and maintained by individual Centers as part of the NBDPS or to data collected as part of local studies by each Center. These guidelines should be followed for any studies or writing projects involving data from two or more Centers. These policies will remain in force until the Data Sharing Committee is formally dissolved.

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III. MEMBERS OF THE DATA SHARING COMMITTEE

1. Members of the Data Sharing Committee will include two representatives from each of the active Centers plus two representatives from CDC. The Center representatives may be the Principal Investigator and one additional representative, or the two Co-Principal Investigators. The Centers may allow substitute members to attend meetings or phone conferences. The substitute may vote on project approvals.
2. The Data Sharing Chair will serve as administrator of the Committee. The Data Sharing Chair will serve at term of 6 months, January-June, July- December. CDC will coordinate the administrative aspects of the Committee as well as represent the Atlanta study site. All correspondence to the committee, including letters of intent, proposals and abstracts, and manuscripts will be sent to CDC for distribution to Committee members. The CDC coordinators will also be responsible for ensuring that all IRB requirements are met for any analyses resulting from the collaborative NBDPS. Committee members from each Center will be responsible for sharing documents submitted to the committee with their Center staff in order to inform them about proposed projects and to obtain their feedback. Each Center can submit 2 reviews to the Data Sharing committee for each proposal or manuscript being considered by the committee.
3. The Data Sharing Editor will assign 2-3 reviewers according to area of interest or specialty and give final approval on all manuscripts involving the shared NBDPS data. The Data Sharing Editor will have a term of 6

months. If a conflict of interest arises, the “editor in waiting” will be asked oversee the review process for that particular manuscript.

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IV. APPROVAL OF PROJECTS FOR ANALYSIS AND PUBLICATION

A. Approval of NBDPS Projects for Analysis and Writing

1. To initiate an analysis and writing project, a participating investigator must first complete the letter of intent template ([Attachment M](#)) and submit to the Data Sharing Committee. The purpose of the letter of intent is to communicate research ideas and facilitate collaboration among Centers. The letter of intent template includes:

- a. the name of the lead investigator
- b. the name of the sponsoring PI
- c. the hypothesis to be tested
- d. collaborators involved in the research
- e. any issues related to conflict with existing or proposed research conducted by other Centers.

Letters of intent should be submitted to the Data Sharing Committee via the CDC Coordinator by the third Thursday of the month ([Attachment J](#), Data Sharing Schedule). The sponsoring PI must review and approve the LOI before submission. The sponsoring PI has the responsibility to assure that all investigators and co-authors who will have access to any NBDPS data (clinical, interview or biologics) have signed the confidentiality and data use oath and that it is on file ([Attachment F](#)). The lead investigator must copy the sponsoring PI and all co-authors when submitting letters of intent to the Data Sharing committee.

2. The CDC Coordinator will distribute the letter to all committee members for review on the day after the Data Sharing conference call. The Committee members will review the letter to determine that the scope of the analysis is reasonable, and that there are no conflicts with existing analyses being conducted by other Centers investigators. The committee members may also make suggestions for collaboration with other Centers investigators.
3. Committee members will send their comments about the letter of intent using the email review form supplied when the letters of intent are distributed ([Attachment A](#)). Reviews are due three weeks after the letters are distributed to the Committee. Comments will be compiled by the CDC Coordinator and distributed to the committee on the Monday before the next Data Sharing call. The compiled comments will include the name of each reviewer, along with his/her comments. During the Data Sharing call, the committee will discuss and informally vote on letters of intent. If the author or sponsoring PI is not on the call the Committee will respond to investigators the following day with their decision and any comments, unless issues are raised that require further discussion. The Data Sharing Committee decision will also be entered in the Data Sharing Database and added to the Centers website.
4. Under very limited circumstances, the CDC administrators of the Data Sharing Committee may call for an expedited review of a letter of intent. Requests for an expedited review should be submitted to the committee with justification for the need to expedite the review.
5. After the committee approves the research proposed in the letter, the investigators should complete the proposal template ([Attachment N](#)) to prepare a 2-5 page study proposal. The sponsoring PI must review and approve the research proposal before submission. If any new co-authors have been added, the sponsoring PI has the responsibility to assure that they have signed and have on file the confidentiality and data use oath. Proposals should be submitted no sooner than 6 months before the time that it is expected that there will be enough cases or exposures of interest to do the study. The lead investigator must copy the sponsoring PI and all co-authors when submitting the proposal to the Data Sharing Committee. The proposal should include:
 - 1) investigators with lead investigator and sponsoring PI noted
 - 2) contribution of each investigator
 - 3) objectives, aim or hypothesis
 - 4) background with relevant references
 - 5) methods describing –

- a) specific outcomes of interest
- b) primary exposures of interest
- c) analysis plan with power calculations if relevant
- d) other data collection or record matching if relevant.

If particular expertise in, for example, molecular genetics, statistics, epidemiology or case classification will be required for the study, plans for obtaining this should be noted in the proposal.

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B. Policy on replication of NBDPS pooled data analyses (Approved 3/10)

1. Analyses of NBDPS pooled data with the intention of publication in a peer-reviewed journal require replication of results. For this policy, replication is defined as:
 - a. Confirmation of case and control counts for analyses
 - b. Confirmation of all main exposure and covariate¹ distributions by case²-control status
 - c. Confirmation of crude main effect analyses
 - d. If the presence of interactions are to be reported, confirmation of interaction effects
2. Replication should take place no later than the time during manuscript review by the NBDPS Committee. A check-box is added to the manuscript submission form ([Attachment O](#)) in which the lead author will indicate that the analysis has been or is currently undergoing replication, and by whom.
3. The lead author may select the analyst to conduct the replication. This individual may be within the lead author's study center, or not, and may be an official project collaborator, or not. Depending on the level of effort undertaken, analysts who conduct replication who are not official project collaborators, may be officially acknowledged in the manuscript or offered co-authorship, although neither is required.
4. The lead author may petition the Committee for a waiver of the replication requirement. This can be done by e-mail and it does not have to wait for a Committee call.
 - a. Justification for the waiver request should include:
 - Quality Control (specify what has been done to limit errors)
 - Short timeline
 - Qualitative Analysis (specify how questions were assessed and how errors are minimized)
5. Policies specific to new analysts:
 - a. New analysts are required to conduct a study replication as part of their training.
 - b. The work of new analysts must be replicated.
 - c. New analysts (or lead authors working with a new analyst) may not petition for a waiver of the replication requirement.

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¹ Covariates that are included in a "table 1" or if there is no such table of characteristics, covariates that are included in the multivariable analyses.

² For spectrum analyses, confirmation of covariate distributions among all included case groups is not necessary. Confirmation of covariate distributions for all cases combined is sufficient.

C. Data Sharing Guidelines: Biologics^(Revision Approved 5/12)

If the proposed research includes use of biologic material, the following guidelines apply:

In addition to the proposal, the **gene one-pager form** for the CDC IRB must be completed for each gene to be studied. The genes from one candidate gene pathway may be grouped on one form if they are not clinically significant. Those genes that are clinically significant must be submitted as separate gene one-pagers. The gene one-pager forms must accompany the proposal, and approval from the CDC IRB must be obtained before the samples will be released. The CDC IRB review will be expedited and is expected to take 1-2 weeks.

I. Limited and Expanded SNP Projects

These guidelines should be followed for those studies that typically include a small number of candidate genes and a small number of SNPs chosen because of known functionality and previous studies (limited SNP projects) and studies that are an expansion of these currently approved and proposed NBDPS LOIs and proposals. Guidelines for whole genome scans are considered separately in section II below.

The proposed guidelines include:

- 1) Typically only a defect or defect group will be proposed for interrogation.
- 2) Priority should be given to questions of public health, clinical, and biologic significance. Priority should be given to projects with high likelihood of success based on power calculations.
- 3) Justification must be provided for the choice and prioritization of target genes and SNPs. A broad array of genes and SNPs may be chosen depending upon the hypothesis. The proposal should clearly articulate the criteria used to select the genes and SNPs, including but not limited to, as appropriate, allele frequencies, known associations, functionality of polymorphism, or LD structure of the gene.
- 4) Additional anonymous SNPs may be selected to define or tag haplotypes or bins of correlated SNPs. In addition, there should be a description of the approach used to select a minimal number of SNPs needed to define haplotypes including racial/ethnic-specific SNP selection methods if necessary.
- 5) *Proficiency Testing*: The proposal must include verification that the lab proposing to perform genotyping on NBDPS samples passed the required annual External Quality Assessment (EQA) [link to EQA protocol on website]
- 6) *Preliminary Data*: Proposals must include preliminary data from a new pilot study or a previously performed study. If from a previous study, the reference must be cited and a summary of the results included. Laboratories using high throughput platforms (e.g., Illumina, Affymetrix) and assays for the first time can include data from 12 subjects (instead of 90) following the same guidelines for gene variants, DNA, and genotyping platform listed below. Assays must be directed by lab staff who will be handling the samples for the proposed research. If the laboratory has genotyping results using NBDPS samples from a higher throughput assay (e.g., Infinium), they can include those data in a proposal that will include lower throughput assays (e.g., Golden Gate). Preliminary Data must include the following:
 - Type and Number of Gene Variants
 - Type of gene variant (SNP, indel, STR, etc) must be consistent with proposed research (for example, if proposed research includes analysis of multiple SNPs and a few deletions, preliminary data must include analysis of SNPs and deletions). Data for specific gene variants to be analyzed in proposed research is not required.
 - Number: minimum of 3 variants
 - Type of DNA: buccal; specify whole genome amplified and/or unamplified gDNA
 - If buccal DNA will be amplified in the proposed research, a description of the WGA method and preliminary data demonstrating the labs experience and proficiency must be provided including genotype concordance rates between paired amplified and unamplified buccal gDNAs.
 - Number of Subjects: minimum of 90
 - Genotyping Platform: must be consistent with proposed research

- 7) Samples with DNA concentrations < 0.1ng/ul (measured using human RNaseP real-time quantitative PCR) should be excluded from analyses
- 8) A proposal section on the methods to be used to determine and account for potential false positive associations should be included.
- 9) If genes are of interest to other researchers, research agendas should be coordinated among interested investigators. Proposals should specify others who were contacted regarding interest in the project. Priority should be given to those proposals that combine genotyping from multiple projects into a single effort.
- 10) *Sharing of initial results with the group and contribution of final data to the NBDPS repository.* Within 6 months, the primary research team should deposit initial study results into the Biologics Genotyping Database. If the team is unable to meet this deadline, they should notify the Data Sharing Committee when to expect the transmission of results.
- 11) Approved proposals may be resubmitted as amended/revised proposals including the expanded aims. The description of the new target genes and SNPs and related material should be incorporated into the approved original proposal with the new text demarcated.

II. Whole Genome Studies

Development of WGS projects are complex, requiring extensive planning for genotyping platforms, DNA quality, costs, data analysis, etc. Additional technical expertise, facilities, and major funding are required. Given that they are typically beyond the scope of usual NBDPS genetic projects these may be undertaken by a team of NBDPS investigators with relevant expertise representing multiple Centers and the CDC. Issues to be considered when planning and preparing LOIs and proposals involving whole genome scans include:

- 1) Typically only a defect or defect group will be proposed for interrogation.
- 2) Priority should be given to questions of public health, clinical, and biologic significance.
- 3) Other groups with potential overlap through ongoing or planned genetic studies of the same defect or defect group should be contacted. Proposals should specify others who were contacted regarding interest in the project.
- 4) *Sharing of initial results with the group and contribution of final data to the NBDPS repository.* Within 6 months, the primary research team should deposit the initial study results into the Biologics Genotyping Database. If the team is unable to meet this deadline they should notify the Data Sharing Committee when to expect the transmission of results.
- 5) *Proficiency Testing:* The proposal must include verification that the lab proposing to perform genotyping on NBDPS samples passed the required annual External Quality Assessment (EQA)
- 6) The primary research team must provide information demonstrating that they are capable of conducting WGS studies with regard to: 1) performing the appropriate laboratory assays and 2) performing primary data analysis. This should be a general description of the laboratory's experience with the relevant WGS platform. It is expected that the laboratory, whether a Center's in-house facility, or a collaborating or contract lab, will provide this summary. Note that the laboratory should present preliminary data from a representative WGS genotyping experiment. The quantity of DNA necessary to perform whole genome amplification and genotyping assays should be included. Other data, as it applies to the specific WGS platform, should include data quality assessments. Where appropriate, specifics regarding the inclusion of negative and positive controls as well as QC replicates, duplicates of selected samples, or the repeat testing of 5-10% of samples should be included. Local NBDPS buccal samples should be used for all feasibility studies and pilot testing. Verification that WGA products were amplified with no allele bias using other sources of DNA should be included. The PI from the Center where the specimens will be taken should sign off on the proposal. The group's experience and expertise in the processing and analysis of WGS and similar high-dimensional gene data should be presented.

- 7) The authorship plan for the primary publications from the scan project and associated secondary papers should be defined in advance. These collaborative efforts will require a list of primary authors with The NBDPS listed last on the authorship line. The PI from the Center that will author the primary publication should sign off on the proposal.
- 8) Decisions may be made by an expanded research team including the PI and co-investigators including those of the primary research team, others with ongoing or planned analyses of candidate genes of the defect(s) under study and those with additional expertise and interest.

The general plan for the project including data sharing and linked analyses will be submitted initially to the genetic analysis working group. The proposals will be reviewed by a minimum of 2 people from the GAWG. They will be distributed to the GAWG for input but the technical review will come from a minimum of 2 members. The intent is to make sure the methods, etc are reviewed by those most knowledgeable of genotyping, etc. The primary research team can submit the proposals to the GAWG early (a minimum of 2 weeks before the DSC deadline) so the technical review can be attached to it for the DSC to review. If they wait to submit it until the DSC deadline, it will be submitted to the GAWG for review and will not be reviewed by the DSC until the following month.

The proposal should include a section addressing the issues raised above. The proposal will then be presented to and reviewed by the Data Sharing Committee for final approval.

III. DNA Methylation Projects

These guidelines should be followed for DNA methylation studies.

The proposed guidelines include:

- 1) Typically only a defect or defect group will be proposed for interrogation.
- 2) Priority should be given to questions of public health, clinical, and biologic significance. Priority should be given to projects with high likelihood of success based on power calculations.
- 3) Other groups with potential overlap through ongoing or planned genetic studies of the same defect or defect group should be contacted. Proposals should specify others who were contacted regarding interest in the project.
- 4) *Proficiency Testing*: The proposal must include verification that the lab proposing to perform methylation assays using NBDPS samples passed the required External Quality Assessment (EQA)
- 5) *Preliminary Data*: The primary research team must provide information demonstrating that they are capable of conducting methylation studies with regard to: 1) performing the appropriate laboratory assays and 2) performing primary data analysis. This should be a general description of the laboratory's experience with the relevant DNA methylation platform (i.e., the same platform as that in the proposed research). It is expected that the laboratory, whether a Center's in-house facility, or a collaborating or contract lab, will provide this summary. Note that the laboratory should present preliminary data from a representative DNA methylation experiment that includes data from a minimum of 12 subjects. The quantity of DNA necessary to perform methylation assays should be included. Bisulfite conversion rates, CpG site call rates, and concordance between technical controls should be included. Other data, as it applies to the specific methylation platform, should include data quality assessments (e.g., removal of samples or individual data points). Where appropriate, specifics regarding the inclusion of negative and positive controls as well as QC replicates, QC standards, or duplicates of selected samples should be included. Local NBDPS buccal samples should be used for all feasibility studies and pilot testing. The PI from the Center where the specimens will be taken should sign off on the proposal. The group's experience and expertise in the processing and analysis of DNA methylation data should be presented.
- 6) Samples with DNA concentrations < 0.1ng/ul (measured using human RNaseP real-time quantitative PCR) should be excluded from analyses
- 7) The authorship plan for the primary publications from the scan project and associated secondary papers should be defined in advance. These collaborative efforts will require a list of primary authors

with The NBDPS listed last on the authorship line. The PI from the Center that will author the primary publication should sign off on the proposal.

- 8) A proposal section on the methods to be used to determine and account for potential false positive associations should be included.
- 9) *Sharing of initial results with the group and contribution of final data to the NBDPS repository.* Within 6 months, the primary research team should deposit initial study results into the NBDPS Genetic Analysis Database. If the team is unable to meet this deadline, they should notify the Data Sharing Committee when to expect the transmission of results.
- 10) Approved proposals may be resubmitted as amended/revised proposals including the expanded aims. The description of the new target genes and methylation sites and related material should be incorporated into the approved original proposal with the new text demarcated.

The general plan for the project including data sharing and linked analyses will be submitted initially to the genetic analysis working group (GAWG). The proposals will be reviewed by a minimum of 2 people from the GAWG. They will be distributed to the GAWG for input but the technical review will come from a minimum of 2 members. The intent is to make sure the methods, etc are reviewed by those most knowledgeable about methylation studies. The primary research team must submit the proposals to the GAWG early (a minimum of 2 weeks before the DSC deadline) so the technical review can be attached to it for the DSC to review. If they wait to submit it until the DSC deadline, it will be submitted to the GAWG for review and will not be reviewed by the DSC until the following month.

Beginning with proposals submitted in September 2003, all proposals involving the use of biologic samples will be reviewed at CDC to ensure compliance with the above guidelines. All proposals that have not followed the guidelines will be returned to the submitting lead investigator with a brief note outlining criteria from the Data Sharing Guidelines that have not been addressed. For example, "Please provide information on the pilot testing of the proposed methods including results of pilot studies." The investigator will then be asked to resubmit the proposal with the next data sharing round.

For proposals approved prior to September 2003, the same review will occur when samples are requested from CASPIR. If the approved proposal does not address the criteria in the Data Sharing Guidelines, it will be necessary to submit an updated proposal that addresses these issues.

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D. Approval of NBDPS Abstracts

1. Abstracts of collaborative NBDPS results presentations at scientific meetings should be sent to the Data Sharing Committee for approval prior to submission. The abstract should be submitted to the Data Sharing Committee via the CDC coordinator and should indicate the meeting to which the abstract will be submitted. Abstracts must be sent to the CDC coordinator at least 5 working days before the deadline for submission; earlier is preferred. Investigators are requested to let the CDC coordinator know ahead of time that an abstract will be coming, so s/he can give the reviewers a heads up.
2. The CDC coordinator will examine the abstract reviewer schedule list and select the top three that are not crossed out. The CDC coordinator will send the abstract, the review deadline (5 working days) and a review form ([Attachment L](#)) to those three reviewers, asking them to determine if the abstract is accurate, scientifically sound, and does not compromise the collaborative study. All abstracts received in one week will be sent to the same three reviewers and will be batched as much as possible.
3. Reviewers will use the form in [Attachment L](#) and will send the form to the CDC coordinator by e-mail. They will respond within 5 working days. If there are no concerns or issues raised, the CDC coordinator will inform the investigator that the committee has approved their abstract. Any comments or suggestions on improving the document will be sent to the lead investigator as well. If there are minor issues raised by the reviewer(s), an attempt will be made to resolve these by e-mail discussions among the lead author and reviewers. If there are major areas of concern, the CDC coordinator will schedule a conference call for the lead author and reviewers to discuss the issue(s). Sometimes it may occur that all 3 reviews are not completed. In those situations, at least one completed review form must be sent back to the CDC coordinator for an abstract to be considered approved.

4. Under very limited circumstances, the lead author may request an expedited review of an abstract (e.g., abstracts that have been previously approved, abstracts for manuscripts that have been approved). Such requests should be submitted to the CDC coordinator with justification for the need to expedite the review. The CDC coordinator can approve the abstract or if needed, consult with the Data Sharing Committee chair or send it out to three reviewers.
5. Abstracts that are disapproved may be revised and resubmitted to the Committee.
6. At the end of a week where the CDC coordinator received one or more abstracts, she/he will cross off the reviewers' names from the abstract reviewer schedule list ([Attachment K](#)). The next time abstracts are received, the next three uncrossed names will be used. When all names are exhausted, selection will start over at the beginning. The list will be comprised of individuals on the NBDPS manuscript reviewer list as well as others associated with the NBDPS who volunteer.
7. The CDC coordinator will maintain a tracking form to ensure that all abstract reviews are received and forwarded to the author before the submission deadline. A copy of accepted abstracts should be sent to the CDC coordinator for record keeping purposes.
8. The CDC coordinator will also maintain a list of the deadlines for submitting abstracts for review. The deadlines will be 5 working days before the conference abstract deadlines. This list will be available to NBDPS investigators, probably on the web site.

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E. Approval of Manuscripts

Manuscripts may be submitted to the Data Sharing Editor at any time. The lead investigator must submit a manuscript submission form ([Attachment O](#)) with their manuscript. The Editor will assign 2-3 reviewers according to area of expertise. Review turnaround time will depend on the number/type of issues that arise during the review process. Reviews will be conducted anonymously and compiled comments will be presented in electronic form to the Committee. Approval status will be communicated to the Data Sharing Committee as a FYI and to the CDC coordinators for recordkeeping purposes.

It is the responsibility of the lead investigator to determine if a re-review of a manuscript by the Data Sharing Committee is necessary when peer review requires substantial revision of the manuscript.

A copy of published manuscripts should be sent to the Data Sharing Committee for recordkeeping purposes.

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F. Guidelines for Presentations

Presentations must be sent to the Committee as an FYI.

G. Theses/Dissertations

The Committee will not conduct formal review of dissertations. [This assumes a DS committee member will be a member of the students academic review committee]. The masters or doctoral candidate must submit an abstract of the dissertation as an FYI to the Committee.

H. Sharing of Unpublished Data

The Data Sharing Committee (DSC) permits pooled NBDPS data to be included in peer-reviewed manuscripts and to be presented at scientific meetings. These uses of the data are reviewed by established DSC procedures in either manuscript or meeting-abstract form. All other public use/public sharing of NBDPS data must be done with caution. All NBDPS investigators must consult the DSC editor before any data are publicly shared in any way. Decisions to permit the sharing of data will be guided by the public health urgency and likely benefit, how well the confidential nature of the data is protected, and the probability that downstream use of the data does not jeopardize the integrity of the NBDPS.

V. AUTHORSHIP

1. Authors who participate in the writing of a manuscript from the collaborative NBDPS should do so in accordance with the International Committee of Medical Journal Editors guidelines (N Engl J Med 1997 Jan 23;336(4):309-15). These guidelines can be found in [Attachment D](#).
2. All papers should include the words "The National Birth Defects Prevention Study" in the authorship line (e.g. Smith JL, Jones KC, Williams ME, and The National Birth Defects Prevention Study). All papers should also include an "Acknowledgements" section that lists each Center unless journal policy prohibits publication of such a list.
3. Also in the "Acknowledgement" section, all papers should include the words "This study was supported by a cooperative agreement from the Centers for Disease Control and Prevention."
4. First Authorship
 - a. First authors will usually be NBDPS investigators. Other scientists may serve as first authors if at least one other NBDPS investigator serves as a co-author and "sponsor" of the project and the scientist has played a major role in the data analysis and writing for the paper.
 - b. Conflicts about first authorship should be resolved, if at all possible, by members of the analysis/writing group. In case the group is unable to resolve a conflict among the Centers, the Data Sharing Committee will adjudicate and may assign first authorship.
 - c. If progress on a given project is unduly slow, the Data Sharing Committee may request an explanation from the lead investigator. If timely progress is not likely to occur in the near future, the Data Sharing Committee may, at its discretion, assign a new lead investigator to the study.
5. Co-Authorship
 - a. The first author should determine the order of authorship on a paper. In general, authors will appear in order of contribution to the writing and analysis of the paper.
 - b. If conflicts among the Centers regarding the order of authorship cannot be resolved by the analysis/ writing group, the Data Sharing Committee will adjudicate and may assign order.

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VI. DATA SHARING WORKING GROUPS

1. Working Groups will be formed of interested scientists from the Centers for specific topics such as congenital heart defects, orofacial clefts, neural tube defects, folate, and environmental exposures. These groups will be formed on an ad hoc basis.
2. The primary role of the Working Groups will be to develop comprehensive research agendas, to be informed about the current state of knowledge in the specific topic area, and to discuss how the research activities might be shared among the interested collaborators. The Working Groups will meet regularly by phone and occasionally in-person and will create reports to keep the rest of the Centers collaborators informed about research findings and progress in the specific topic area.
3. A minor role of these groups will be to discuss letters of intent or proposals that are in conflict or overlap for the specific topic area. The Working Group may help the investigators reach agreement as to how the research will be apportioned to the interested Centers. The Data Sharing Committee, however, has the ultimate responsibility for working out any conflicts between Centers investigators.

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VII. AVAILABILITY AND ANALYSIS OF DATA BY OUTSIDE INVESTIGATORS

1. Investigators outside the NBDPS who are interested in accessing the data must identify a collaborator and sponsoring PI from one of the participating centers. If outside investigators are unable to identify a potential collaborator their own, they may submit a brief letter describing their research interest (maximum of 2 pages) to the Data Sharing committee in care of Tineka Yowe-Conley. The Data Sharing committee will forward it to

the appropriate NBDPS working group. All submissions will be considered in terms of potential for collaboration, priority for the current NBDPS research agenda, and scientific merit. Because of the limited amount of DNA currently available, proposals involving the use of biological specimens will be carefully evaluated to ensure that the study is an optimal use of the available material.

A sample response to inquiries from outside investigators is located in [Attachment E](#).

2. It is the intention of the Data Sharing Committee to supply data tapes with the collaborative NBDPS data to each Center at the end of the study so that additional analyses can proceed after termination of the Cooperative Agreement. So long as the Data Sharing Committee remains active, the committee must still approve projects and review manuscripts prior to submission even if the analyses are done locally.
3. The Data Sharing Committee will determine the format of the public use data tapes and will specify the variables which are to be included in the database.

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VIII. CONFIDENTIALITY AND DATA USE OATH AND DATA TRACKING

1. Scientists, colleagues, and collaborators who are given access to clinical, interview and biologic data from the NBDPS must sign a confidentiality and data use oath that describes how the data should be used, stored and returned at the conclusion of a research project ([Attachment F](#)).
2. The Principal Investigator at each Center has full and direct responsibility for assuring that each person who has access to the data has read and signed the confidentiality and data use oath. The Principal Investigator also has the responsibility of tracking the use of the NBDPS data at their Center using the Data Tracking Sheet ([Attachment G](#)). Copies of the data tracking sheets will be kept on file at CDC. Oaths must be signed by study staff/collaborators and copies sent to CDC on a yearly basis.
4. Each Center should maintain files of the signed confidentiality and data use oaths. Signed oaths will also be kept on file at the CDC. It will be left to the discretion of the individual Centers to determine when the oaths should be renewed for specific individuals or projects.
5. The CDC local data sharing policy is located in [Attachment H](#).

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IX. PROJECT UPDATES

Project update forms must be completed at least annually for every active NBDPS project. Any project either actively terminated or not updated by the deadline will have the project status changed to "terminated." New letters of intent may be submitted on these topics.

If project is not terminated but taken over by a different group of investigators, a new LOI must be submitted to the Committee.

The project update form is located in [Attachment I](#).

X. LOCAL STUDIES

In order to decrease potential duplication of effort, to ensure that the quality of publications of the data meet a consistent standard, and to enhance collaboration, all local study abstracts and manuscripts using NBDPS data must be submitted to the data sharing committee as a courtesy. Committee members are encouraged to comment but the Committee will not vote on local studies.

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Data Sharing Guidelines Attachment A

Review of NBDPS Letters of Intent (to be distributed in email form)

LOI Title:

APPROVE:

OUR CENTER WOULD LIKE TO DISCUSS COLLABORATION:

NEEDS DISCUSSION:

COMMENTS:

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Review of NBDPS Proposals

Title of Proposal: _____

Lead Investigator: _____

Sponsoring PI: _____

Center: _____

Date reviewed: _____

Reviewed by: _____

Center: _____

1. Investigators with lead investigator noted
Comment: _____ YES NO NA

2. Objectives, aim or hypothesis stated
Comment: _____ YES NO NA

3. Background with relevant references
Comment: _____ YES NO NA

4. Methods
- specific outcomes of interest YES NO NA
- primary exposures of interest YES NO NA
- analysis plan with power calculations YES NO NA
- other data collection or record matching YES NO NA
Comment: _____

5. Scope of analysis is reasonable
Comment: _____ YES NO NA

6. Plans for particular expertise in statistics, epidemiology, molecular genetics or case classification described
Comment: _____ YES NO NA

6a. Biologics criteria have been addressed YES NO NA

7. Conflicts with existing research
Comment: _____ YES NO NA

8. Suggestions for collaboration
Comment: _____ YES NO NA

9. Need for additional IRB approval
Comment: _____ YES NO NA

10. Other Comments: _____

APPROVE DISAPPROVE RESUBMIT NEEDS DISCUSSION:

AUTHOR MUST RESPOND TO THE FOLLOWING COMMENTS:

NBDPS Manuscript Review Form

Title of Document: _____

Lead Investigator: _____

Sponsoring PI: _____

Center: _____

Reviewer No: _____

Date reviewed: _____

1. Author list includes "and the NBDPS"
Comment: _____ YES NO NA
2. Participating Centers and funding source acknowledged
Comment: _____ YES NO NA
3. Slone Epidemiology Unit acknowledged for Drug Dictionary
Comment: _____ YES NO NA
4. UNC Nutrition Epidemiology Core acknowledged for use of
nutrient database. Comment: _____ YES NO NA
5. Comments on other issues (e.g. authorship, conflict with other NBDPS research, etc): _____

Recommendation:

- APPROVE AS IS
- APPROVE WITH MINOR REVISIONS (requires final approval from DSC editor only)
- REVISE AND RESUBMIT, REVIEWER REQUESTS TO SEE REVISED MANUSCRIPT
- REVISE AND RESUBMIT, REVIEWER DOES NOT WISH TO SEE REVISED MANUSCRIPT
- DISAPPROVE (*please explain*) _____

Please provide comments on scientific aspects of the manuscript (*use as much space as necessary*): _____

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Data Sharing Guidelines Attachment D

Uniform requirements for manuscripts submitted to biomedical journals.
International Committee of Medical Journal Editors.

N Engl J Med 1997 Jan 23;336(4):309-15

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Data Sharing Guidelines Attachment E

Response to Inquiry from Outside Investigator

Dear <name of person making inquiry>,

Thank you for your inquiry about access to the data from the National Birth Defects Prevention Study (NBDPS). This study is being conducted as part of a cooperative agreement between 9 sites (state health departments and universities) and the Centers for Disease Control and Prevention (CDC). We have just begun the analytic phase of this study, and there is currently no public use data set available.

Because of the collaborative nature of the study, we have established clear guidelines for data sharing among the investigators participating in the study. All research proposals must be sponsored by one of the collaborating Principal Investigators, and be submitted to NBDPS Data Sharing committee for review and approval.

At this time, researchers outside the NBDPS centers who are interested in accessing the data must identify a collaborator and sponsoring PI from one of the participating centers. If you are unable to identify a potential collaborator on your own, you may submit a brief letter describing your research interest (maximum of 2 pages) to the Data Sharing committee in care of Mrs. Tineka Yowe-Conley (TYoweConley@cdc.gov). The Data Sharing committee will forward it to the appropriate NBDPS working group. All submissions will be considered in terms of potential for collaboration, priority for the current NBDPS research agenda, and scientific merit. Because of the limited amount of DNA currently available, proposals involving the use of biological specimens will be carefully evaluated to ensure that the study is an optimal use of the available material. You will be notified of the status of your submission.

I have listed 2 references below which you may find helpful. Thank you for your interest in the NBDPS.

Sincerely,
<name of person responding>

1. Yoon P, et al. The National Birth Defects Prevention Study. *Public Health Reports*, 2001;116(Suppl 1):32-40.
2. Rasmussen SA, et al. Integration of DNA sample collection into a multi-site birth defects case-control study. *Teratology* 66(4):177-84, 2002

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NATIONAL BIRTH DEFECTS PREVENTION STUDY (NBDPS) CONFIDENTIALITY AND DATA USE OATH

Each Center for Birth Defects Research and Prevention (Centers) has been awarded a Certificate of Confidentiality from the Centers for Disease Control and Prevention (CDC). In accordance with Section 301(d) of the Public Health Service (PHS) Act (42 U.S.C. 241(d)), I, as a _____ (Centers employee, CDC employee, scientist, colleague), am permitted access to personally identifiable data. As a condition of this access and my participation in this project, I am required to comply with the following safeguards and policy commitments for individuals against invasions of privacy.

1. I agree to be bound by the following promise:

In accordance with Section 301(d) of the PHS Act (42 U.S.C. 241(d)), all respondents are assured that the confidentiality of their responses in this study will be maintained, and that the privacy of research subjects is protected by the withholding of, from all persons not connected with the study, any personally identifying characteristics of the research subjects.

2. I agree to maintain the following safeguards to assure that confidentiality is protected and to provide for the physical security of the records:

To preclude observation of confidential information by persons not authorized to have access to the information on this project, I shall maintain all records that identify individuals, or from which individuals could be identified, in locked containers or protected computer files, when not under immediate supervision by me or another authorized member of the project. The keys or means of access to these containers or files are not to be given to anyone other than NBDPS authorized staff. I further agree to abide by any additional requirements imposed by CDC for safeguarding the identity of individuals.

3. The NBDPS Data Sharing Committee must approve uses of the NBDPS data. No analysis of data or dissemination of findings from the NBDPS may occur without approval from the committee for a specific research purpose. Instructions for submission of research proposals are specified in the Data Sharing Guidelines document available from each Center.
4. The Principal Investigator of the NBDPS from each Center is responsible for tracking the use of the NBDPS data at their Center and assuring that each person who has access to the data has read and signed this agreement.
5. I understand that the Data Sharing Committee must approve any manuscripts, abstracts, or public presentations based on the analyses before they can be submitted for consideration.
6. I agree not to attempt to identify any individual person whose information is contained in the NBDPS data.
7. I agree not to distribute, copy, or share the data with any person(s) other than those designated by the Principal Investigator of the Center.
8. At the conclusion of the research covered by this agreement, I agree to promptly return to the Center from which the data were obtained, any documentation and manuals about the NBDPS, and to remove (delete) any electronic files containing data or output from any computer equipment which I have used to gain access to and/or to analyze NBDPS data.

My signature below indicates that I have carefully read and understand this agreement and the oath which pertains to the confidential nature of all records to be handled in regard to this project. As a _____ (Center employee, CDC employee, scientist, colleague), I understand that I am prohibited from disclosing any such confidential information that has been obtained under this project to anyone other than authorized staff of NBDPS. I understand that any disclosure in violation of this Confidentiality Oath may lead to termination of my employment, as well as other penalties.

(Typed/Printed Name)

(Signature)

(Date)

(Center PI)

(Date)

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Data Sharing Guidelines Attachment G

Local Data Tracking Sheet

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Data Sharing Guidelines Attachment H

National Birth Defects Prevention Study: Use of the Atlanta and Pooled NBDPS Analytic Data

1) Confidentiality

- a) Read and sign data confidentiality pledge prior to receiving data (See Tineka Yowe-Conley for a copy of the pledge)
- b) Submit a request to ITSO asking for the NBDPS analytic tools and Access 2000 to be installed on your computer.
- c) Provide Tineka with the computer barcode for the computer on which the data are installed. Also provide the building and room number where your computer is located, your phone number and email address.
- d) All NBDPS data must be removed from your computer before leaving the group or changing computers. Please email Tineka to verify that you have uninstalled the Analytic database/tools and deleted all created files (CSV, SAS files, etc.) from the hard drive.
- e) Do not send any NBDPS data by non-secure methods.
- f) No information that would allow identification of an individual should be included in a publication or be shared in any manner with an individual who is not an NBDPS collaborator. Researchers should only review identifying information that is critical to their analysis.

2) Data Sharing

- a) NBDPS data sharing guidelines (normal, expedited, local)
- b) For Atlanta data only analyses, submit a one-pager outlining planned analysis to your supervisor and then to the PI (Peggy or Jennita). These analyses should not conflict with existing letters of intent (LOIs) and proposals for the pooled data. These will be shared with the NBDPS data sharing committee, and may in the future be subject to approval by the data sharing committee.
- c) For analyses of pooled NBDPS data, LOIs must be submitted to your supervisor and then to the Atlanta PI for review prior to submission to the NBDPS Data Sharing Committee. Same procedure must be used for proposals.
- d) All abstracts and manuscripts using pooled NBDPS data must be reviewed and approved by the NBDPS Data Sharing Committee prior to submission.
- e) All abstracts and manuscripts using Atlanta-NBDPS data must be sent to the Atlanta PI and the NBDPS Data Sharing Committee on an informational basis prior to submission.

3) Analysis

- a) New NBDPS investigators must be carefully oriented to NBDPS and the documentation.
- b) Please review all documentation before beginning any analysis or requesting further assistance.
- c) Duplication and/or review of work are essential to minimize errors.
- d) Epidemiologists/Analysts should complete the NBDPS data exercises and compare their work to the answer key prior to commencing other analytic work.
- e) Communicate all potential data issues/problems to Jennita Reefhuis.
- f) All investigators should be using version 4.06 of the data. If you have an older version, please have ITSO remove/uninstall it from your computer have them install the current version. Earlier versions should NOT be used for any analysis. Be sure to let Tineka know when you have a new version installed on your computer.
- g) Calculated variables should be used whenever possible to improve consistency across studies.

4) Key Do's and Don'ts

- a) Do ensure you have the most current version of the analytic data
- b) Do use calculated variables
- c) Do read all documentation before seeking assistance
- d) Do maintain the confidentiality of participants at all times
- e) Do promptly communicate problems with the data to Jennita.
- f) Do attend NBDPS analytic meetings to be aware of current issues
- g) Do use the tools to extract the data from the Access database
- h) Do not access the data via the back-end
- i) Do not release any unpublished data to anyone who is not an NBDPS collaborator
- j) Do not attempt to convert the database to a different version of Access
- k) Do not ask Chris for assistance with the analytic database/tools
- l) Do not begin analysis of NBDPS data without submitting a one-pager or LOI to your supervisor and the PI

5) Documentation

- a) Included with analytic database/tools
 - i) Documentation of the tools and analytic database
 - ii) NBDPS data cleaning document
 - iii) SAS field labels
 - iv) SAS short labels
- b) Other key documentation
 - i) Study background
 - ii) CATI database
 - iii) Clinical database
 - iv) Summary of changes to CATI
 - v) Summary of changes to protocol

6) Attachments

- a) Confidentiality pledge
- b) Data sharing guidelines
- c) Data sharing schedule for 2010

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NBDPS Data Sharing Update Form

Date _____

Project ID _____ Letter of Intent Doc ID _____ Proposal Doc ID (if applicable) _____

Title: _____

Sponsoring PI _____

Center: _____

Name of current lead investigator: _____

Names of all current collaborators: _____

Associated with existing project?
If yes, please list project # _____.

YES NO

Project Status:

- Not yet begun
 In progress
 Completed
 Project terminated (no longer plan to pursue this research project)
 Published? List citation: _____

Not Yet Begun?

Projected date when proposal was submitted/will be submitted: _____

Projected date when adequate sample size will be available: _____

Projected date when analysis may realistically begin: _____

In Progress?

Briefly describe progress to date (2-3 sentences): _____

Additional Information Needed:

High Priority YES NO

Main Exposure: _____

Genetics YES NO

Outcome: _____

Exposures: _____

Other comments: _____

-
- Data sharing updates for **ALL** approved letters and proposals are due **December XX, 20xx**. Any projects either actively terminated or not updated by the deadline will have the project status changed to "terminated". New letters of intent/proposals may be submitted on these topics.
 - A final update for each project should be submitted when the project is complete. For completed projects, please provide the citations for any published abstracts/manuscripts in the project status section.

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2010 Data Sharing Schedule

Submission Deadline	Date of Distribution	Review Due Date	Date of Call
21-Jan-2010	29-Jan-2010	18-Feb-2010	25-Feb-2010
18-Feb-2010	26-Feb-2010	18-Mar-2010	25-Mar-2010
18-Mar-2010	26-Mar-2010	15-Apr-2010	22-Apr-2010
15-Apr-2010	23-Apr-2010	20-May-2010	27-May-2010
20-May-2010	28-May-2010	17-Jun-2010	24-Jun-2010
17-Jun-2010	25-Jun-2010	15-Jul-2010	22-Jul-2010
15-Jul-2010	23-Jul-2010	19-Aug-2010	26-Aug-2010
19-Aug-2010	27-Aug-2010	16-Sep-2010	23-Sep-2010
16-Sep-2010	24-Sep-2010	21-Oct-2010	28-Oct-2010
21-Oct-2010	29-Oct-2010	18-Nov-2010	6-Jan-2011*
18-Nov-2010	26-Nov-2010	16-Dec-2010	6-Jan-2011*
16-Dec-2010	24-Dec-2010	20-Jan-2011	24-Feb-2011**

*The November and December data sharing rounds will be discussed on **January 6, 2011**

The January data sharing rounds will be discussed on **February 24, 2011

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Abstract Reviewer Schedule

Review Period	Reviewer	Center	Review Batch
1	Anderka, Marlene	Massachusetts	
2	Bell, Erin	New York	
2	Beres-Sochka, Leslie	New Jersey	
2	Botto, Lorenzo	Utah	
3	Browne, Marilyn	New York	
3	Burns, Trudy	Iowa	
3	Byrne, Jan B.	Utah	
4	Canfield, Mark	Texas	
4	Carey, John C.	Utah	
4	Carmichael, Suzan	California	
5	Carter, Tonia	New York	
6	Caton, Alissa	New York	
5	Cleves, Mario	Arkansas	
5	Correa, Adolfo	CDC	
6	Cragan, Jan	CDC	
7	Druschel, Charlotte	New York	
6	El-Shanti, Hatem	Iowa	
7	Feldkamp, Marcia	Utah	
7	Finnell, Rick	Texas	
8	Gilboa, Suzanne	CDC	
8	Hecht, Jacqui	Texas	
8	Herdt-Losavio, Michele	New York	
9	Hobbs, Charlotte	Arkansas	
9	Holmes, Lewis	Massachusetts	
9	Honein, Peggy	CDC	
10	Jenkins, Mary	CDC	
10	Kahler, Steve	Arkansas	
10	Kepler-Noreuil, Kim	Iowa	
11	Lammer, Ed	California	
1	Langlois, Peter	Texas	
11	Lin, Angela	Massachusetts	
12	Louik, Carol	Massachusetts	
11	MacLeod, Stewart	Arkansas	
12	Malik, Sadia	Arkansas	
12	Marshall, Betsy	New Jersey	
13	Meyer, Bob	North Carolina	
13	Mitchell, Allen	Massachusetts	
13	Mosley, Bridget	Arkansas	
14	Munger, Ron	Utah	
14	Murray, Jeff	Iowa	

Review Period	Reviewer	Center	Review Batch
14	Olney, Richard	CDC	
15	Olshan, Andy	North Carolina	
15	Ramadhani, Tunu	Texas	
15	Rasmussen, Sonja	CDC	
16	Reefhuis, Jennita	CDC	
17	Riehle, Tiffany	CDC	
16	Robbins, Jim	Arkansas	
16	Romitti, Paul	Iowa	
17	Royle, Marge	New Jersey	
17	Schaffer, Donna	California	
18	Scheuerle, Angela	Texas	
18	Selvin, Steve	California	
18	Shapira, Stuart	CDC	
19	Shaw, Gary	California	
19	Siega-Riz, Anna Maria	North Carolina	
19	Werler, Martha	Massachusetts	
20	Yeung, Lorraine	CDC	
20	Zhu, Huiping	Texas	

Note: Reviewers are sorted alphabetically by last name. Each period has a reviewer from a different Center. The current reviewers are shaded and the past reviewers' names are red with strike-outs.

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NBDPS Abstract Review Form

Title of Document: _____

Lead Investigator: _____

Sponsoring PI: _____

Center: _____

Date reviewed: _____

Reviewed by: _____

Center: _____

6. Investigators with lead investigator noted

YES NO NA

Comment: _____

7. Comments on scientific aspects of the document: _____

8. Comments on other issues (e.g. authorship, conflict with other NBDPS research, etc): _____

Recommendation:

APPROVE

DISAPPROVE

RESUBMIT

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Letter of Intent (LOI) Template

Date Submitted:

Title of LOI:

Lead Investigator:

Sponsoring PI:

Center:

Co-Authors:

Associated with existing project? YES NO

If yes, please list project # _____.

Objectives:

Background:

Methods:

Conflicts (Include Project #):

References:

Proposal Template

Date Submitted:

Title of Proposal:

Project ID#:

Lead Investigator:

Sponsoring PI:

Center:

Co-Authors and their contributions:

List plans for obtaining particular expertise in statistics, epidemiology, molecular genetics or case classification, if relevant:

All investigators and co-authors signed a confidentiality and data use oath? YES NO

Need additional IRB approval? YES NO

If yes, list specifics:

List biologics criteria:

List objectives, aim or hypothesis:

Background:

Methods:

Exposures of Interest:

Outcomes of Interest:

Analysis:

Power Calculations:

Conflicts (Include Project #):

Other:

References:

NBDPS Manuscript Submission Form

Title of Manuscript: _____

Lead Investigator: _____

Sponsoring PI: _____

Center: _____

1. Data Sharing Committee documents that cover this manuscript (provide document numbers and titles):

LOI: _____

Proposal: _____

Comments (please note any discrepancies in what is in the manuscript versus what is in the proposal):

2. Manuscript acknowledges overlap with results using NBDPS data that have been published previously or are In Press and discusses potential explanations for substantial differences in findings.

YES

NO

N/A

If no, please comment on why previous results are not acknowledged: _____

3. Has analysis been replicated or currently undergoing replication?

YES

NO

N/A

If yes, by whom? _____

4. Author plans to submit manuscript to: _____

Attachment 20A
Genotyping EQA

This document was produced for the National Birth Defects Prevention Study;
a similar document will be created for BD-STEPS.

NBDPS Genotyping External Quality Assessment Protocol

Approved July 2011

Create a standard protocol using control samples for external quality assessment (EQA). The primary objective of establishing EQA is to ensure that each lab actively involved in genotyping NBDPS samples is proficient in their respective genotyping techniques independent of the source material or extraction procedure.

EQA Samples: Blood-Buccal Trios

- **Composition of Blood-Buccal Trio Samples:**
 - Recruit a total of 6 parent-offspring trios (n=18) following appropriate human subjects requirements. Obtain 4 buccal specimens per participant using the dry brush method and two whole blood specimen from each participant.
 - Ship the specimens (n=108) to the NBDPS Central Lab where DNA will be isolated and quantified, Mendelian inheritance will be checked using a microsatellite panel, DNA concentrations will be normalized, and aliquots will be prepared in micropackaging vials labeled with only a CDC unique (ASTRO) ID. (n=36 total samples; 18 blood + 18 buccal)
 - Labs using lower throughput platforms (e.g., TaqMan, Pyrosequencing): Blinded DNA aliquots with concentrations of 5ng/μl from buccals (DNA yield= 100ng) and whole blood (DNA yield= 100ng) and DNA negative controls will be sent to each genotyping lab.
 - Labs using higher throughput platforms (e.g., Illumina, Affymetrix): Blinded DNA aliquots with higher concentrations and yields, dependent on assay requirements, will be sent to each genotyping lab
 - All labs will be responsible for performing whole genome amplification (WGA) on the samples using their preferred methodology if they propose to perform WGA on NBDPS samples.
 - The same genotyping methods/platforms that will be used with NBDPS samples will be used with EQA samples.

- **Use of Blood-Buccal Trio Samples:**
 - Labs using lower throughput platforms (e.g., TaqMan, Pyrosequencing): The samples will be used prior to initiating NBDPS genotyping with annual re-assessment to test 2 - 5 SNPs selected by GAWG members. SNPs chosen will include those the investigator is proposing to perform on NBDPS samples and those assayed by more than one lab when possible.
 - Each genotyping lab will be required to genotype one SNP that is agreed upon by the GAWG.
 - Laboratories using high throughput platforms (e.g., Illumina, Affymetrix) with NBDPS samples will include one SNP that is agreed upon by the GAWG to genotype samples from one blood-buccal trio family (6 gDNA and 6 WGA products). In addition to results from the one agreed-upon SNP, labs should also report results from all variants tested. The samples will be used prior to initiating NBDPS genotyping and will be required one time per lab per project.

- Paired Blood-Buccal Trios Will Allow:
 - Intra-lab comparison of results from blood compared to buccals and to WGA products
 - Intra-lab verification of genotype accuracy by Mendelian inheritance
 - Inter-lab comparison for results of one SNP each lab will genotype
 - Inter-lab comparison of SNPs labs assay in common when possible

EQA Samples: Pre-Characterized (Polymorphism Discovery Resource from Coriell)

- Composition of Pre-Characterized Samples:
 - Determine which gene variants approved for NBDPS are listed on the website for the pre-characterized samples.
 - Purchase pre-characterized sample set or subset.
 - Coriell ships 96-well plates to each investigator that contain 86 PDR samples, 4 duplicate PDR samples, 2 water controls, and 4 empty wells for internal genotyping controls. Investigators are blinded to samples in all wells and will genotype the samples for SNPs that they plan to genotype in the NBDPS. The same genotyping methods/platforms that will be used with NBDPS samples will be used with EQA samples. Results will be reported back to CDC and compared to results from other labs and the published results.
- Use of Pre-Characterized Samples:
 - Pre-characterized samples will be used prior to initiating NBDPS genotyping with annual re-assessment to test 2 - 5 SNPs selected by GAWG members. SNPs chosen will include those the investigator is proposing to perform on NBDPS samples and those assayed by more than one lab when possible.
 - Pre-characterized samples will not be included in arrays from high throughput platforms (e.g., Illumina, Affymetrix).
- Pre-Characterized Samples Will Allow:
 - Comparison to published third-party results
 - Inter-lab comparison of SNPs labs assay in common

Standards Required to Pass EQA:

- 90% genotyping call rate per gene variant
- 99% concordance between successful genotyping data for:
 - paired blood and buccal DNA
 - gDNA and WGA product
 - inter-lab SNPs assayed in common
 - pre-characterized DNA and published third-party results
- No results reported for negative controls
- Genotyping results of trios consistent with Mendelian inheritance

- If inter-lab results for SNP assays performed in common are discordant, results from SNP assays performed on pre-characterized samples will be compared to third party published results to determine if a lab needs to identify and resolve problems.
- If a genotyping lab does not pass EQA standards, they must discontinue all genotyping and repeat EQA. If the genotyping lab does not pass EQA standards a second time, no manuscripts will be completed until the problems are identified and resolved.

Additional Items:

- Choose one gene variant that all genotyping labs agree to assay: MTHFR C677T
- Results reported to CDC are final (e.g., if errors are made transcribing data to results template and the data do not meet the standards required to pass EQA, the lab must repeat EQA).

Attachment 20B
NBDPS EQA Methylation

This document was produced for the National Birth Defects Prevention Study;
a similar document will be created for BD-STEPS.

NBDPS Methylation Study External Quality Assessment Protocol **Approved May 2012**

Create a standard protocol using control samples for external quality assessment (EQA). The primary objective of establishing EQA is to ensure that each lab actively involved in testing NBDPS samples is proficient in their respective laboratory techniques independent of the source material or extraction procedure.

The protocol differs depending on the type of methylation study being completed.

Genome-Wide Arrays:

- Bisulfite conversion will typically be completed using kits from either
 - Zymo Research - EZ DNA Methylation (specified in Illumina protocol)
 - QIAGEN - EpiTect (allows longer storage)Other commercial kits can be used but beware of home brew kits (lower QC)
- Batch entire process – convert all samples at the same time using the same kit with reagents from the same lot, when possible
- Each array can accommodate 12 samples; require 1 CEPH sample per array for EQA using the same sample for each array and each lab. If a Core Facility is used, require reporting of results from 1 technical control per array from a minimum of 3 arrays for EQA. To build a comparison dataset of results for the common CEPH sample, it is requested (but not required) that each lab include the common CEPH sample on each array for all arrays run during their actual study and report these results.
- No negative controls are included on these arrays
- Laboratories should report results from all methylation sites and samples tested. The protocol will be used prior to initiating methylation studies using NBDPS repository samples.
- The same methods/platforms that will be used with NBDPS samples will be required.
- The following QC should be performed on Illumina data (these steps are strongly encouraged but are not required for EQA):
 - Removal of samples with low signal (sample has total signal intensity that is <50% of the median signal for all samples)
 - Removal of data points with detection p-values >.001
This can be accomplished in R via the `cpg.qc` function in CpGassoc (available at <http://genetics.emory.edu/conneely>)
- CEPH Samples Run on Each Array Will Allow:
 - Intra-lab comparison of results from duplicate samples
 - Inter-lab comparison of methylation sites that labs assay in common, when possible
- Standards Required to Pass EQA:
 - 95% bisulfite conversion rates
 - 95% CpG site call rate
 - 99% concordance between CEPH (or other technical control) sample results for all CpG sites across the genome for intra-lab comparison of results, where

concordance is computed as the percentage of sites with beta values differing by <0.1

- 95% concordance between CEPH (or other technical control) sample results for all CpG sites across the genome for inter-lab comparison of results, where concordance is computed as the percentage of sites with beta values differing by <0.2

Candidate Gene Studies (e.g., Pyrosequencing, EpiTYPER, Bisulfite Sequencing)

- Bisulfite conversion will typically be completed using kits from either
 - Zymo Research - EZ DNA Methylation (specified in Illumina protocol)
 - QIAGEN – EpiTect (allows longer storage)Other commercial kits can be used but beware of home brew kits (lower QC)
- Batch entire process – convert all samples at the same time using the same kit with reagents from the same lot, when possible
- Run using 96 or 384-well plates; require 1 CEPH sample per array for EQA using the same sample for each array and each lab; require enzymatically-methylated samples from QIAGEN at 0%, 50%, and 100% run in duplicate or triplicate for a standard curve. If a Core Facility is used, require reporting of results from 1 technical control per array from a minimum of 3 arrays for EQA. To build a comparison dataset of results for the common CEPH sample, it is requested (but not required) that each lab include the common CEPH sample on each array for all arrays run during their actual study and report these results.
- Negative (no template) controls are included on each plate
- Laboratories should report results from all methylation sites and samples tested. The protocol will be used prior to initiating methylation studies using NBDPS repository samples.
- The same methods/platforms that will be used with NBDPS samples will be required.
- CEPH Samples Run on Each Plate Will Allow:
 - Intra-lab comparison of results from duplicate samples
 - Inter-lab comparison of methylation sites that labs assay in common, when possible
- Standards Required to Pass EQA:
 - Assess bisulfite conversion rate by a platform-specific method
 - > 50% CpG site call rate (lower call rate but successful calls are reliable)
 - 90% concordance between CEPH (or other technical control) sample results for all CpG sites investigated, where concordance is computed as the percentage of sites with beta values differing by <0.1 for intra-lab comparison of results and differ by <0.2 for inter-lab comparison of results.
 - Samples used to generate the standard curve should be within 10% of the target methylation amount (0%, 50%, and 100%)
 - No results reported for negative (no template) controls

CEPH sample ID = NA12335

http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ind.cgi?ind_id=94

If a laboratory does not pass EQA standards, they must discontinue all methylation assays and repeat EQA. If the lab does not pass EQA standards a second time, no manuscripts will be completed until the problems are identified and resolved.

Results reported to CDC are final (e.g., if errors are made transcribing data to results template and the data do not meet the standards required to pass EQA, the lab must repeat EQA).