Congenital Cytomegalovirus (cCMV) & Connecticut

CMV: Leading Viral Cause of Birth Defects
by
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Elizabeth Saunders (1989-2006), a child born severely mentally and physically disabled by congenital cytomegalovirus (cCMV), with her mother, Lisa Saunders.
In May 2015, Connecticut became the second state in the U.S., after Utah, to pass a law on the leading viral cause of birth defects, which causes more disabilities than Down syndrome. Governor Dan Malloy signed House Bill 5525: An Act Concerning Cytomegalovirus, which requires “a screening test for cytomegalovirus for newborns who fail a newborn hearing screening.”

The act states: “…the administrative officer or other person in charge of each institution caring for newborn infants shall cause to have administered to (1) every such infant in its care [(1)] a screening test for …and (2) any newborn infant who fails a newborn hearing screening, as described in section 19a-59, a screening test for cytomegalovirus, provided such screening test shall be administered within available appropriations on and after January 1, 2016. Such screening tests shall be administered as soon after birth as is medically appropriate.”

The State Senate Democrats of the Connecticut General Assembly stated in a press release: "With bipartisan support, the legislature approved and the governor signed a bill that will help mitigate the devastating impact that this disease has on families. The bill requires that hospitals and other health care institutions test newborn infants for CMV if they fail a newborn hearing test. This will help parents intervene early and get their newborn child the help it needs."
What is CMV?

- CMV, or cytomegalovirus (sī-to-MEG-a-lo-vī-rus), is a common virus.
- Between 50% and 80% of adults in the U.S. are infected with CMV by 40 years of age.
- Most infections with CMV are “silent,” meaning most people who are infected with CMV have no signs or symptoms.
- **Congenital CMV is the #1 viral cause of birth defects. It causes mental retardation, liver disease, cerebral palsy and deafness as a result of infection in pregnant women. Congenital CMV “is the most common cause of nonhereditary sensorineural hearing loss in childhood.”**
Who Does CMV harm?

- CMV can cause disease in unborn babies
- CMV may cause severe and occasionally life-threatening disease in immunocompromised persons (meaning people with weakened immune systems), such as:
  1. Organ and bone marrow transplant recipients,
  2. Cancer patients
  3. Patients receiving immunosuppressive drugs, and
  4. HIV-infected patients
How is CMV Spread?

• Person to person contact (kissing, sexual contact, getting saliva or urine on hands and then touching eyes, or the inside of nose or mouth)

• Through the breast milk of an infected woman

• Infected pregnant women can pass the virus to their unborn babies

• Blood transfusions and organ transplantations
Pregnant Women and CMV

- Contact with the saliva or urine of young children is a major cause of CMV infection among pregnant women.

- Risk of CMV infection is likely to be reduced by careful attention to good personal hygiene, such as hand washing, and refraining from kissing toddlers around the mouth or sharing food/drinks with them.
Symptoms of Congenital CMV

**Temporary Symptoms**
Liver problems
Spleen problems
Jaundice (yellow skin and eyes)
Purple skin splotches
Lung problems
Small size at birth
Seizures

**Permanent Symptoms or Disabilities**
Hearing loss
Vision loss
Mental disability
Small head
Lack of coordination
Seizures
Death
Is this the “kitty litter” disease?

- No, that is toxoplasmosis, which causes fewer birth defects than congenital cytomegalovirus (cCMV).
- Like toxoplasmosis, cCMV is preventable, but most women of childbearing age have never heard of the precautions to take.
My CMV Story

- Miscarriage on Christmas Eve of 1988—was offered no blood test to help determine cause.

- Pregnant three months later and very happy. I had no idea what lay ahead…
Elizabeth Ann arrived on Dec. 18, 1989

• Her head was small, misshapen.
• She had difficulty breathing.
• Purple skin splotches on cheeks.
• Diagnosed with congenital CMV.
As Elizabeth Grew

• Profoundly mentally impaired
• Severe Cerebral Palsy
• Progressive hearing loss
• Cortically Blind
• Non-verbal
• Central and structural apnea
• Developed epilepsy
• Stayed as a three-month-old
• Could only eat pureed food and wore diapers
• Surgeries: spinal fusion, hip reconstruction, hamstring lengthening
• Despite all this, she was extremely happy and adorable--to her parents anyway!
Elizabeth working hard at school and enjoying a stroller trip
The Centers for Disease Control and Prevention (CDC) states that in the U.S.:

- Every hour, cCMV causes one child to become disabled.
- Approximately 1 in 150 children is born with cCMV infection (30,000 each year).
- About 1 in 750 children is born with or develops permanent problems due to congenital CMV infection.
- More than 5,000 children in the U.S. each year suffer permanent problems caused by cCMV.
CDC Compares Causes of Birth Defects

U.S. Children Born with or Developing Long-Term Medical Conditions Each Year

- Cytomegalovirus (CMV): 5,500
- Fetal Alcohol Syndrome (FAS): 5,000
- Down Syndrome: 4,000
- Spina Bifida/Anencephaly: 3,000
- Pediatric HIV/AIDS: 200
- Invasive Haemophilus Influenzae Type B: 60
- Congenital Rubella Syndrome (CRS): 10

Annual Number
“Perhaps no single cause of birth defects and developmental disabilities in the United States currently provides greater opportunity for improved outcomes in more children than congenital CMV.” --BMC Public Health 2005, 5:70
What is the benefit of new Connecticut law?

- “CMV is known to cause hearing loss and therefore to test for it is reasonable. Testing infants who fail their newborn hearing screen will not only increase awareness and hopefully prevention of CMV transmission, but we will be able to identify early those infants with congenital CMV and therefore have the opportunity to intervene earlier to optimize their outcomes,” states Dr. Brenda Kinsella Balch, a Connecticut pediatrician and Chapter Champion for the American Academy of Pediatrics Early Hearing Detection and Intervention Program.

- “The law encourages the proper timing of the test, so that diagnosis is not delayed beyond the critical time period of diagnostic accuracy for congenital CMV—the first three weeks of life,” states Dr. Demmler-Harrison of Texas, Director, Congenital CMV Disease Research, Clinic & Registry.

- "This is a game-changing step forward in our ability to determine CMV causality and give parents a viable option for early treatment," said Scott R. Schoem, MD, FAAP, Director of Otolaryngology, Connecticut Children’s Medical Center.
What does this law mean to CT health care providers?

- “Timing is key when identifying CMV infection. Providers should test via viral urine culture or urine PCR within the first three weeks of life. If a newborn tests positive, the next step is to refer the infant immediately to a pediatric disease specialist…” states Clinical Advisor’s article, “Connecticut passes cytomegalovirus screening law for newborns.”

- “This law is not dictating what doctors should do, but rather provides them the tools to practice good medicine in all arenas, including newborn care of babies with congenital hearing loss. Often, CMV is the last thing doctors think of, and it should be one of the first things they think of,” said Dr. Demmler-Harrison, Director, Congenital CMV Disease Research, Clinic & Registry.
Why don’t OB/GYNs warn how to prevent about CMV in the first place?

- **Less than half (44%) of OB/GYNs warn patients** about CMV (surveyed by the American College of Obstetricians and Gynecologists in 2007)

- **Don’t want to frighten their patients** (An OB/GYN quoted in FitPregnancy magazine (June/July '08) said, "The list of things we're supposed to talk about during women's first visit could easily take two hours and scare them to death.” )

- **Don’t realize the prevalence of congenital CMV.** In the article, “Washing our hands of the congenital cytomegalovirus disease epidemic,” Drs. Cannon and Davis state: “The virtual absence of a prevention message has been due, in part, to the low profile of congenital CMV. Infection is usually asymptomatic in both mother and infant, and when symptoms do occur, they are non-specific, so most CMV infections go undiagnosed.”
What about a vaccine against CMV?

- Researchers have been working on a vaccine against HCMV (human cytomegalovirus) for years.
- One reason for delay in successful development is “there has been insufficient education about the problem of HCMV infection…”
- Pharmaceutical companies need to know that a vaccine will be used because people know about the disease.
Number of newborns affected by cCMV in Connecticut?

- In 2013, the number of live births in Connecticut was 36,085. Assuming that is the approximate number born in Connecticut each year, and using the CDC's statistics that 1 in 750 babies are born disabled by cCMV, then,

- It can be estimated that there are **47 children born disabled by cCMV in Connecticut each year** [36,085 births $\times 0.0013 (1/750)$ cCMV disabled $= 47$ babies born with cCMV in Connecticut].
How many women are infected with cytomegalovirus while pregnant?

- “The annual rate of a pregnant woman who is CMV antibody negative catching CMV for the first time in pregnancy has been estimated to be between 1-4% of all pregnant women. Higher risk groups may have higher rates of infection per year: day care workers estimated 10%, and women who have a toddler shedding CMV in the home, who do not practice precautions, up to 50%,” states Dr. Demmler-Harrison of Texas, Director, Congenital CMV Disease Research, Clinic and Registry.
Which women are most at risk for contracting CMV?

- A. “75% of women with a primary infection during pregnancy acquire CMV from their own child under two years of age,” said Stuart Adler, M.D.

- Data from a variety of day care center studies indicate that between 44 to 100% of two year olds at a single given time were shedding CMV. Day-care workers are at greater risk according to the article, Cytomegalovirus as an occupational risk in daycare educators.
Nurses are NOT at high risk

“Nurses and other health care workers are not at risk for acquiring CMV from patients--even patients shedding CMV. Primary infection during pregnancy accounts for over 90% of severely affected babies and approximately 75% of women with a primary infection during pregnancy acquire CMV from their own child under two years of age. These are very high risk,” said Stuart Adler, M.D., Professor of Pediatrics, Microbiology and Medicine and Director of Infectious Diseases at the Children’s Medical Center, Virginia Commonwealth University Medical Center. Dr. Adler has specialized in CMV infections among women and children for over 28 years and has published extensively on this topic.
What is the estimated cost of caring for children disabled by cCMV in Connecticut?

- “In the early 1990s, the expense to the US health care system associated with congenital HCMV [Human Cytomegalovirus] infection was estimated at approximately $1.9 billion annually, with an average cost per child of over $300,000.” Although $300,000 per child annually is an old cost figure, Connecticut’s annual cost of caring for children disabled by cCMV can still be estimated at: 36,085 births X .0013 cCMV disabled = 47 babies (born disabled by cCMV in Connecticut each year) X $300,000/year = $14,100,000, or, over $14 million annually.

- “This figure is almost certainly an underestimate, especially now with enhanced mobility aids, surgical interventions, cochlear implants, antiviral therapies, occupational and physical therapies, etc., which were not likely included in the older cost estimates,” says Dr. Demmler-Harrison of Texas, Director, Congenital CMV Disease Registry and Research Program.
What are the costs of screening?

- The House Bill 5525 webpage states: “The cytomegalovirus test costs approximately $150.00. As only a few infants annually fail the newborn hearing screening at UCHC [University of Connecticut Health Center], any cost incurred at UCHC is expected to be minimal.”
How does the cost of screening compare to the costs saved through early detection?

1. “Usually, if the CMV test is positive, no further testing, such genetic testing (which can cost thousands of dollars and may require pre-approvals), is done, unless there are unusual circumstances. Certainly, on rare occasion, a poor baby can be born with two conditions, but that is not at all common. Therefore, early diagnosis of a clear condition with a clear diagnostic test saves the doctor and the family a costly and heart breaking/stressful diagnostic odyssey,” states Dr. Demmler-Harrison, Director, Congenital CMV Disease Registry and Research Program.

2. In addition to saving on the cost of more expensive diagnostic tests, an earlier diagnosis of cCMV means earlier intervention, which can mean a less disabled child. The less disabled a child is, the less they cost the state to care for.
What do we do if a baby tests positive for cCMV?

- Until Connecticut develops their own protocol, Utah posts informational flyers on cCMV to health care providers on their webpage at: http://www.health.utah.gov/cshcn/CHSS/CMV.html. There, you will find:
  - CMV Core Facts (Datos Fundamentales de CMV)
  - CMV Utah Flyer (Citomegalovirus)
  - PRINTABLE BROCHURES:
    - Congenital CMV and Hearing Loss (CMV Congenito y la Perdida de Audicion)
    - CMV What Women NEED TO KNOW (Lo Que Una Mujer Necesita Saber Acerca de CMV)
    - CMV What Childcare Providers NEED TO KNOW (Lo qué los proveedores de cuidado infantil NECESITAN SABER sobre CMV)
  - For Health Care and Newborn Hearing Screening Providers:
    - CMV for Pediatric Care Providers (PCP)
    - CMV for Obstetrical Health Care Providers
    - CMV PCR Testing
    - CMV Testing Information for PCPs
    - CMV Newborn Hearing Screening (NBHS) and PCP Flowchart
    - CMV and NBHS Testing Status FAX Form
    - CMV Testing Declination Form
    - ***FREE ONLINE WEBINAR!***
    - "cCMV 101: Congenital Cytomegalovirus from Prevention to Treatment"
    - Presented by: Dr. Michael Cannon of the Centers for Disease Control and Prevention (CDC)
    - cCMV 101 Webinar Recording
    - cCMV 101 Webinar Slides [PDF]
Can cCMV be treated if diagnosed?

- The treating physician may recommend treating the child with an antiviral if it is believed the benefits outweigh any side effects. “CMV infection in newborns can be treated with ganciclovir by IV or valganciclovir by oral route -- treatment reduces hearing loss progression and improves growth and head size/brain growth and improves developmental milestones,” says Dr. Demmler-Harrison, Director, Congenital CMV Disease Research, Clinic and Registry.

- According to the article, “Valganciclovir for Symptomatic Congenital Cytomegalovirus Disease,” by Kimberlin, M.D., et al. (2015), which studied very affected babies, “Treated infants had fewer developmental delays…than untreated infants.”
How much does this cCMV antiviral cost?

- Cost is estimated at $1,000 TO $1500 per 100 ML bottle. One bottle is needed each month for a 6-month treatment. [This figure needs confirmation.]
Will all babies destined to lose their hearing from cCMV show a hearing loss in the newborn screen?

- No. Hearing loss from cCMV is known to be progressive, and therefore, not all children who will have disabilities from cCMV will be detected early. That is why many in the medical community are proponents of screening every newborn for CMV. But this new Connecticut law will help 25% of the children who will experience a hearing loss from cCMV receive early intervention.
How can CMV be avoided?

- See CDC: CMV Prevention tips at: http://www.cdc.gov/cmv/index.html. Prevention tips include:
- Wash hands often with soap and water for 15-20 seconds, especially after wiping runny noses, changing diapers, picking up toys, etc. If soap and water are not available, use alcohol-based hand gel.
- Use soap and water or a disinfectant to clean hard surfaces that have been contaminated by secretions.
- Don’t kiss young children on the lips or share food, drinks, or eating utensils with them.
- If you work in a day care center, limit close contact with children younger than 2½ years of age, especially if you've never been infected with CMV or don't know if you've been infected.
Will Connecticut save money if CMV prevention is taught?

- Yes. According to studies in the U.S. and France, teaching prevention reduced the rate of transmission of CMV. “Studies have shown that women who know they are CMV seronegative, know they are pregnant, and know about their toddler's CMV shedding are the most likely to prevent CMV transmission and reduce their risk from over 50 percent during pregnancy to a risk of less than 5 percent during pregnancy. It is not likely that isolated instances of exposure to saliva or drool will result in transmission. Most studies suggest prolonged repeated exposures over time are important for CMV transmission,” says Dr. Demmler-Harrison.
In addition to testing newborns for CMV if they fail their hearing screen test, Utah’s H.B 81 requires CMV prevention brochures for doctors, parents, and daycare providers. Why doesn’t the Connecticut law require prevention education?

- There is a cost to prevention education. In 2014, Connecticut estimated the cost to the state at $40,000 the first year, then $26,000 the following years.
Shouldn’t we try to educate the public that pregnant women shouldn’t kiss their toddlers around the mouth or share food with them? Shouldn’t that be common knowledge like pregnant women shouldn’t change the kitty litter to prevent the birth defects caused by toxoplasmosis?

- “Yes. In addition to saving money by preventing congenital CMV through education, you can prevent indescribable human suffering,” says Lisa Saunders, parent representative, Congenital Cytomegalovirus (CMV) Foundation. “In fact, the United States Senate passed legislation designating the month of June as National Congenital CMV Awareness Month, while recommending that ‘more effort be taken to counsel women of childbearing age of the effect this virus can have on their children.’” Saunders’ daughter, Elizabeth, was born severely disabled by cCMV because she didn’t know she was putting her pregnancy at risk when operating a licensed daycare center in her home. Saunders hopes Connecticut will now add cCMV prevention information to their daycare licensing literature and post cCMV flyers at daycare centers.
The cost for prevention education seems minimal compared to cost of caring for a child disabled by cCMV ($40,000 annually for prevention education versus $300,000 annually to care for EACH child disabled by cCMV). Without using state dollars, how can we start our own prevention campaign?

- "You can start by providing cCMV prevention education on your website. Perhaps you know an organization that would provide grant money for printing brochures and posters, and/or you can contact colleges who have an internship programs for medical, public health or marketing students. Since daycare workers are at higher risk for contracting CMV and passing it onto their unborn, daycare centers can easily post flyers on how to minimize one’s risk. You can also post downloadable cCMV prevention brochures such as the CDC’s flyer: ‘What Women Should Know About Cytomegalovirus (CMV)’ on your website, found at: http://congenitalcmv.org/CDCbrochure.pdf,” says Lisa Saunders, parent representative, Congenital Cytomegalovirus (CMV) Foundation.

- If you would like to replicate Utah’s prevention brochures for doctors, parents, and daycare providers by inserting your organization’s contact information and logo, contact Stephanie Browning McVicar, Au.D., CCC-A, Utah Department of Health, Director, Early Hearing Detection and Intervention / Cytomegalovirus Public Health Initiative at at (801) 584-8215 orsmcvicar@utah.gov.

- McVicar said, “I am so excited that another state is bringing attention to congenital cytomegalovirus. Utah is looking forward to partnering with Connecticut in their upcoming endeavors."
For More Information

- To see Utah’s cCMV brochures and information, which also includes the free webinar, "cCMV 101: Congenital Cytomegalovirus from Prevention to Treatment," by Dr. Michael Cannon of the Centers for Disease Control and Prevention (CDC), visit their website at: http://www.health.utah.gov/cshcn/CHSS/CMV.html.

- For more information on how Utah is handling their CMV law, contact the Utah Department of Health Early Hearing Detection and Intervention program at (801) 584-8215 orsmcvicar@utah.gov.

- To learn more about congenital cytomegalovirus and how to prevent it, visit the Centers for Disease Control and Prevention at: http://www.cdc.gov/cmv/index.html.
CONGENITAL CYTOMEGALOVIRUS CONTACTS

- **Brenda K. Balch**, MD, CT’s American Academy of Pediatrics Early Hearing Detection & Intervention Chapter Champion. She has a strong interest because congenital CMV is a major cause of hearing loss. bkbalch@sbcglobal.net.

- **Gail J Demmler-Harrison**, MD, Professor, Pediatrics, Section Infectious Diseases, Baylor College of Medicine, Attending Physician, Infectious Diseases Service, Texas Children's Hospital, CMV Registry, CMV Research and CMV Clinic. Contact: 832-824-4330, gjdemmle@texaschildrens.org. The CMV Registry supports CMV research, disseminates information and provides parent support. (Sent Letter of Testimony to CT’s HB 5525).

- CDC’s **Michael Cannon, Ph.D.** mrc7@cdc.gov, a research epidemiologist at the Centers for Disease Control and Prevention. Dr. Cannon is particularly interested in developing strategies to prevent congenital CMV infection through public awareness and education.

- **Lenore Pereira, Ph.D.**, Founder of Congenital Cytomegalovirus Foundation, and Professor, Cell and Tissue Biology Department, University of California San Francisco. lenore.pereira@ucsf.edu, or visit www.congenitalcmv.org. The Congenital CMV Foundation raises awareness about maternal testing for first infection during pregnancy, newborn testing and the need to develop a vaccine.

- **Stuart Adler, M.D.**, Professor Emeritus of Pediatrics and Professor of Microbiology and Immunology, Virginia Commonwealth University. sadler@vcu.edu (sent Letter of Testimony to CT’s HB 5147).

- **Staley Plotkin, MD**, Professor Emeritus of Pediatrics, University of Pennsylvania, Vaccinology Consultant (sent Letter of Testimony to CT’s HB 5147). Contact: stanley.plotkin@vaxconsult.com

- **Sara Menlove Doutre**, President and Education Policy Consultant at Doutre Consulting (her daughter was affected by congenital cytomegalovirus) and co-founder of Utah CMV Council. Contact:sara@doutreconsulting.com

- **Stephanie Browning McVicar**, Au.D., CCC-A, DOCTOR OF AUDIOLOGY (worked tirelessly to pass the Utah bill), Specialty Services Program Manager, State EHDI Director, State of Utah Department of Health, Children with Special Healthcare Needs, Children’s Hearing and Speech Services, (801) 584-8218, smcvicar@utah.gov.

- **Ronda Rudd Menlove**, PhD. She was the representative responsible for passing and enacting the bill in Utah (2013) and has offered to advise CT politicians about the legislation and needed funding. Utah CMV Council, Ronda.menlove@gmail.com.
ABOUT LISA SAUNDERS

- Lisa Saunders of Mystic, Connecticut, is author of memoir, *Anything But a Dog! The perfect pet for a girl with congenital CMV (cytomegalovirus)*, and the parent representative of the Congenital Cytomegalovirus Foundation, which raises awareness about maternal testing for first infection during pregnancy, newborn testing and the need to develop a vaccine (Lenore Pereira, Ph.D., Professor, Cell and Tissue Biology Department, University of California San Francisco, is the Foundation founder and can be reached at: lenore.pereira@ucsf.edu).

- Saunders said, “My OB/GYNs didn’t tell me how to prevent congenital CMV, namely by avoiding kissing my toddler near the mouth or sharing food with her, until after my second daughter was born profoundly mentally and physically disabled by the disease. It was then that I received literature stating women who work in daycare, or have a young child in daycare, are at a higher risk for catching it as toddlers are the majority of carriers. While I was pregnant with Elizabeth, I not only had a toddler of my own, I was also running a licensed daycare center in my home. Nowhere in the licensing literature was there a CMV prevention message. In milder cases, children may lose hearing or struggle with learning, but Elizabeth's case was not a mild one.” Elizabeth died at age 16 during a seizure in 2006.
Lisa’s memoir, *Anything But a Dog! The perfect pet for a girl with congenital CMV* includes interviews with CMV experts.
More images from the life of my daughter, Elizabeth Saunders:
My older daughter Jackie was proud of her little sister Elizabeth.
(My father-in-law made Elizabeth’s walker.)
Daddy’s little girl
Elizabeth at age four
Big, formerly homeless dog keeps Elizabeth company
Sisters giggle at private slumber party
Elizabeth (at 15) and Jackie on a N.J. boardwalk on last family vacation together
Elizabeth died during a seizure at 16
"I WILL DWELL IN THE HOUSE OF THE LORD FOREVER"
PS 23:6

"THEN WILL THE LAME LEAP LIKE A DEER AND THE MUTE TONGUE SHOUT FOR JOY"
IS 35:6
CMV Awareness Among Women

- After Elizabeth died in 2006, I began researching CMV awareness among women.
- Only 22% have heard of it. (A 2006 survey published in the article, "Knowledge and Awareness of Congenital Cytomegalovirus Among Women," concluded that of the 643 women surveyed about their CMV awareness, only 22% had heard of it and most of those could not correctly identify modes of CMV transmission or prevention.)
- I had a tormenting dream about parents who were wondering why I didn’t do more to warn about them about congenital CMV.
Fairytale about surviving the loss of a loved one also raises CMV Awareness
(available in softcover or free e-book)
All my books include CMV prevention
Considering getting pregnant?

- **Check your CMV status.** Your doctor can perform a simple blood test. If you are currently infected for the first time, consider avoiding pregnancy until your primary CMV infection has resolved. Ask your doctor when it is safe to become pregnant.

- **Daycare workers:** The CDC website states: "Adults who have not had CMV and who work with children in day care, especially children 1 to 2 ½ years of age, are at high risk for CMV infection."
Pregnant with active CMV infection?

- Contact the National Congenital CMV Disease Registry at cmv@bcm.edu or visit: http://www.bcm.edu/pedi/infect/cmv

- Contact an expert at the Texas Children’s Hospital Fetal Center for advice. Visit: http://www.texaschildrens.org/CareCenters/fetalurgery/default.aspx
Treatment

**Pregnant Women:** CMV hyperimmune globulin is showing promising results.

Scientific papers on CMV stats and emerging treatments:
http://www.congenitalcmv.org/research.htm
Carlson, Amanda, MD; Norwitz, Errol R MD, PhD; Stiller, Robert J , MD. (Fall 2010). Cytomegalovirus Infection in Pregnancy: Should All Women Be Screened? Retrieved from National Center for Biotechnology Information: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3046747/


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