Society for Birth Defects Research & Prevention
EST. 1960 AS THE TERATOLOGY SOCIETY

OTIS Organization of Teratology Information Specialists

Identifying Teratogens: Challenges and Opportunities

Josef Warkany lecture

Sonja A. Rasmussen, MD, MS
Johns Hopkins University School of Medicine

DENVER COLORADO

"When I heard that I had become an Allan Award winner, I was filled with many emotions:

- surprise that I should join such a group of distinguished scientists;
- pleasure that an honor always brings;
- gratitude to all who made it possible; and
- dismay at the prospect of giving this talk."

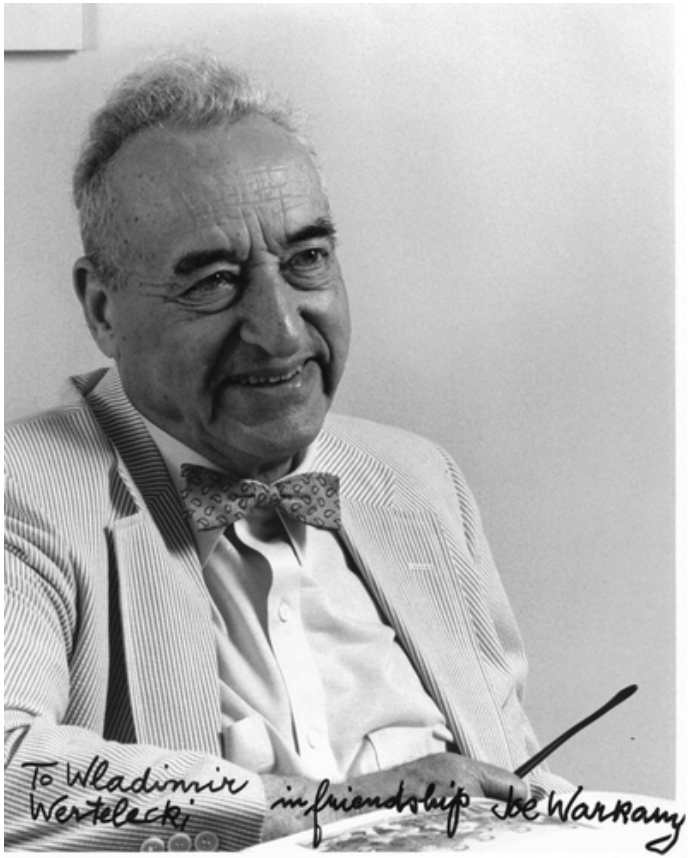
Fraser FC, *Am J Hum Genet* 32:796-813, 1980

Dr. Josef Warkany

- Born in Vienna in 1902, died in Ohio in 1992
- Considered to be the father of teratology
- Challenged the dogma that the embryo was well protected from environmental assaults -- that congenital malformations were reflections of genetic cause, mostly inherited from “flawed” parents
- First president of the Teratology Society
- Persuaded Basil O’Connor, president of the National March of Dimes Foundation, to shift funding from polio to prevention of birth defects

Wertelecki W. *Birth Defects Res* 112:885-889, 2020

Dr. Josef Warkany



Wertelecki W. *Birth Defects Res* 112:885-889, 2020

APPEARANCE OF SKELETAL ABNORMALITIES IN THE OFFSPRING OF RATS REARED ON A DEFICIENT DIET

THE following observations were made when rats, which were reared on deficient diets, were bred. All rats used were of the Sprague-Dawley strain. One group of females was reared on a diet consisting of yellow cornmeal 76 per cent., wheat gluten 20 per cent., calcium carbonate 3 per cent., sodium chloride C.P. 1 per cent. (Steenbock and Black rachitogenic diet No. 2965),[1] which was supplemented with viosterol (each rat received 60 I.U. every tenth day). On this diet the animals were retarded in growth and

[9] O. Warburg, K. Posener and E. Negelein, *Biochem. Zeit.*, 152: 309, 1924.
[10] F. Dickens and A. Greville, *Biochem. Jour.*, 27: 1123, 1933.
[1] H. Steenbock and A. Black, *Jour. Biol. Chem.*, 64: 263, 1925.

JOSEF WARKANY
ROSE C. NELSON
THE CHILDREN'S HOSPITAL RESEARCH FOUNDATION AND DEPARTMENT OF PEDIATRICS, UNIVERSITY OF CINCINNATI COLLEGE OF MEDICINE

Warkany and Nelson. *Science* 92(2391):383-4, 1940.

Shepard's Criteria for Teratogenicity

Shepard T, Teratology 50:97-98, 1994

TERATOLOGY 50:97–98 (1994)

Letters

"Proof" of Human Teratogenicity

To the Editor:

TABLE 1. Amalgamation of criteria for proof of human teratogenicity[1]

1. Proven exposure to agent at critical time(s) in prenatal development (prescriptions, physicians' records, dates).
2. Consistent findings by two or more epidemiologic studies of high quality
   a. control of confounding factors,
   b. sufficient numbers,
   c. exclusion of positive and negative bias factors,
   d. prospective studies, if possible, and
   e. relative risk of six or more (?).
3. Careful delineation of the clinical cases. A specific defect or syndrome, if present, is very helpful.
4. Rare environmental exposure associated with rare defect. Probably three or more cases (e.g., oral anticoagulants and nasal hypoplasia, methimazole and scalp defects(?), and heart block and maternal rheumatism).
5. Teratogenicity in experimental animals important but not essential.
6. The association should make biologic sense.
7. Proof in an experimental system that the agent acts in an unaltered state. Important information for prevention.

[1]Note: Items 1–3 or 1, 3, and 4 are essential criteria. Items 5–7 are helpful but not essential. From Brent ('78), Stein et al. ('84), Hemminki and Vineis ('85), Wilson ('77), and Shepard ('86a,b,'89,'92).

Rare Exposure-Rare Defect

1 – Proven exposure to agent at critical time

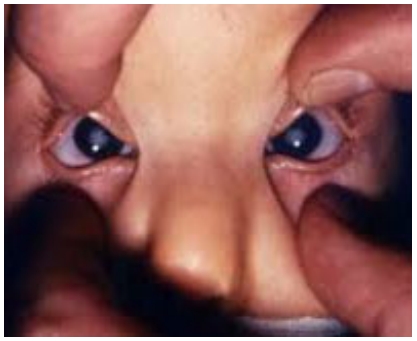
3 – Careful delineation of the clinical cases – a specific defect or syndrome, if present, is helpful

4 – Rare environmental exposure associated with rare defect – probably 3 or more cases

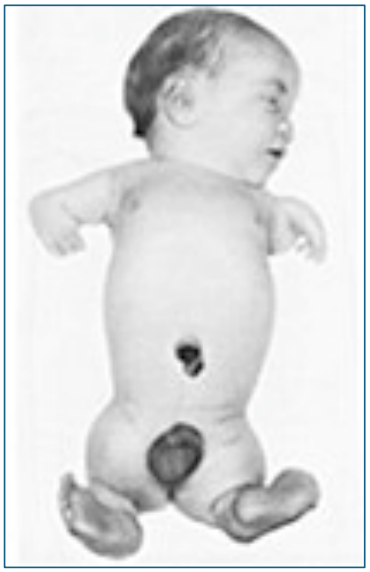
Examples from Shepard (1994) – congenital rubella, diethylstilbestrol, rheumatic disease (and congenital heart block), cyclophosphamide, and retinoic acid

Identification of Teratogens

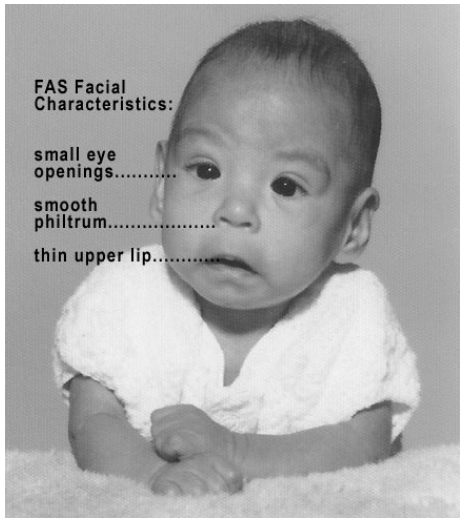
- Rubella embryopathy (Gregg, 1941)
- Thalidomide embryopathy (McBride, 1961; Lenz, 1962)
- Fetal alcohol syndrome (Jones et al., 1973)
- Congenital Zika syndrome (Schuler-Faccini et al., 2016)



Rubella



Thalidomide



Alcohol

Zika

Role of the "Astute Clinician"

American Journal of Medical Genetics Part C (Seminars in Medical Genetics) 157:188–194 (2011)

ARTICLE

The Importance of Dysmorphology in the Identification of New Human Teratogens

KENNETH LYONS JONES* AND JOHN C. CAREY

Selected Teratogens Categorized by Types of Evidence
Established human teratogens recognized by acute observer and confirmed by epidemiological methods/animal models
Alcohol
Valproic acid
Isotretinoin
Warfarin
Human teratogens based on clinical evidence
Aminopterin/methotrexate
D-Penicillamine
Fluconazole
Mycophenolate mofetil

As is well recognized in the clinical teratology community, most of the well-established human teratogens were initially identified by astute clinicians making observations during the course of clinical practice. The basic premise of this approach is that the occurrence of the unique pattern of malformation associated with the rare gestational exposure suggests causation in and of itself because of the rarity of the events occurring together by chance alone.

Epidemiologic Evidence

1 – Proven exposure to agent at critical time

2 – Consistent findings of 2 or more high-quality epidemiologic studies

a) Control of confounding factors
b) Sufficient numbers
c) Exclusion of positive and negative bias factors
d) Prospective studies, if possible, and
e) Relative risk of 6 or more (?)

3 – Careful delineation of the clinical cases – a specific defect or syndrome, if present, is helpful

Valproic Acid

Elizabeth Robert , MD

CDC | CDC Home | Search | Health Topics A-Z

MMWR

Weekly

October 29, 1982 / 31(42);565-566

Persons using assistive technology might not be able to fully access information in this file. For assistance, please send e-mail to: mmwr
Accommodation and the title of the report in the subject line of e-mail.

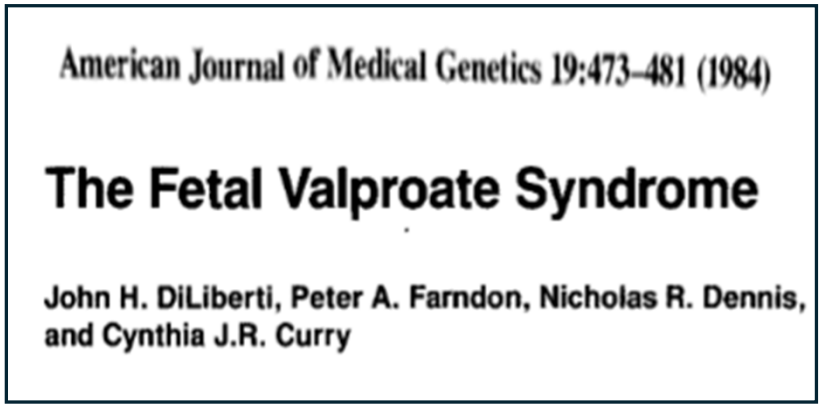
International Notes Valproic Acid and Spina Bifida: A Preliminary Report -- France

Valproic acid use during the first trimester of pregnancy has been reported among an unusually high proportion of mothers of infants with spina bifida. During 1976 and from 1978 through September 1982, the birth defects surveillance system at the Institut Europeen des Genomutations in Lyon, France, ascertained 146 cases of spina bifida aperta. Among these cases, nine (6.2%) of the mothers had epilepsy and had taken valproic acid during the first trimester at dosages between 400 mg and 2,000 mg per day. Five of the nine patients with spina bifida were exposed to valproic acid alone, and four were exposed to additional anticonvulsants. Twenty-one (0.32%) of the mothers of the 6,616 infants in the surveillance system with other malformations had taken the drug (Table 1). These data show a highly statistically significant odds ratio of 20.6.* To isolate the effect of valproic acid from the possible effects of seizure disorders and other drug therapy, the analysis was then confined to the 71 epileptic mothers. Nine (90%) of the 10 such mothers of spina bifida infants had taken valproic acid, compared with 21 (34.4%) of the 61 mothers of infants with other defects (Table 2). The odds ratio of 17.1 is statistically significant. Reported by E Robert, MD, Institut Europeen des Genomutations, Lyon, France; Epidemiology Development Br, Div of Drug Experience, Food and Drug Administration; Birth Defects Br, Chronic Diseases Div, Center for Environmental Health, CDC. *The odds ratio is an estimation of relative risk in case-control studies.

Robert et al., *MMWR Morb Mortal Wkly Rep* 31(42):565-6, 1982

Fetal Valproate Syndrome

- In 1984, DiLiberti et al. noted a consistent craniofacial phenotype (epicanthal folds, flat nasal bridge, small upturned nose, long upper lip with shallow philtrum, thin upper vermillion border of lip, and downturned angles of the mouth), along with hypospadias, strabismus, and developmental delay. They noted that cases with congenital heart defects, and neural tube defects had also been reported.

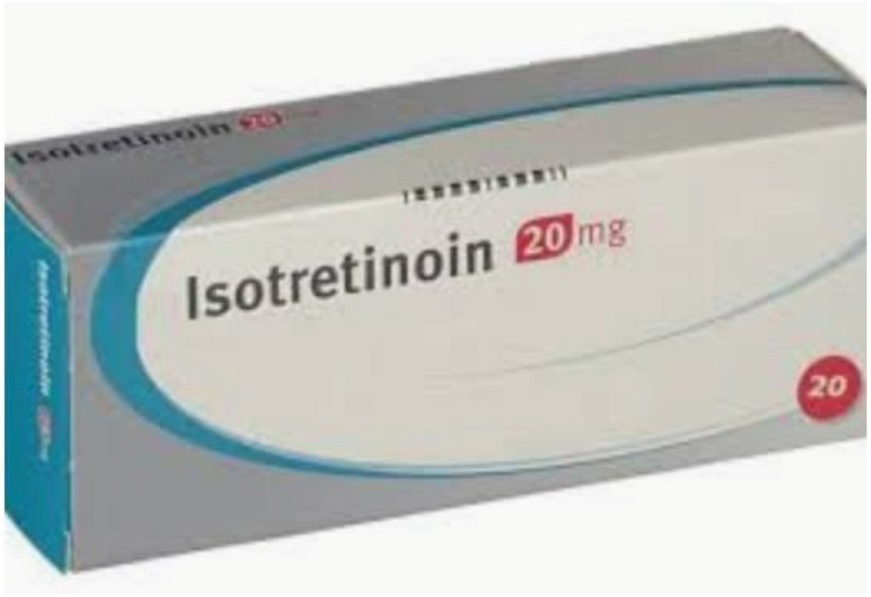

American Journal of Medical Genetics 19:473–481 (1984)

The Fetal Valproate Syndrome

John H. DiLiberti, Peter A. Farndon, Nicholas R. Dennis, and Cynthia J.R. Curry

Isotretinoin

- Oral isotretinoin introduced in the US in September of 1982 for treatment of severe recalcitrant acne
- Based on animal studies, the drug was FDA Pregnancy Category X - meaning that there is no indication for its use during pregnancy



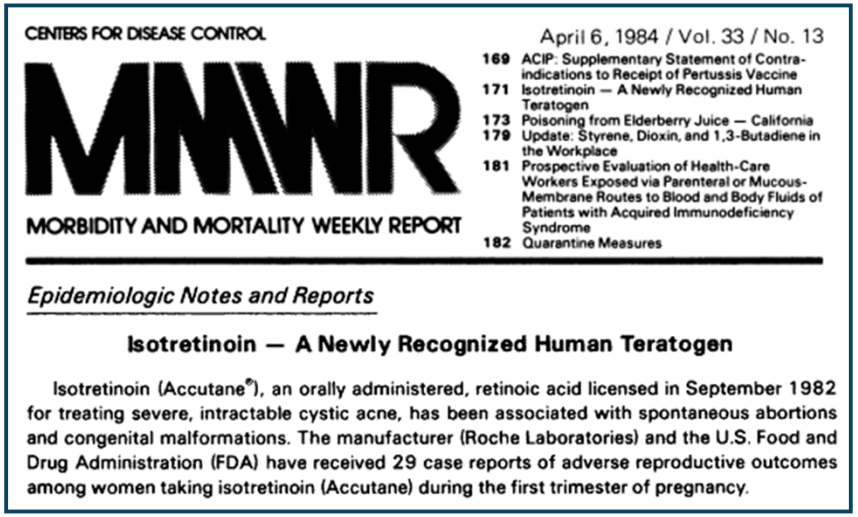
Isotretinoin

- Package insert at time of marketing carried the following warning:

Since the drug was first marketed in the United States in September 1982, the isotretinoin package insert has carried the following warning: "Because teratogenicity has been observed in animals given isotretinoin, patients who are pregnant or intend to become pregnant while undergoing treatment should not receive Accutane. Women of childbearing potential should not be given Accutane unless an effective form of contraception is used, and they should be fully counseled on the potential risks to the fetus should they become pregnant while undergoing treatment. Should pregnancy occur during treatment, the physician and patient should discuss the desirability of continuing the pregnancy." In July 1983, after the first reports of malformed newborns, Roche Laboratories mailed letters to U.S. physicians and pharmacists reiterating important portions of the package insert and suggesting a pregnancy test before initiation of therapy.

Isotretinoin Case Reports

- FDA received 29 case reports of adverse reproductive outcomes among women taking isotretinoin during the first trimester
  - ✓ 18 pregnancies prospectively identified by the manufacturer – 13 SABs, 4 normal infants, one infant with malformations
  - ✓ 16 pregnancies identified retrospectively – 6 SABs, one normal infant, and 9 with malformations (characteristic pattern)



CENTERS FOR DISEASE CONTROL

April 6, 1984 / Vol. 33 / No. 13

MMWR

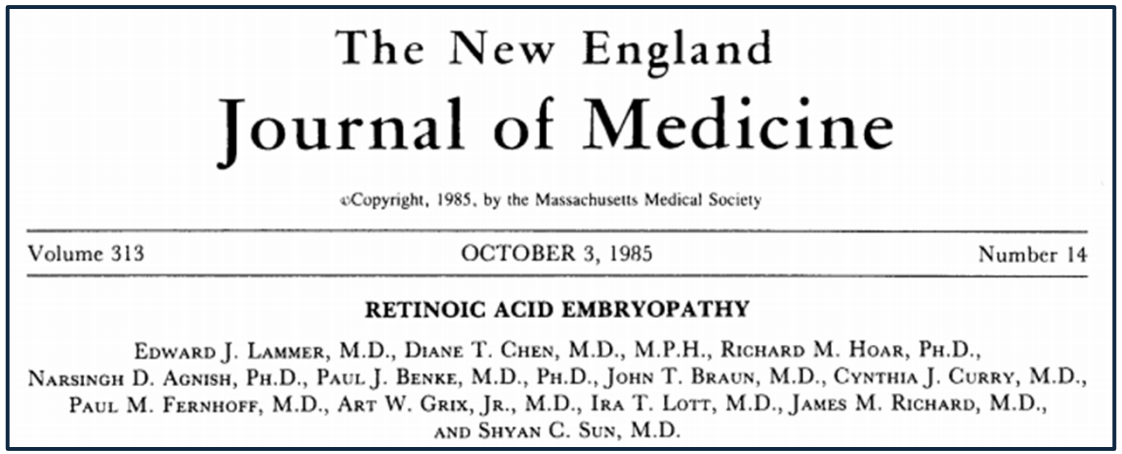
MORBIDITY AND MORTALITY WEEKLY REPORT

Epidemiologic Notes and Reports

Isotretinoin — A Newly Recognized Human Teratogen

Isotretinoin (Accutane®), an orally administered, retinoic acid licensed in September 1982 for treating severe, intractable cystic acne, has been associated with spontaneous abortions and congenital malformations. The manufacturer (Roche Laboratories) and the U.S. Food and Drug Administration (FDA) have received 29 case reports of adverse reproductive outcomes among women taking isotretinoin (Accutane) during the first trimester of pregnancy.

- "Although the total number of exposed pregnant women is unknown, the consistency of the laboratory and human experiences with isotretinoin exposure during pregnancy provides sufficient evidence to conclude that the drug is a human teratogen."



The New England
Journal of Medicine

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Volume 313 OCTOBER 3, 1985 Number 14

RETINOIC ACID EMBRYOPATHY

EDWARD J. LAMMER, M.D., DIANE T. CHEN, M.D., M.P.H., RICHARD M. HOAR, PH.D., NARSINGH D. AGNISH, PH.D., PAUL J. BENKE, M.D., PH.D., JOHN T. BRAUN, M.D., CYNTHIA J. CURRY, M.D., PAUL M. FERNHOFF, M.D., ART W. GRIX, JR., M.D., IRA T. LOTT, M.D., JAMES M. RICHARD, M.D., AND SHYAN C. SUN, M.D.

Edward J. Lammer, MD

- Among 154 pregnancies – 95 elective abortions, 26 without major malformations, 12 spontaneous abortions, and 21 malformed infants
  - 36 pregnancies observed prospectively – 8 SABs, 23 normal infants, and 5 malformed infants
- Relative risk=25.6, 95% CI 11.4-57.5 -- compared rate of selected major malformations in the prospective cohort (5/28 or 18%) with the rate in MACDP (7 per 1000)
- Among 21 malformed infants – characteristic pattern of malformation involving craniofacial, cardiac, thymic, and CNS structure
- Concluded (1) pattern closely resembles that in animal studies of retinoid teratogenesis and (2) isotretinoin teratogenesis is a deleterious effect on cephalic neural-crest cell activity

Recognizing Teratogenic Exposures

- What we want
  - Data from randomized, controlled clinical trials
- What we've got
  - A combination of case reports, case series, case-control studies, pregnancy registries, studies using claims data, etc. – all with significant limitations

Consequences of our Current System

- Among 290 drugs approved between 2010-2019, 90% have no human data on risk or benefit during pregnancy
- About 80% of >1800 active ingredients in the Teratogen Information System are assessed as having ”none to limited quality” evidence regarding teratogenic risk
- With current system, the mean time for evidence development in pregnancy is estimated at 27 years

Adam MP et al., *Am J Med Genet C Semin Med Genet* 157C(3):175-82, 2011
Byrne et al., *JAMA Netw Open* 3(8):e2015094, 2020.

Mitchell AJOG 2011, Byrne JAMA Open 2020, Adam Am J Med Gen 2011, Mukherjee AJE 2013, CDC Stillbirth Data and Statistics, 2021

Use of Epidemiologic Studies in Assessment of Teratogenicity

- "Well-powered epidemiology studies of teratogenic birth defects usually require many hundreds or thousands of babies to be born with birth defects before causality can be established."

Jan M. Friedman, MD, PhD

Editorial

In Bed with The Devil: Recognizing Human Teratogenic Exposures

Jan M. Friedman[1]

[1]Department of Medical Genetics and Genomics, University of British Columbia, Vancouver, Canada

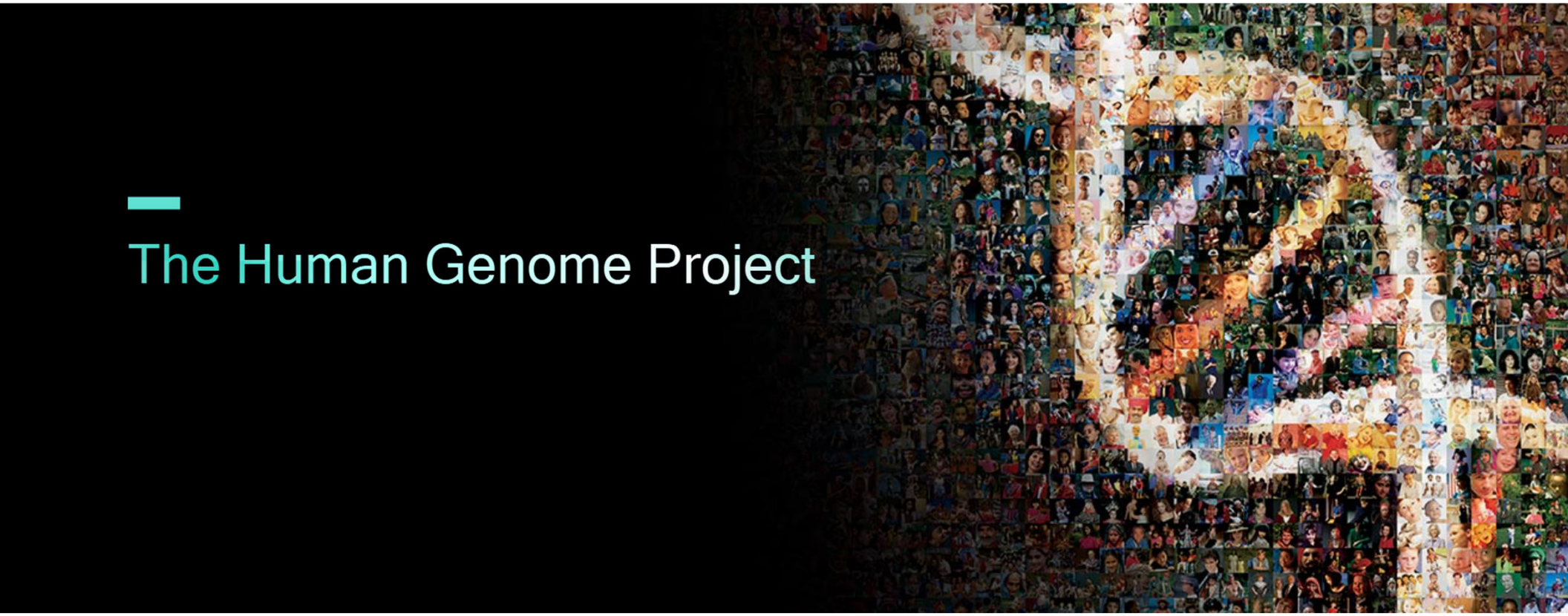
BIRTH DEFECTS RESEARCH 109:1407–1413 (2017)

"The only way we can ever know with certainty that an exposure is teratogenic in humans is to recognize that it has caused birth defects in children. Our challenge is to do this as quickly and efficiently as possible, when the fewest babies have been harmed." JM Friedman, MD, PhD

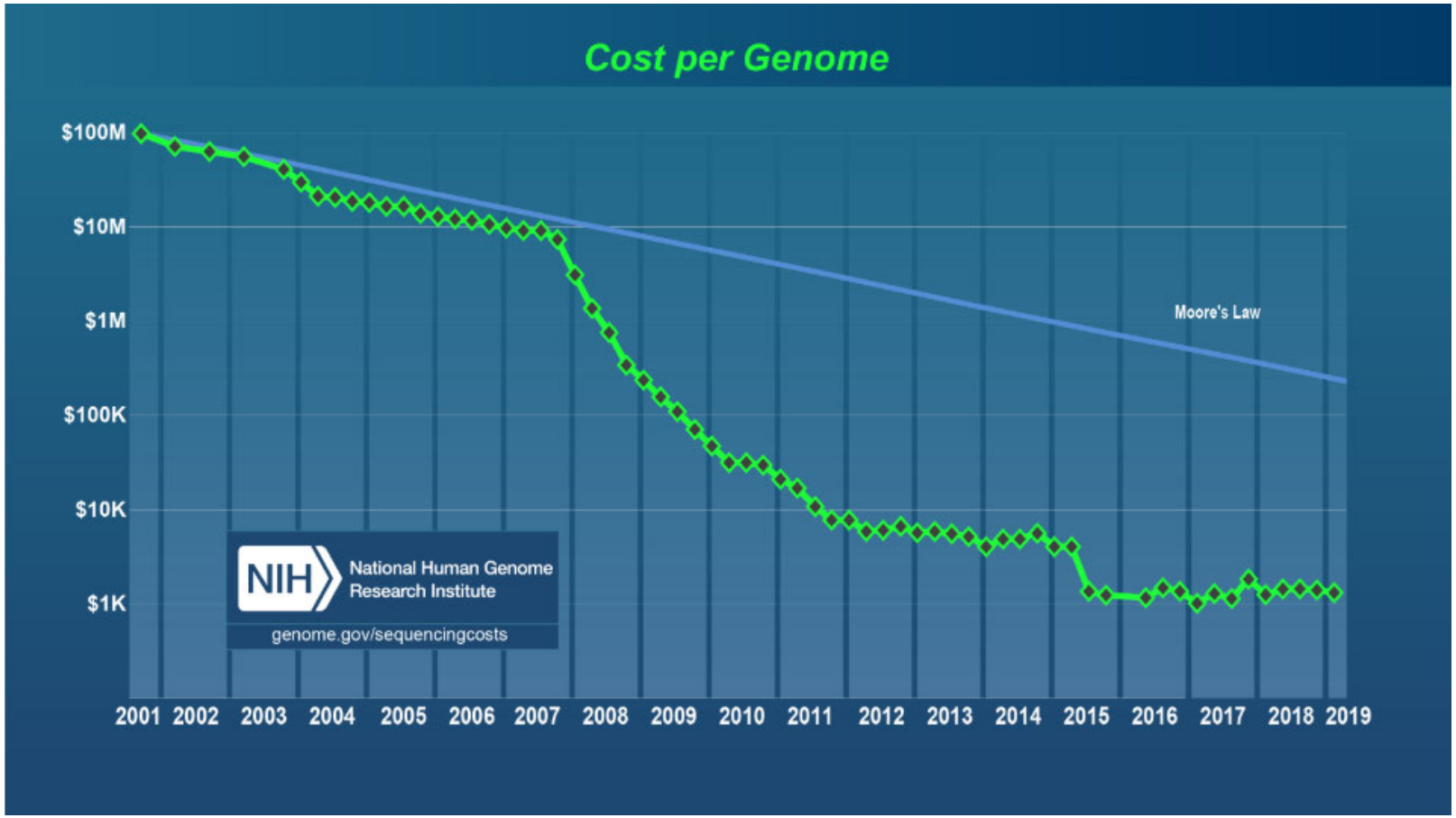
Friedman JM. *Am J Med Genet Part C Semin Med Genet* 157:170–174, 2011.

Can We Use Advances in Genetics to Identify Teratogens More Quickly?

The Human Genome Project



https://www.genome.gov/human-genome-project



https://www.genome.gov/about-genomics/fact-sheets/DNA-Sequencing-Costs-Data

Case Classification Guidelines developed for the National Birth Defects Prevention Study (NBDPS)

Birth Defects Research (Part A) 67:193–201 (2003)

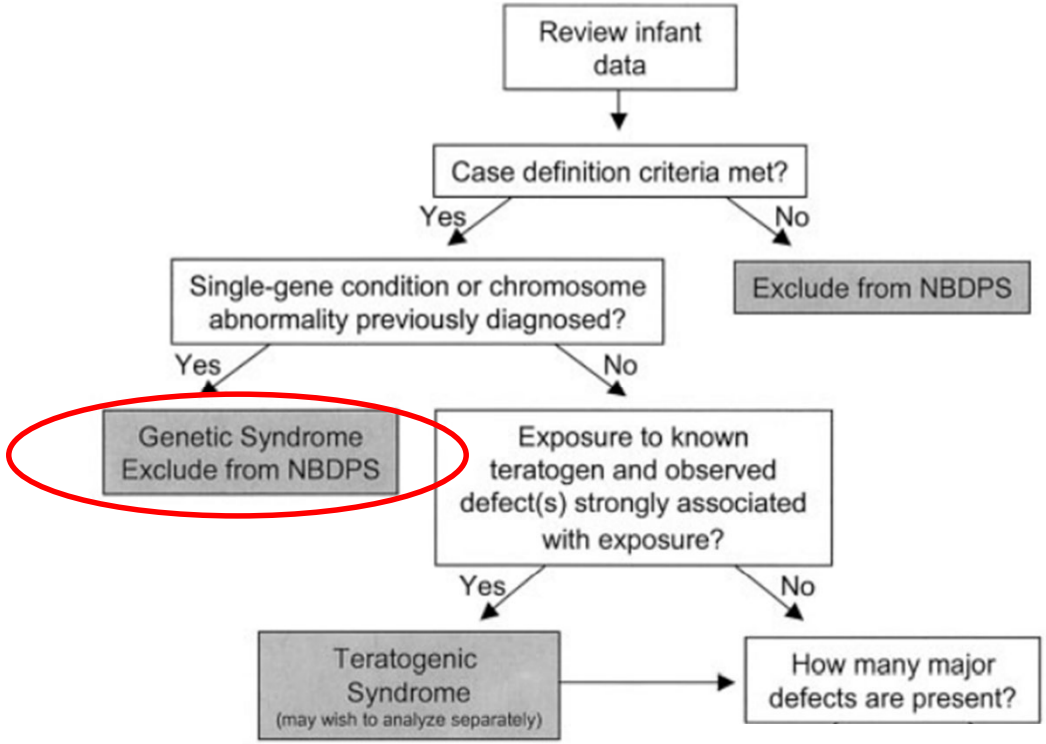
Guidelines

Guidelines for Case Classification for the National Birth Defects Prevention Study

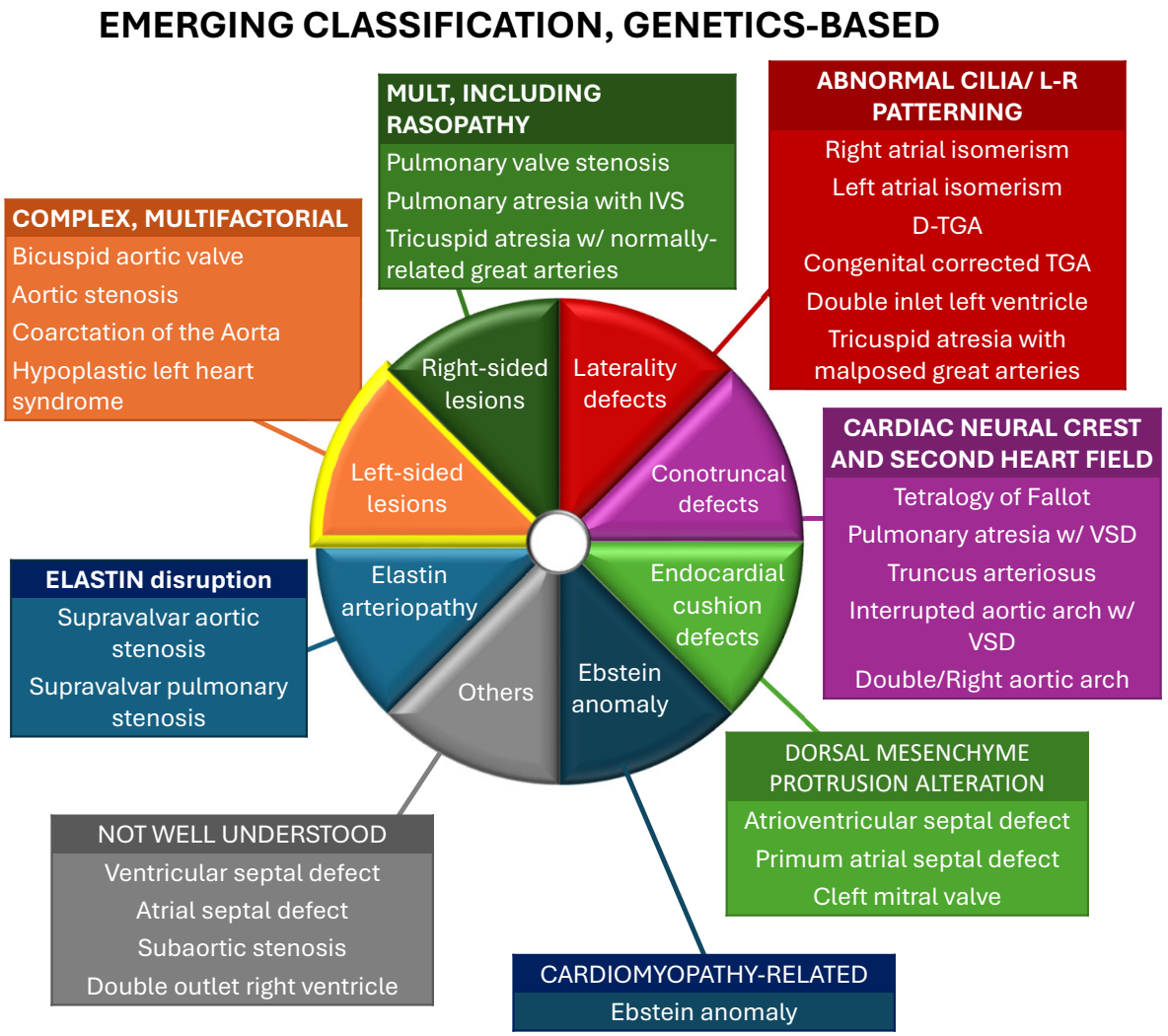
Sonja A. Rasmussen,[1]* Richard S. Olney,[1] Lewis B. Holmes,[2] Angela E. Lin,[2] Kim M. Keppler-Noreuil,[3] Cynthia A. Moore,[1] and the National Birth Defects Prevention Study

[1]National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia
[2]Genetics and Teratology Unit, Pediatric Service, Massachusetts General Hospital, Boston, Massachusetts
[3]Department of Pediatrics, Division of Medical Genetics, University of Iowa Hospitals and Clinics, Iowa City, Iowa

Exclusion of Single-gene Conditions and Chromosome Abnormalities



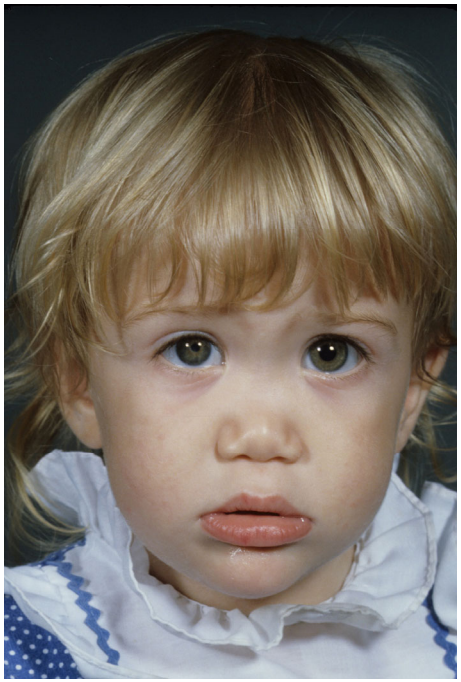
Can we use knowledge about genetics to better classify defects?

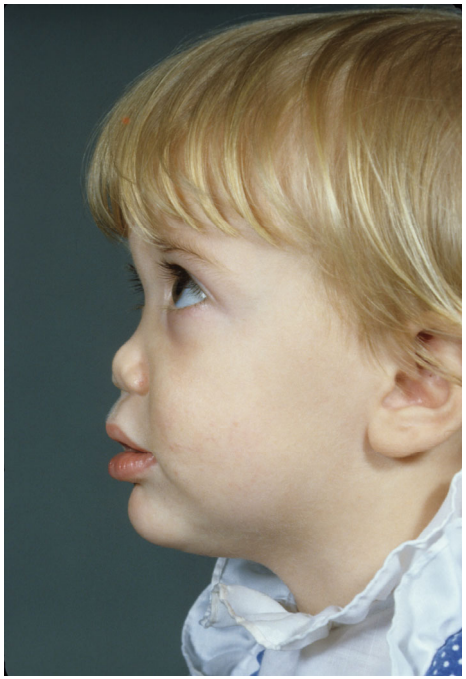


Slide courtesy of Shaine Morris, MD

Can Phenocopies Help us to Identify Pathways of Teratogenicity?

Fetal Warfarin Syndrome





Photos courtesy of J Friedman, MD, PhD

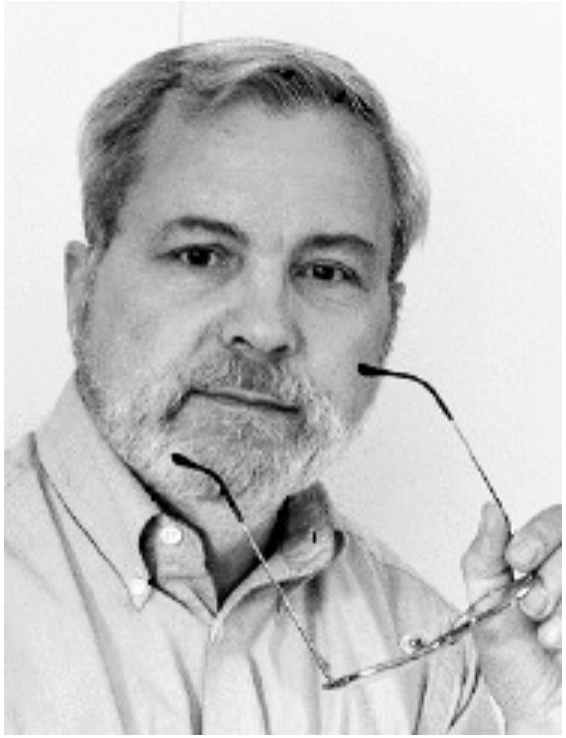
- Nasal hypoplasia (depressed nasal bridge)
- Stippled epiphyses (chondrodysplasia punctata)
- Growth restriction
- Associated with first trimester exposure to warfarin

Am. J. Hum. Genet. 41:566–583, 1987

Association of Congenital Deficiency of Multiple Vitamin K–dependent Coagulation Factors and the Phenotype of the Warfarin Embryopathy: Clues to the Mechanism of Teratogenicity of Coumarin Derivatives

RICHARD M. PAULI,*·† JANE B. LIAN,# DEANE F. MOSHER,§·‖ AND JOHN W. SUTTIE‡

Departments of *Pediatrics, †Medical Genetics, ‡Biochemistry, §Medicine, and ‖Physiological Chemistry, University of Wisconsin—Madison; and #Department of Biological Chemistry, Harvard Medical School, Cambridge, MA



Richard M. Pauli, MD, PhD

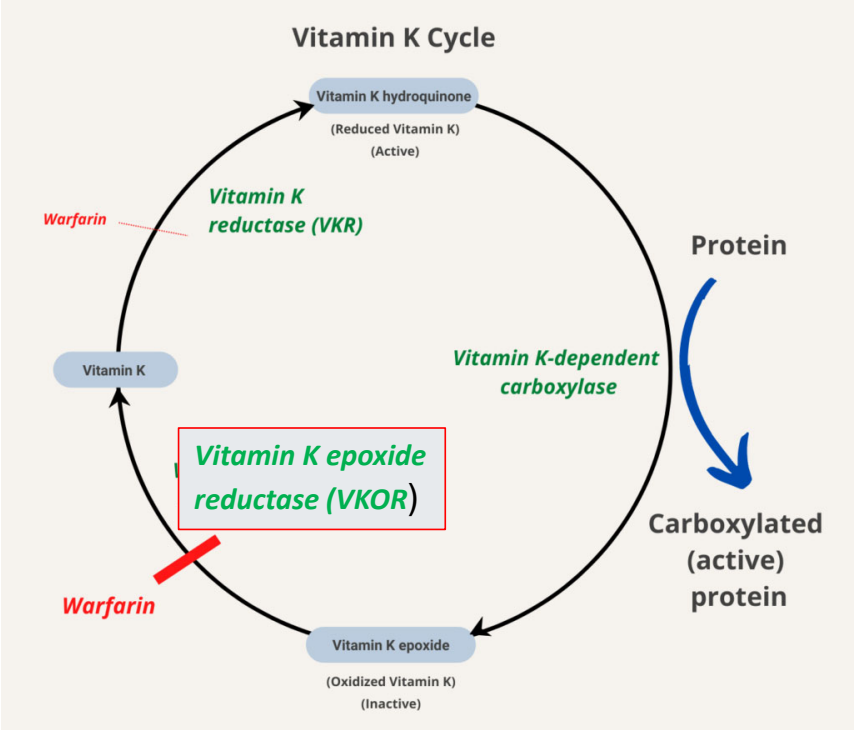
Comparison of Features in Warfarin Embryopathy to Patient with Inborn Error of Vitamin K Epoxide Reductase

Feature	Warfarin embryopathy	Proband
Warfarin exposure	+	-
Nasal hypoplasia	+++	++
Stippled epiphyses	+++	+
Brachydactyly	+	+
Conductive hearing loss	+/-	+
Coagulopathy	-	++

Pauli RM et al., *Am J Hum Genet* 41:566-83, 1987

Inborn Error of Vitamin K Metabolism and Warfarin Embryopathy

- Since then, 7 patients from 2 families described – all with homozygous pathogenic variants in *VKORC1* gene, resulting in reduced activity of vitamin K dependent coagulation factors compared to controls
- VKORC1 catalyzes the reduction of vitamin K 2,3 epoxide to vitamin K quinone and to vitamin K hydroquinone



https://www.thebloodproject.com/ufaq/how-do-vitamin-k-antagonists-vkas-work/

Warfarin Embryopathy and Genetic Phenocopies

Disorder	Gene	Mode of Inheritance	Nasal Hypoplasia	Stippling of Epiphyses	Brachydactyly	Other anomalies
Warfarin exposure	-	-	+	+	+	Occasional defects: choanal atresia, facial clefts, short limbs, hearing loss, heart, urogenital, vertebral and brain defects
Combined deficiency of Vitamin K-Dependent Clotting Factors	*GGCX* *VKORC1*	AR	+	+	+	Bleeding diathesis, hearing loss, cardiac anomalies
Keutel syndrome	*MGP*	AR	+	+	+	Peripheral pulmonary stenosis, cardiac anomalies, calcifications in larynx, trachea, bronchi, hearing loss, short stature, skin lesions
X-linked recessive chondrodysplasia punctata	*ARSE*	XLR	+	+	+	Calcifications in larynx, trachea, bronchi, vertebral abnormalities, hearing loss.

Cassina M et al., *Eur J Med Genet* 60:22-31, 2017

Other Examples of Phenocopies of Embryopathies due to Prenatal Exposure to Medications

Medication	Action of medication	Features	Genetic Syndrome	Genetic abnormality
Fluconazole (high-dose)	Inhibits the cytochrome P450 dependent enzyme lanosterol 14-alpha-demethylase	Dysmorphic features, cleft palate, and various skeletal anomalies	Antley-Bixler syndrome	Reduced activity of lanosterol-14 demethylase due to mutations in the POR (cytochrome P450 reductase) gene (autosomal recessive)
ACE inhibitors and angiotensin II receptor antagonists	Act on renin-angiotensin-aldosterone system (inhibition of ACE or block angiotensin II receptor)	Renal tubular dysplasia, oligohydramnios, pulmonary hypoplasia – with $2^{nd}/3^{rd}$ trimester exposure	Renal tubular dysgenesis (MIM #267430)	Genes in the renin-angiotensin-aldosterone system – REN, AGT, AGTR1, ACE (autosomal recessive)

Cassina M et al., *Eur J Med Genet* 60:22-31, 2017

Is there a Fetal Fentanyl Syndrome?

Genetics in Medicine Open (2023) 1, 100834

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Genetics in Medicine OPEN
An Official Journal of the ACMG

www.journals.elsevier.com/genetics-in-medicine-open

BRIEF REPORT

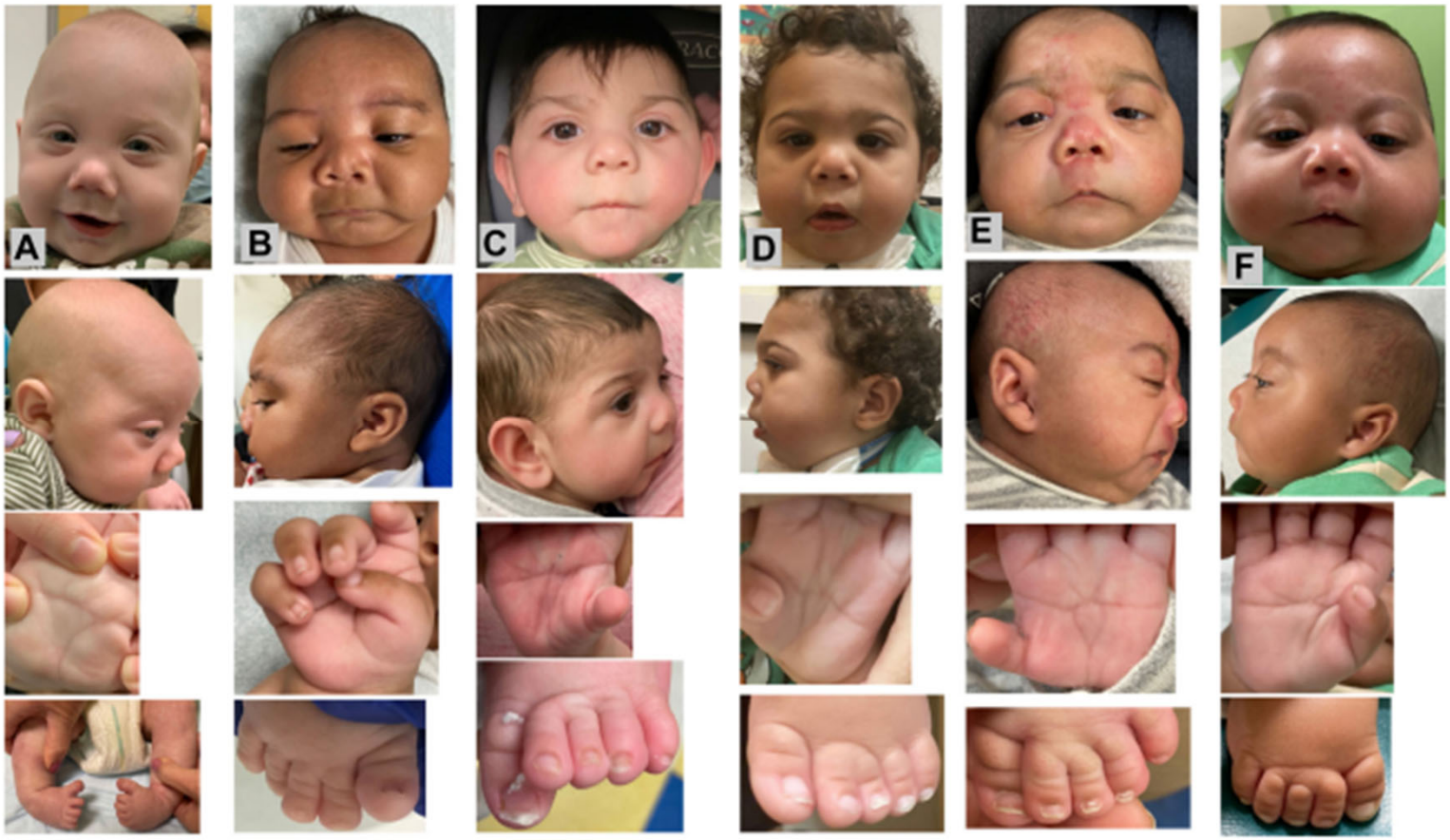
A novel syndrome associated with prenatal fentanyl exposure

Erin Wadman[1], Erica Fernandes[1], Candace Muss[1], Nina Powell-Hamilton[1], Monica H. Wojcik[2,3], Jill A. Madden[3], Chrystalle Katte Carreon[4], Robin D. Clark[5], Annie Stenftenagel[6], Kamal Chikalard[6], Virginia Kimonis[6], William Brucker[7], Carolina Alves[8], Karen W. Gripp[1,*]

Karen W. Gripp, MD

Findings

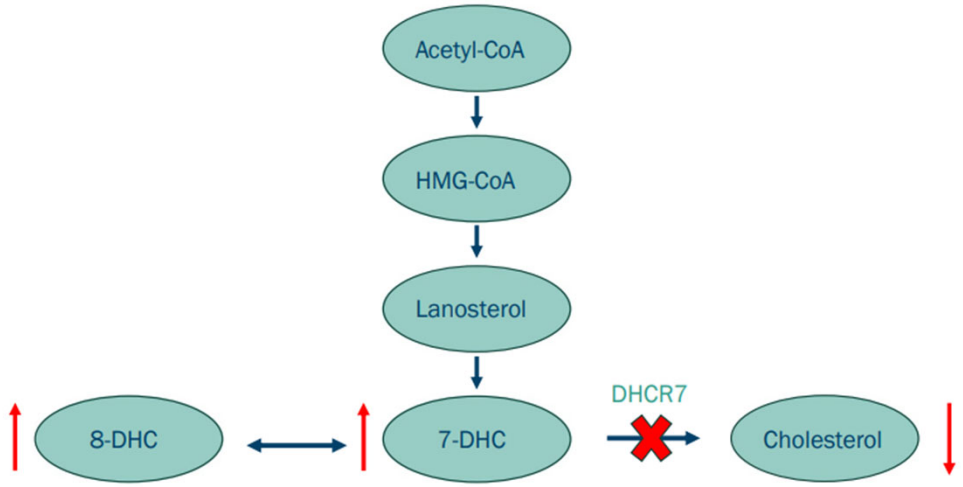
- 6 infants were born after pregnancies complicated by multiple drug exposures including fentanyl
- Infants had relatively low growth parameters, feeding difficulties, distinctive facial features, physical findings
  - Single palmar crease and adducted thumb
  - Cleft palate (5/6)
  - Genital anomalies (4/5 males)
  - Foot position abnormalities (talipes equinovarus in 3 and rocker bottom anomaly in 2)
- Suspicion for Smith-Lemli-Opitz syndrome led to biochemical testing – elevated 7-DHC or 8-DHC present early, later normalized
- Chromosome microarray and exome sequencing – non-diagnostic
- 4 similar cases from other institutions with prenatal fentanyl exposure, abnormal 7-DHC or 8-DHC shortly after delivery, and nondiagnostic genetic testing



Courtesy of Karen Gripp, MD

Smith-Lemli-Opitz Syndrome (SLOS)

- Multiple congenital anomaly disorder
- Autosomal recessive disorder due to variants in DHCR7 gene
- DHCR7 encodes delta-7-sterol reductase → converts 7-dehydrocholesterol (7-DHC) to cholesterol (final step in cholesterol metabolism)
- Cholesterol – critical during embryogenesis

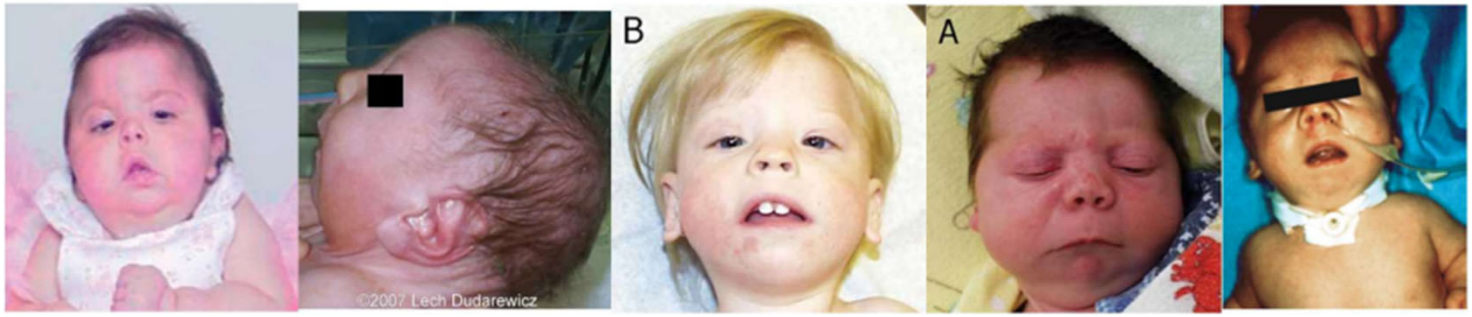


Features shared between Smith-Lemli-Opitz Syndrome and Possible Fetal Fentanyl Syndrome

Feature	SLOS	FFS
IUGR	+	+
Microcephaly	+	+
Bitemporal narrowing	+	+
Cleft palate	+	+
GU anomalies	+	+
2,3 toe syndactyly	+	+
Short, adducted thumbs	+	+
Developmental delay	+	+
Short stature	+	+
Corpus callosum abnormalities	+	+
Ptosis	+	+
Short nose, anteverted nares	+	+
Congenital heart defects	+	+
Elevated 7-DHC	+	+
Hypotonia, then hypertonia	+	+

NEMOURS CHILDREN'S HEALTH

SLOS

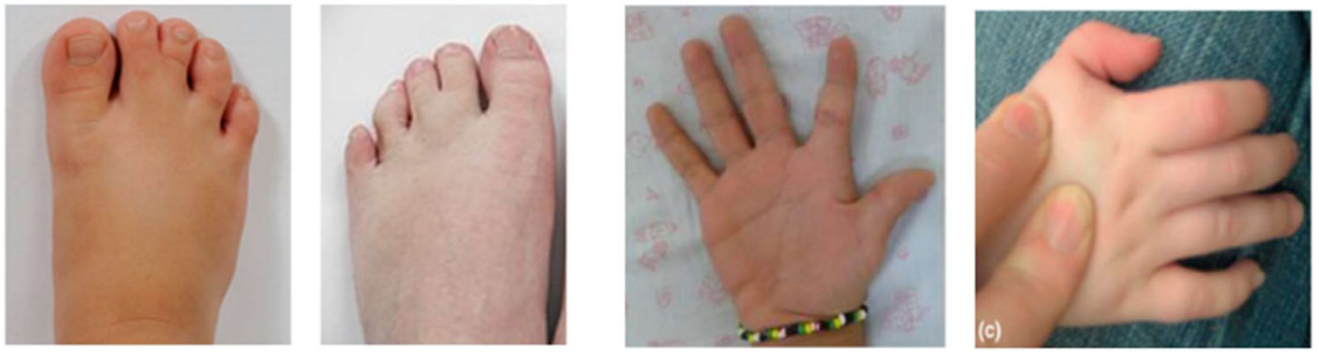


FFS

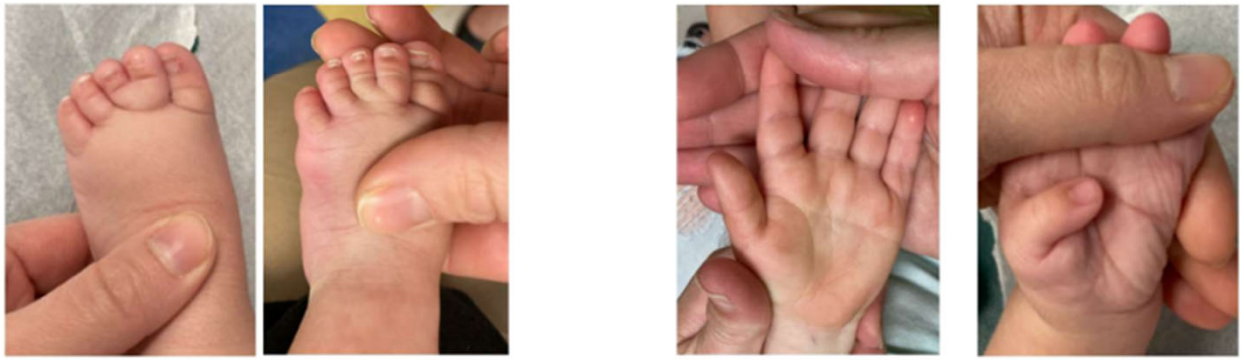
Courtesy of Karen Gripp, MD

NEMOURS CHILDREN'S HEALTH

SLOS



FFS



Courtesy of Karen Gripp, MD

Is there a fetal fentanyl syndrome?

	1	2	3	4	5 twin	6 twin	7	8	9	10	total
Sex	m	m	m	m	m	f	m	m	m	f	
Short nasal tip	+	+	+	+	+	+	+	+	+	+	10/10
Thin upper lip	+	+	+	+	+	+	+	+	+	-	9/10
Cleft palate	-	+	+	+	+	+	+	+	-	-	7/10
Micrognathia	+	+	+	+	+	+	+	+	+	+	10/10
Single palmar crease	+	+	+	+	+	+	+	+	+	+	10/10
Short, slightly broad adducted thumb	+	+	+	+	+	+	+	+	-	+	9/10
Foot position (talipes; rocker bottom)	t	-	t	t	r	r	-	r	-	-	3 t; 3r
2,3 toe syndactyly	+	+	+	+	+	+	+	-	-	+	8/10
Genital anomalies	+	-	+	+	+	-	+	+	-	-	6/10
Diffusely thin corpus callosum	-	-	+	+	+	?	+	-	-	+	5/9
Elevated 7,8 DHC; normalized later	-	+	+	+	?	?	+	+	+	+	7/8
Genetic testing non diagnostic	+	+	+	+	+	+	+	+	+	+	

Courtesy of Karen Gripp, MD

Evidence

- 10 children with shared facial and physical features
- Features suggestive of SLOS
- Abnormal 7, 8 DHC early, resolved later
- Non-diagnostic genetic testing
- Prenatal exposures with fentanyl due to opioid use disorder

Conclusions

- Fentanyl exposure during pregnancy MAY cause a distinctive pattern of anomalies (fetal fentanyl syndrome)
- Cannot rule out other substances or contaminants as causal
- More studies are needed

Fentanyl and Cholesterol

- Why do these children with prenatal exposure to fentanyl have features similar to Smith-Lemli-Opitz syndrome?
- Hypothesis: Fentanyl might disrupt 7-dehydro-cholesterol reductase (7DHCR)

Abstract presented at 2025 American College of Medical Genetics meeting

P216

The clinical spectrum of the fetal fentanyl syndrome in 23 cases

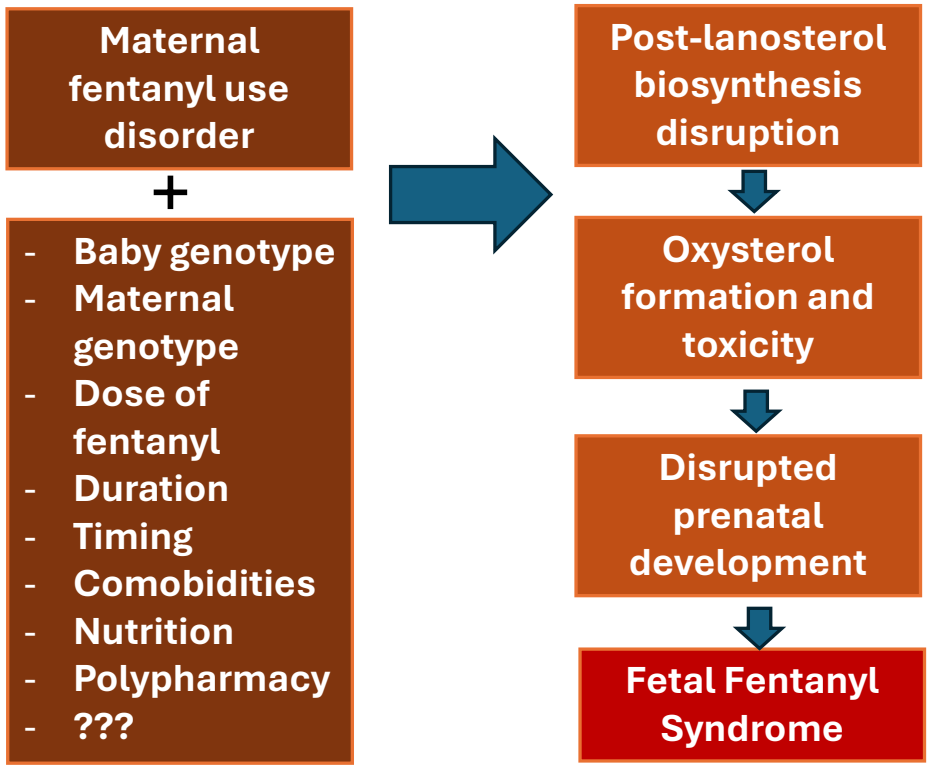
Álvaro Martín-Rodríguez[1], Adriana Gomes[1], Marilyn Jones[2], Lynne Bird[2], Miguel Del Campo[2]

[1]Department of Pediatrics, University of California San Diego; [2]Department of Pediatrics, University of California San Diego, Rady Children's Hospital

Conclusion: Prenatal exposure to Fentanyl may alter fetal growth and morphogenesis and most often affects growth and development in the postnatal period. Our case series supports the delineation of a novel syndrome associated with prenatal Fentanyl exposure. The Fetal Fentanyl Syndrome (FFS) is characterized by a distinctive combination of dysmorphic features, major malformations (cleft palate, club feet, hypospadias), feeding difficulties, growth deficits and developmental delays. Our results also indicate that there might be a Fetal Fentanyl Spectrum of Disorders (FFSD) that goes beyond FFS. Further studies are needed to better understand the variability of the consequences of the exposure to this newly recognized teratogen.

Inhibition of Post-Lanosterol Biosynthesis by Fentanyl

- *In vitro* exposure to fentanyl disrupted sterol biosynthesis
- Results suggested that maternal fentanyl use leads to fetal fentanyl syndrome through strong disruption of the post-lanosterol pathway
- Heterozygous DHCR7+/- cells were significantly more susceptible to the sterol biosynthesis inhibitory effects of fentanyl than wild-type DHCR7+/+ cells



Korade et al.,. *Molec Psychiatr* 29:3942-3949, 2024

Can We Use Advances in Data Mining to Identify Teratogens More Quickly?

Big Data Appr**O**aches f**O**r **S**afe **T**herapeutics in **H**ealthy **P**regnancy

Scanning for teratogenic effects of medications

BOOST-HP

CoDES
CENTER FOR DRUG EVALUATION & SAFETY

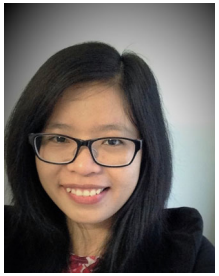
UF

JOHNS HOPKINS
MEDICINE


Almut Winterstein
RPh, PhD, FISPE,MPI


Judy Maro
PhD, MPI


Sonja Rasmussen
MD, MS


Thuy Thai
MS, PhD


Earl Morris
PharmD, MS, PhD


Nicole Smolinski
PharmD, PhD

Expert Panelists

- Margaret Adam
- David Aronoff
- Christina Chambers
- Claire Coles
- Jan Friedman
- Julie Kable
- Emily Oken


Yanning Wang
MPH


Celeste Ewig.
PharmD


Yehua Wang
MS


Carl Henricksen
MS

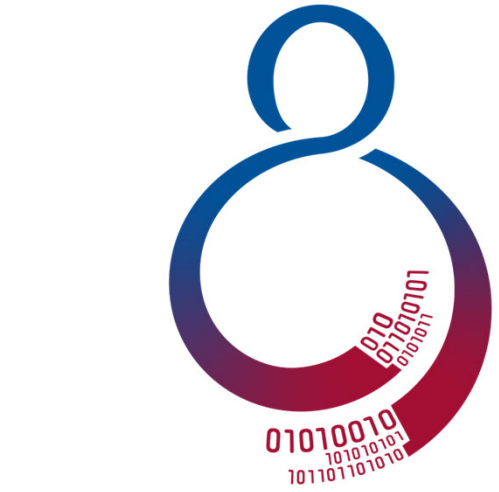
NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

Healthy pregnancies. Healthy children. Healthy and optimal lives.

Slides courtesy of Almut Winterstein, RPh, PhD, FISPE

BOOST-HP: Long-term goal

To build a reusable, scalable approach and infrastructure to accelerate evidence generation on the safety and effectiveness of medication use during pregnancy. By leveraging data-mining methodologies successfully deployed in public health surveillance along with infrastructure used by multiple federal government agencies, we will focus research efforts on novel, high-priority signals that pose the greatest risk to healthy pregnancies.



Aims

BOOST-HP

- **Aim 1**: To scan for associations between

  (1a) the 50 most prevalent drugs in pregnancy with incomplete information on teratogenic risk and a broad selection of live birth adverse outcomes

  (1b) pregnancy loss and antecedent prenatal exposures on the individual drug, chemical and therapeutic class level

  (1c) to prioritize signals via expert panel review

- **Aim 2**: To employ careful pharmacoepidemiologic designs to evaluate the two top prioritized signals

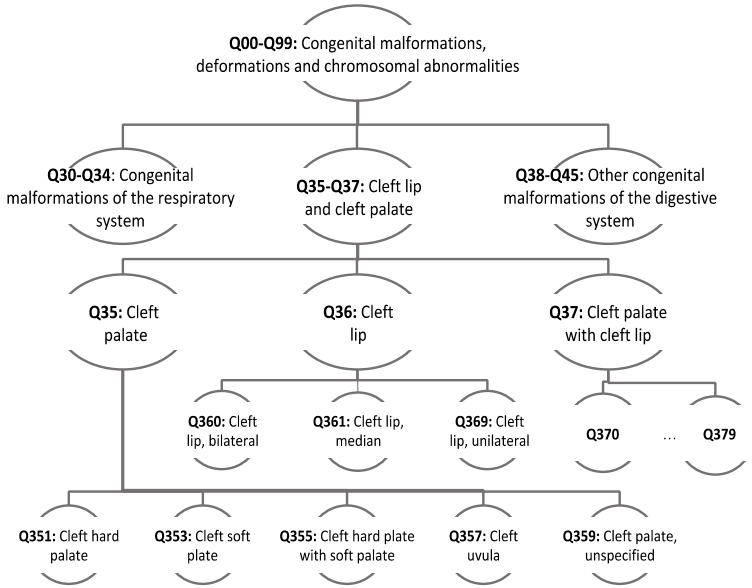
TreeScan™

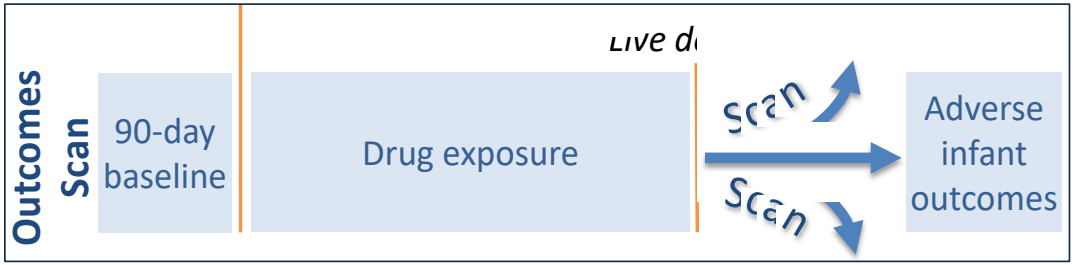
- Signal identification method that can evaluate thousands of outcomes simultaneously to identify potential adverse events
- Does not require selecting a specific exposure-outcome pairing for hypothesis testing
- Automatically adjusts for multiple scenarios

Kulldorff, Biometrics, 2003; Kulldorff, PDS 2013; Maro *EGEMS* 2017; https://www.treescan.org/


Treescan helps to find a needle in a haystack.

TreeScan™ Outcome scans





- Thousands of outcomes are organized in a hierarchical tree using existing Multi-Level Clinical Classification Software (MLCCS)
  - Major malformations; small for gestational age, preterm, neonatal seizures, pneumonia, NICU admission
- Observed and expected event counts (based on rates of a control group) in the exposure group are calculated for each node.
- Hypothesis testing at multiple levels; one-sided test.
  - H_o: for all nodes on the tree, an outcome is expected to occur in proportion to the underlying expected count of that node
  - H_a: ≥1 node on the tree occurs with higher probability than the specified expected counts of those nodes

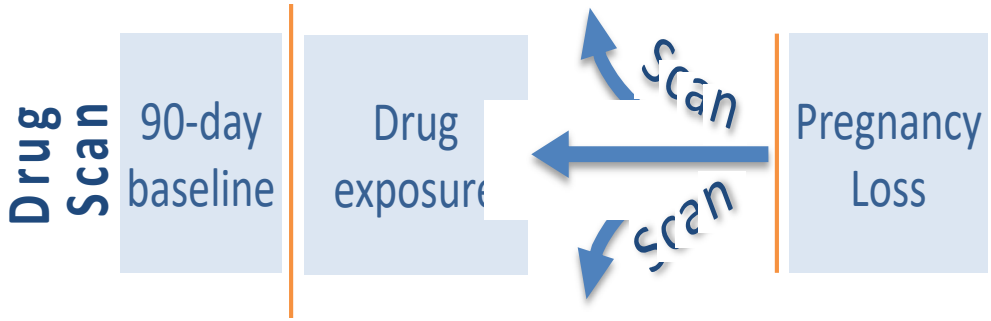
Potential Teratogen List

BOOST-HP

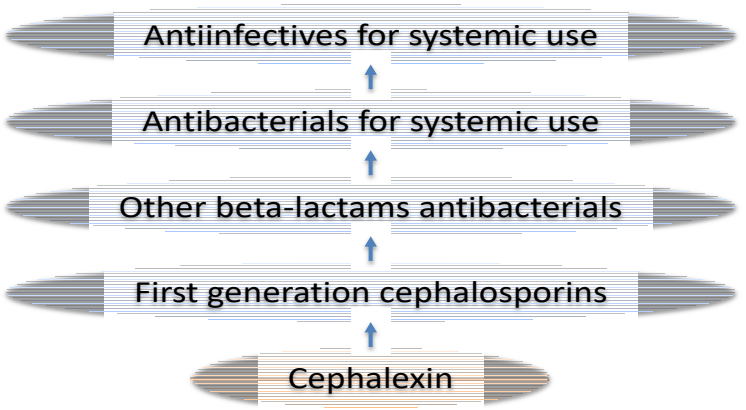
Selected based on comprehensive review of existing evidence and prevalence of use during pregnancy

ALENDRONATE	CEFPROZIL	FLECANIDE	LEUPRORELIN	RISEDRONATE
ALLOPURINOL	CEFUROXIME	FLUPHENAZINE	LEVOFLOXACIN	RIZATRIPTAN
ALPROSTADIL	CELECOXIB	FORMOTEROL	LISDEXAMFETAMINE	SIMVASTATIN
AMLODIPINE	CHENODIOL	FORMOTEROL; BUDESONIDE	MACROGOL	SODIUM SULFATE
ARIPIPRAZOLE	CICLOSPORIN	FUROSEMIDE	MEPHOBARBITAL	SPIRONOLACTONE
AZELASTINE	CLINDAMYCIN	GENTAMICIN	METHIMAZOLE	SUCRALFATE
BACLOFEN	CLONIDINE	KETOROLAC	METHYLERGOMETRINE	TAMSULOSIN
BETAMETHASONE	CYCLOBENZAPRINE	OFLOXACIN	METYRAPONE	TELAVANCIN
BICALUTAMIDE	CYCLOSPORINE	OLOPATADINE	MINOCYCLINE	TERCONAZOLE
BUSPIRONE	CYPROHEPTADINE	OSPEMIFENE	MONTELUKAST	TERIFLUNOMIDE
CABERGOLINE	DENOSUMAB	OXCARBAZEPINE	MOXIFLOXACIN	TINIDAZOLE
CARISOPRODOL	DESVENLAFAXINE	OXYBUTYNIN	NIFEDIPINE	TIZANIDINE
CEFADROXIL	DIPHENOXYLATE	POLYMYXIN B	NORTRIPTYLINE	TOBRAMYCIN
CEFDINIR	ELETRIPTAN	POTASSIUM IODIDE	RALOXIFENE	TRAMADOL
CEFIXIME	ERGOTAMINE	PROPYLTHIOURACIL	RETINOL	VARENICLINE
CEFPODOXIME	FAMCICLOVIR	RABEPRAZOLE	RIBAVIRIN	VERAPAMIL

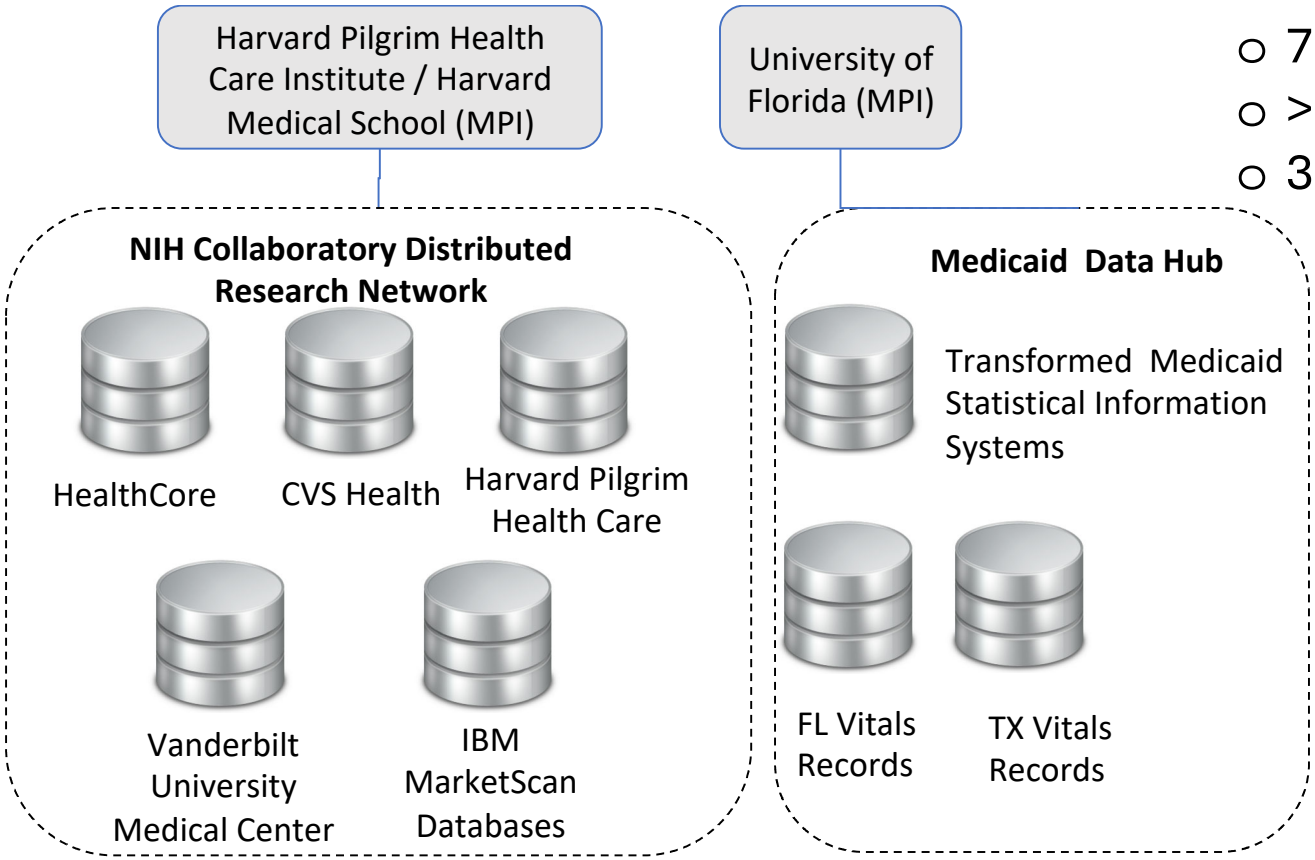
Drug Scan



- For evaluation of drugs associated with pregnancy loss, the original Treescan methodology was converted into a drug scan: single outcome – many exposures
- Drugs are organized in hierarchical fashion using ATC classification

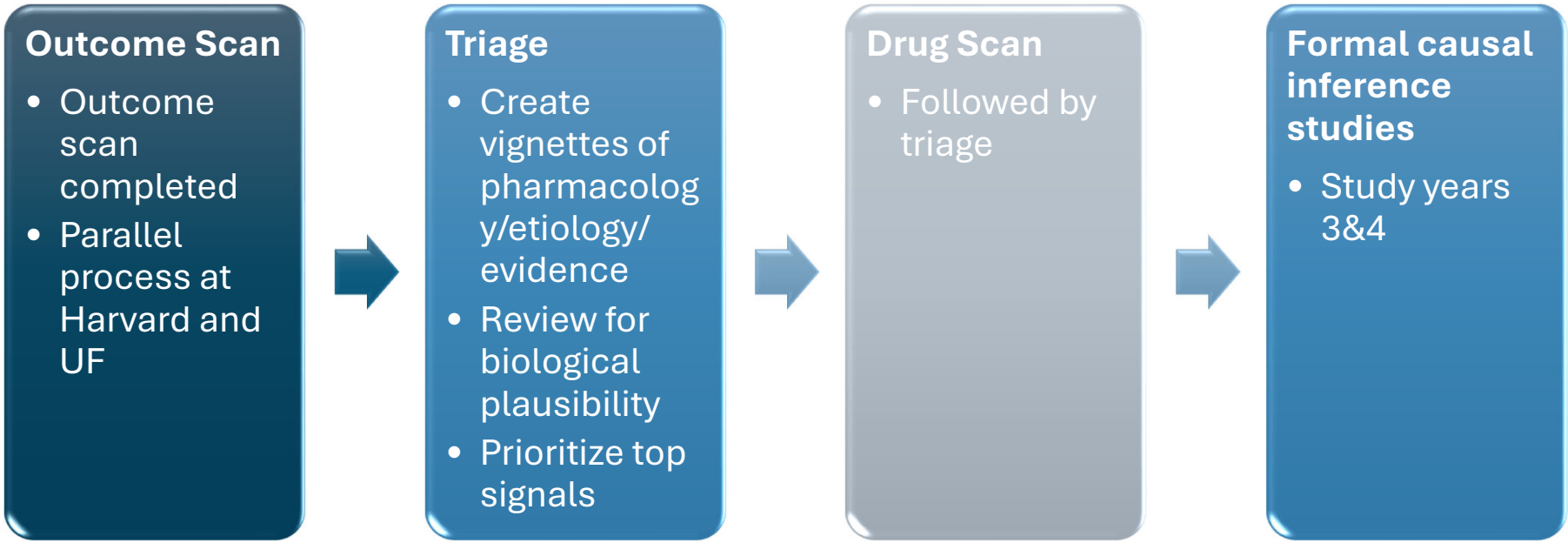


Data sources



- 7 million live deliveries
- >1 million miscarriages
- 30,000 stillbirths

Study plan


Outcome Scan
• Outcome scan completed
• Parallel process at Harvard and UF
Triage
• Create vignettes of pharmacology/etiology/ evidence
• Review for biological plausibility
• Prioritize top signals
Drug Scan
• Followed by triage
Formal causal inference studies
• Study years 3&4

Signals Selected by Expert Panel for Formal Study

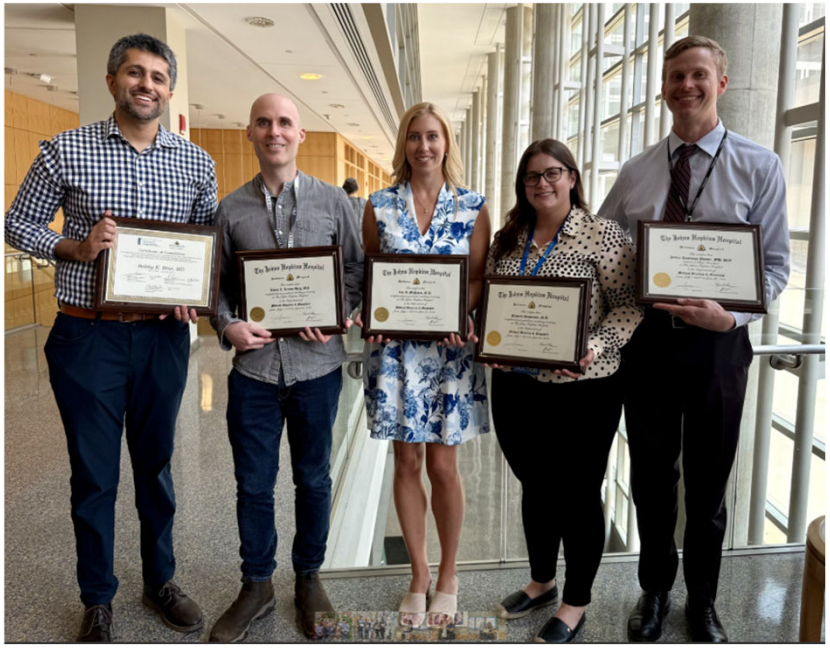
Drug	Outcome
Montelukast	All other congenital musculoskeletal deformities
Montelukast	Congenital anomalies of limbs
Montelukast	Congenital anomalies of nervous system
Montelukast	Other bulbus cordis anomalies and anomalies of cardiac septal closure and connections
ACEI Combinations, ACEIs, ARBs	Pregnancy loss
Amlodipine	Low birthweight / Small for gestational age / Fetal growth problems
Cefpodoxime	Short gestation; low birth weight
Eye/ear fluoroquinolones	Other musculoskeletal anomalies
Fluoroquinolones	Pregnancy loss
Formoterol	Other circulatory congenital anomalies
Furosemide	Pregnancy loss
Gentamicin	Tetralogy of Fallot
Indomethacin	Pregnancy loss
Nifedipine	Other circulatory anomalies
Nifedipine	Neonatal Jaundice Associated with Preterm Delivery
Nifedipine	NICU Admissions
Rizatriptan	Pregnancy loss
Semaglutide	Pregnancy loss
Terbinafine	Pregnancy loss
Travopost	Pregnancy loss

Challenges to Identifying Teratogens

- Are we training future “astute clinicians”?
- Impact of the Dobbs decision on women’s interest in engaging in pregnancy-related research
- Funding cuts to research
- Staffing cuts at federal agencies

Are we training future “astute clinicians”?

- Fellowship Match – Medical Genetics
  - Medical Genetics fellowship match in 2024 - 51.2% of fellowship positions filled
  - The specialty with the highest % of positions filled by non-U.S. citizen graduates of international medical schools (54.5 percent) is Medical Genetics
- Decreasing attendance at BDRP meetings by physicians



Impact of the Dobbs Decision on Women's Interest in Engaging in Pregnancy-related Research

Received: 16 October 2023 | Revised: 8 April 2024 | Accepted: 12 April 2024

DOI: 10.1111/ppe.13080

WILEY

BRIEF REPORT

Evaluating participant engagement in a preconception cohort study in relation to the *Dobbs* decision

Mary D. Willis[1] | Molly N. Hoffman[1] | Tanran R. Wang[1] | Erika L. Sabbath[2] | Andrea S. Kuriyama[1] | Amelia K. Wesselink[1] | Lauren A. Wise[1]

Likelihood of Clicking on Link to Fertility App Invitation before or after Dobbs Decision

Type of state	Before	After	Adjusted change* Difference (95%CI)
State-level protected abortion rights	182 (57.7)	156 (57.7)	0.37 (-10.28, 11.01)
State-level limited abortion access	55 (47.3%)	50 (56%)	9.11 (-10.67, 28.89)
State-level abortion bans or restricted abortion rights	84 (63.1%)	58 (36.2%)	-27.12 (-43.68, -10.57)

*Adjusted for age and parity

Funding Cuts to Research

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June 03, 2025

Details of Trump's Budget Cuts Alarm Researchers

The billions in proposed funding cuts would involve restructuring and consolidating the National Institutes of Health and slashing the majority of the National Science Foundation's budget for scholarships and fellowships.

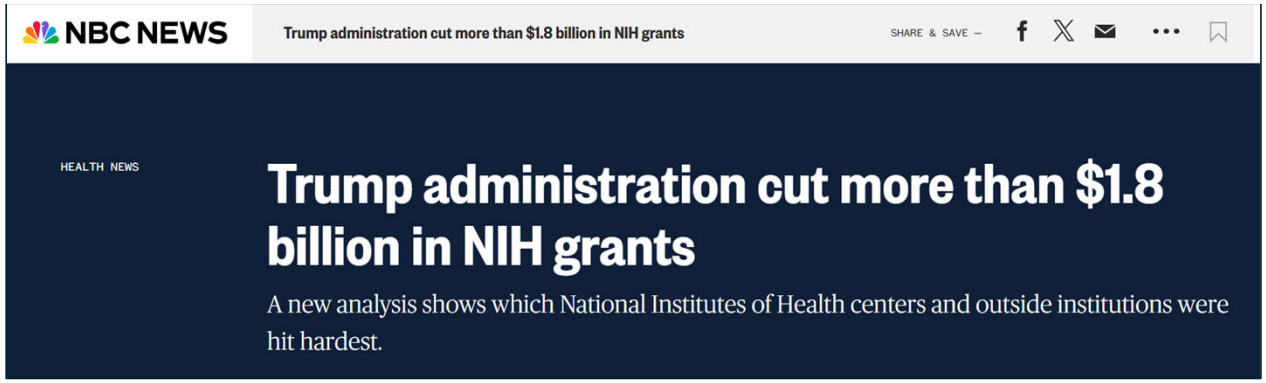
By Kathryn Palmer

STAT+ | POLITICS

NIH details how Trump budget would cut support for grants, training, and research centers

Nearly 1,800 fewer new grants would be awarded under 2026 spending plan

By Jonathan Wosen and Daniel Payne June 6, 2025


NBC NEWS
Trump administration cut more than $1.8 billion in NIH grants
SHARE & SAVE –
HEALTH NEWS
Trump administration cut more than $1.8 billion in NIH grants
A new analysis shows which National Institutes of Health centers and outside institutions were hit hardest.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COMMENTARY
The Trump administration's NIH and FDA cuts will negatively impact patients


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Editorial: US science-funding cuts—Are we throwing the baby out with the bathwater?
Spending reductions could negatively affect US scientific advancement and global competitiveness
by C&EN editorial staff
February 11, 2025

PBS NEWS

Menu

Researchers warn U.S. is on the 'precipice' of brain drain as Trump cuts federal grants

Dr. Josef Warkany

He stayed 60 years. Dr. Warkany remarked that he never left Cincinnati because

> As a resident in Vienna, I had the good fortune to land in a small babies' hospital that had a sunny laboratory with many shiny bottles. The Chief, who was strongly in favor of research, had to approve additional supplies and chemicals. It was a time when vitamin D concentrates became available and spectacular cures of rickets could be achieved. How did these compounds cure rickets? I was able to acquire a rabbit and study the increase in blood phosphorous levels after a single dose of sodium phosphate and could repeat the experiment after the rabbit had been saturated with irradiated ergosterol. There was a marked increase in the rise of these phosphatemic curves, and I was jubilant, thinking I had solved the riddle of vitamin D action. I was ready to publish this work when one of my mentors suggested I repeat the experiment with another rabbit. So I approached the Chief and said, 'Herr Professor, I need a rabbit.' Whereupon his amicable attitude changed to indignation and he said, 'But you already have one.'

In America, he was given 12 rabbits instead of the one rabbit he had in Austria.

Willhite C. *Toxicol Sci* 58:220-221, 2000

Staffing cuts at federal agencies

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Special Reports > Features

Nearly Half of CDC Birth Defects and Disabilities Staff Cut

— Programs in blood disorders, Special Olympics affected

by Cheryl Clark, Contributing Writer, MedPage Today
April 10, 2025 · 3 min read

Reuters

World · Business · Markets · Sustainability · Legal · More

Trump begins mass layoffs at FDA, CDC, other US health agencies

By Leah Douglas, Marisa Taylor and Julie Steenhuysen
April 1, 2025 5:44 PM EDT · Updated 2 months ago

Summary

- FDA's tobacco chief fired, new drugs regulator quits
- Some employees turned away at building doors, sources say
- Former commissioner Califf says "FDA as we've known it is finished"

The Atlanta Journal-Constitution

OPINION

Cuts at CDC birth defect center will harm millions

Protecting children from preventable birth defects and disabilities must remain a national priority

By José Cordero, Coleen Boyle and Edwin Trevathan – contributors

April 24, 2025

José F. Cordero, MD, MPH

English Edition

Invitations Dr. S Rasmussen

Medscape Tuesday, June 17, 2025

Medscape

COMMENTARY

Why Is Oropouche Spreading so Fast?

Robert D. Glatter, MD; Julia Sader Neves Ferreira, MD

DISCLOSURES | May 19, 2025

13 757

Add to Email Alerts

WHO warns of ORVO as outbreaks surge and health risks rise

Download PDF Copy

By Hugo Francisco de Souza

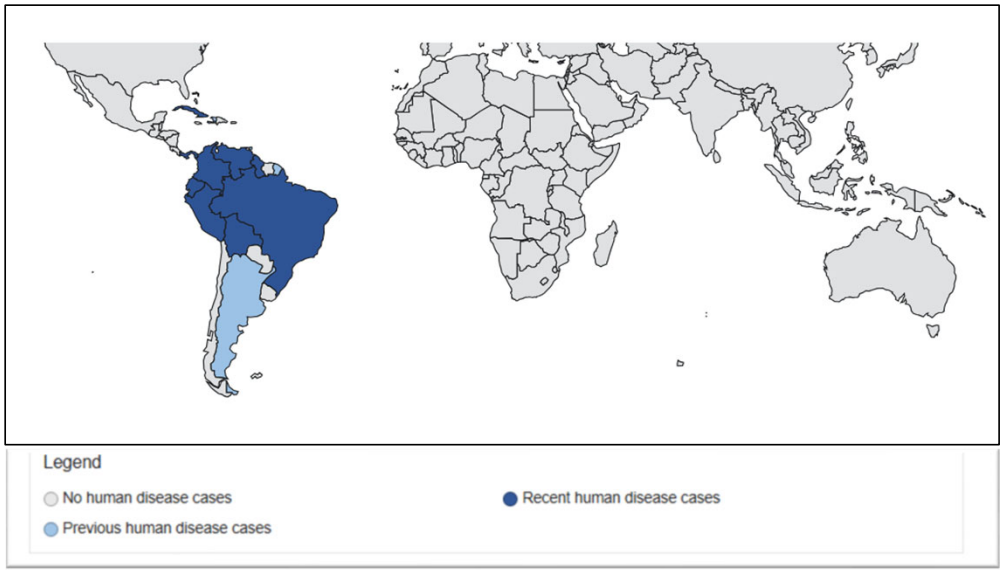
Reviewed by Lauren Hardaker

Jun 13 2025

As Oropouche virus outbreaks sweep Brazil, Cuba, and beyond, a major WHO report warns that this overlooked tropical disease could be the next global health emergency.

Oropouche Virus

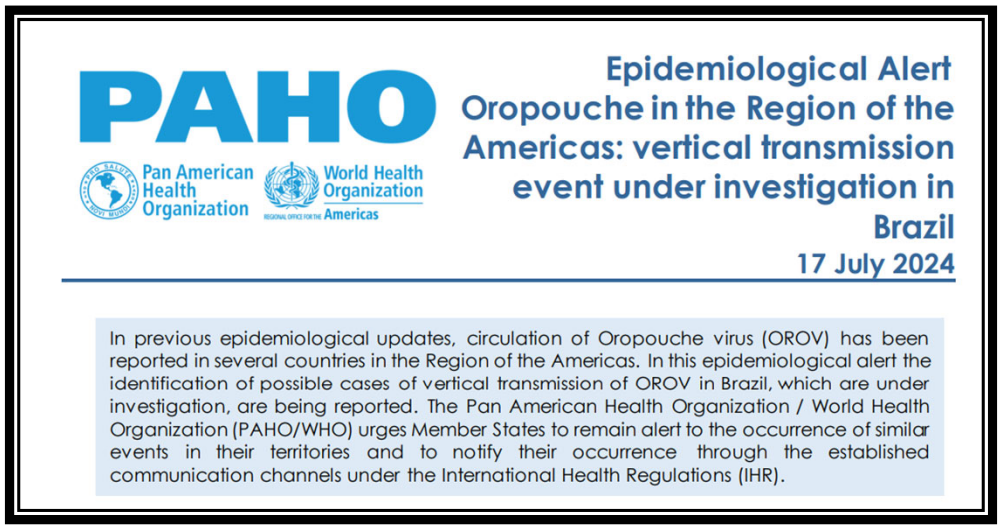
- Reported in parts of South America, Central America, and the Caribbean, including Cuba
- Transmitted by biting midges and some mosquitoes - ?sexual transmission
- Presents as abrupt onset of fever, severe headache, chills, myalgia, arthralgia
- Vertical transmission has been associated with adverse pregnancy outcomes including fetal deaths and congenital abnormalities



https://www.cdc.gov/oropouche/data-maps/countries-and-territories-at-risk-for-oropouche.html

Oropouche Infection during Pregnancy

- Brazil has reported cases of Oropouche virus being passed from pregnant person to their fetus – possibly resulting in fetal deaths and birth defects
- This led to publication of an Epidemiological Alert by PAHO in July of 2024
- The risk of an infected person passing the virus to their fetus is not currently known



PAHO

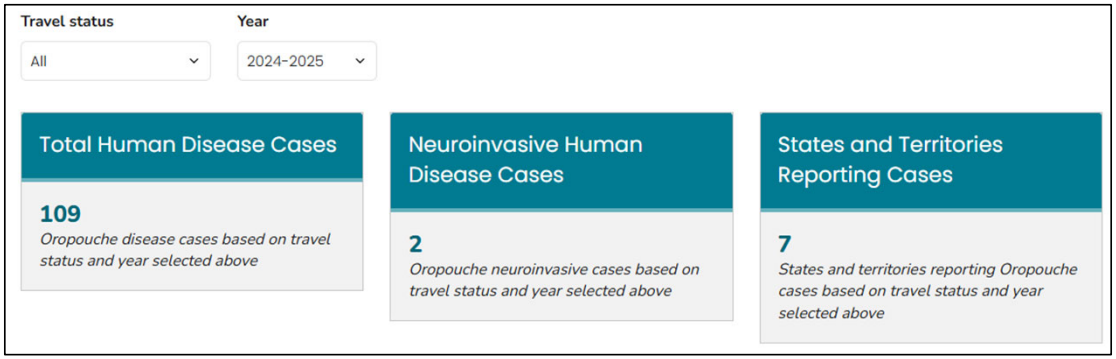
Pan American Health Organization

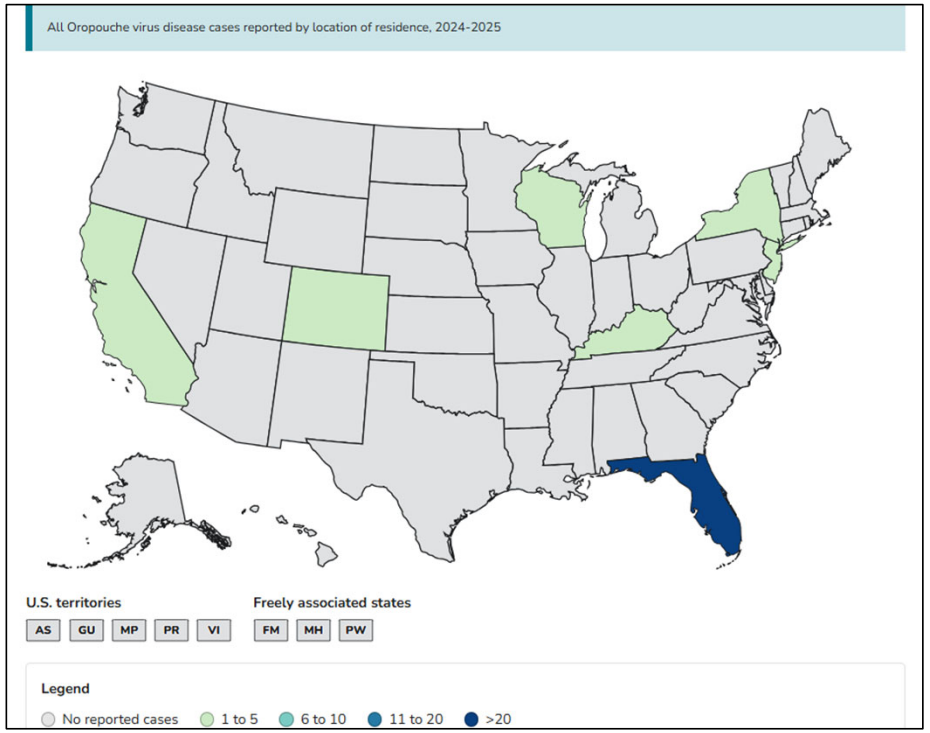
World Health Organization Americas

Epidemiological Alert
Oropouche in the Region of the Americas: vertical transmission event under investigation in Brazil
17 July 2024

In previous epidemiological updates, circulation of Oropouche virus (OROV) has been reported in several countries in the Region of the Americas. In this epidemiological alert the identification of possible cases of vertical transmission of OROV in Brazil, which are under investigation, are being reported. The Pan American Health Organization / World Health Organization (PAHO/WHO) urges Member States to remain alert to the occurrence of similar events in their territories and to notify their occurrence through the established communication channels under the International Health Regulations (IHR).

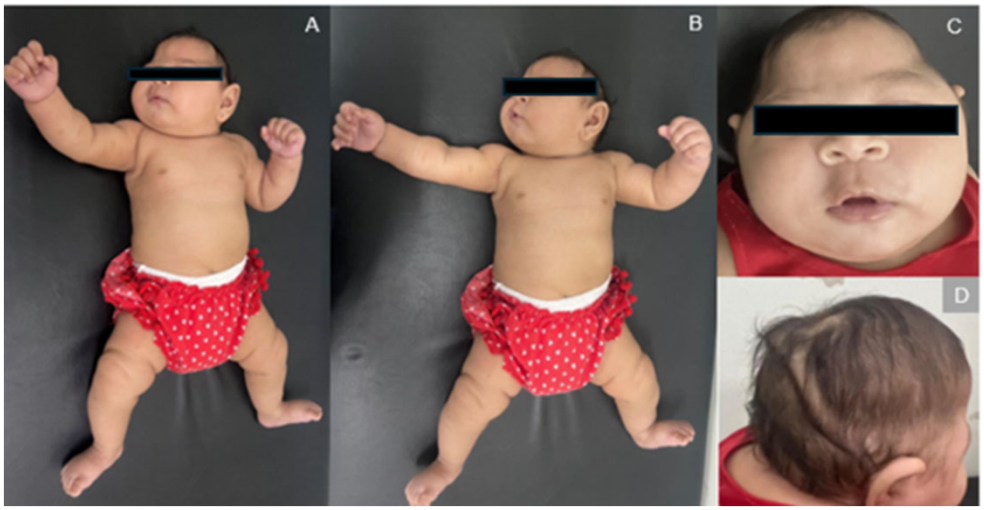
Oropouche Virus in the United States





https://www.cdc.gov/oropouche/data-maps/current-year-data.html

Oropouche Virus: Possible New Teratogenic Syndrome



Photos courtesy of Lavinia Schuler-Faccini, MD, PhD

viruses

MDPI

Case Report

Congenital Oropouche in Humans: Clinical Characterization of a Possible New Teratogenic Syndrome

Bethânia de Freitas Rodrigues Ribeiro [1], André Rodrigues Façanha Barreto [2], André Pessoa [3], Raimunda do Socorro da Silva Azevedo [4], Flávia de Freitas Rodrigues [5], Bruna da Cruz Beyruth Borges [1], Natália Pimentel Moreno Mantilla [1], Davi Dantas Muniz [6], Jannifer Oliveira Chiang [4], Lucas Rosa Fraga [7,8,9], Fernanda Sales Luiz Vianna [8,9,10], Maria Teresa Vieira Sanseverino [8,10,11], Lilith Schuler Faccini [9], Fernanda Eduarda das Neves Martins [12], Rafael da Silva Azevedo [13], Lívia Carício Martins [4], Livia Medeiros Neves Casseb [4], Consuelo Silva Oliveira [4], Pedro Fernando da Costa Vasconcelos [4,14], Juarez Antônio Simões Quaresma [15], Alberto Mantovani Abeche [8,16], Vania de Mesquita Gadelha Prazeres [10,17], Lucia Andreia Nunes de Oliveira [18], Simone de Menezes Karam [19], Giulia Radin [8], Miguel Del Campo [20], Camila V. Ventura [21] and Lavinia Schuler-Faccini [8,10,18,22,*]

The newborns presented with severe microcephaly secondary to brain damage and arthrogryposis, suggestive of an embryo/fetal disruptive process at birth. Brain and spinal images identified overlapping sutures, cerebral atrophy, brain cysts, thinning of the spinal cord, corpus callosum, and posterior fossa abnormalities. Fundoscopic findings included macular chorioretinal scars, focal pigment mottling, and vascular attenuation. The clinical presentation of vertical OROV infection resembled congenital Zika syndrome to some extent but presents some distinctive features on brain imaging and in several aspects of its neurological presentation**. A recognizable syndrome with severe brain damage, neurological alterations, arthrogryposis, and fundoscopic abnormalities can be associated with in utero OROV infection.**

“I am only one, but I am one. I cannot do everything, but I can do something. And because I cannot do everything, I will not refuse to do the something that I can do.”

Edward Everett Hale

NBC NEWS Researchers have a radical plan to thwart Trump's war on science: Talking to people SHARE & SAVE

U.S. NEWS

Researchers have a radical plan to thwart Trump's war on science: Talking to people

Faced with federal funding cuts, scientists are learning to communicate about what they do – and why it matters.

A host of new programs aims to build excitement about science at a time when research is under attack. Nicolas Ortega for NBC News

Acknowledgments

- Dr. Jan Friedman, University of British Columbia
- Dr. Karen Gripp, Nemours
- Dr. Almut Winterstein, University of Florida
- Dr. Judy Maro, Harvard
- Dr. Lavinia Schuler Faccini, Brazilian Teratogen Information System

Questions

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