X-LINKED ADRENOLEUKODYSTROPHY

A 3-in-1 Medical Reference

A Bibliography and Dictionary
for Physicians, Patients,
and Genome Researchers

TO INTERNET REFERENCES

ICON Group International, Inc.

X-Linked Adrenoleukodystrophy

A Bibliography and Dictionary for Physicians, Patients, and Genome Researchers

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and Philip M. Parker, Ph.D., Editors

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FORWARD

In March 2001, the National Institutes of Health issued the following warning: "The number of Web sites offering health-related resources grows every day. Many sites provide valuable information, while others may have information that is unreliable or misleading."[1] Furthermore, because of the rapid increase in Internet-based information, many hours can be wasted searching, selecting, and printing. Since only the smallest fraction of information dealing with X-linked adrenoleukodystrophy is indexed in search engines, such as **www.google.com** or others, a non-systematic approach to Internet research can be not only time consuming, but also incomplete. This book was created for medical professionals, students, and members of the general public who want to know as much as possible about X-linked adrenoleukodystrophy, using the most advanced research tools available and spending the least amount of time doing so.

In addition to offering a structured and comprehensive bibliography, the pages that follow will tell you where and how to find reliable information covering virtually all topics related to X-linked adrenoleukodystrophy, from the essentials to the most advanced areas of research. Special attention has been paid to present the genetic basis and pattern of inheritance of X-linked adrenoleukodystrophy. Public, academic, government, and peer-reviewed research studies are emphasized. Various abstracts are reproduced to give you some of the latest official information available to date on X-linked adrenoleukodystrophy. Abundant guidance is given on how to obtain free-of-charge primary research results via the Internet. **While this book focuses on the field of medicine, when some sources provide access to non-medical information relating to X-linked adrenoleukodystrophy, these are noted in the text.**

E-book and electronic versions of this book are fully interactive with each of the Internet sites mentioned (clicking on a hyperlink automatically opens your browser to the site indicated). If you are using the hard copy version of this book, you can access a cited Web site by typing the provided Web address directly into your Internet browser. You may find it useful to refer to synonyms or related terms when accessing these Internet databases. **NOTE:** At the time of publication, the Web addresses were functional. However, some links may fail due to URL address changes, which is a common occurrence on the Internet.

For readers unfamiliar with the Internet, detailed instructions are offered on how to access electronic resources. For readers unfamiliar with medical terminology, a comprehensive glossary is provided. We hope these resources will prove useful to the widest possible audience seeking information on X-linked adrenoleukodystrophy.

The Editors

[1] From the NIH, National Cancer Institute (NCI): **http://www.cancer.gov/**.

CHAPTER 1. STUDIES ON X-LINKED ADRENOLEUKODYSTROPHY

Overview

In this chapter, we will show you how to locate peer-reviewed references and studies on X-linked adrenoleukodystrophy. For those interested in basic information about X-linked adrenoleukodystrophy, we begin with a condition summary published by the National Library of Medicine.

Genetics Home Reference

Genetics Home Reference (GHR) is the National Library of Medicine's Web site for consumer information about genetic conditions and the genes or chromosomes responsible for those conditions. Here you can find a condition summary on X-linked adrenoleukodystrophy that describes the major features of the condition, provides information about the condition's genetic basis, and explains its pattern of inheritance. In addition, a summary of the gene or chromosome related to X-linked adrenoleukodystrophy is provided.[2]

The Genetics Home Reference has recently published the following summary for X-linked adrenoleukodystrophy:

What Is X-Linked Adrenoleukodystrophy?[3]

X-linked adrenoleukodystrophy is a disorder that mainly affects the nervous system and the adrenal glands (small glands located on top of each kidney). People with this disorder often have progressive destruction of the fatty covering (myelin) that insulates nerves in the brain and spinal cord. They may also have hormone deficiencies caused by damage to the outer

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[2] This section has been adapted from the National Library of Medicine: **http://ghr.nlm.nih.gov/**.

[3] Adapted from the Genetics Home Reference of the National Library of Medicine: **http://ghr.nlm.nih.gov/condition=xlinkedadrenoleukodystrophy**.

layer of the adrenal glands (adrenal cortex). This hormonal deficiency is also known as adrenocortical insufficiency.

In males, there are three distinct types of X-linked adrenoleukodystrophy: a childhood cerebral form, adrenomyeloneuropathy, and a type called Addison disease only. Male children with the cerebral form of this disorder experience learning and behavioral problems that usually appear by age 10. Over time the symptoms worsen and these children may have difficulty reading, writing, understanding speech, and comprehending written material. They may also exhibit aggressive behavior and have vision problems. Most affected individuals also have impaired adrenal gland function. The rate at which this disorder progresses is variable; however, total disability within several years is not uncommon.

Signs and symptoms of the adrenomyeloneuropathy type appear in men anytime between their twenties and middle age. These men develop progressive stiffness and weakness in their legs (paraparesis), urinary disorders, and often show some degree of brain involvement. Most men with this disorder also have adrenocortical insufficiency.

The Addison disease only form affects approximately 10 percent of males with X-linked adrenoleukodystrophy. This form is characterized primarily by adrenocortical insufficiency, which may result in unexplained weakness, weight loss, skin changes, vomiting, and coma. Most men with this condition eventually develop all of the signs of adrenomyeloneuropathy by the time they reach middle age.

Females are affected by X-linked adrenoleukodystrophy far less often than males. When females do have signs of this disorder, they are usually similar to the adrenomyeloneuropathy type, although they rarely exhibit impaired adrenal gland function. In rare cases, females have signs of the childhood cerebral form of this condition.

How Common Is X-Linked Adrenoleukodystrophy?

The prevalence of X-linked adrenoleukodystrophy is approximately 1 in 20,000 individuals. This condition occurs with a similar frequency in all populations.

What Genes Are Related to X-Linked Adrenoleukodystrophy?

Mutations in the **ABCD1** (**http://ghr.nlm.nih.gov/gene=abcd1**) gene cause X-linked adrenoleukodystrophy.

Mutations in the ABCD1 gene cause a shortage (deficiency) of a cellular transporter known as adrenoleukodystrophy protein. This protein is thought to play a role in the breakdown of certain fats (very long-chain fatty acids or VLCFAs) inside peroxisomes. Peroxisomes are small sacs in the cell that process many types of molecules. When this transporter is lacking, the breakdown of very long-chain fatty acids is compromised and results in abnormally high levels of these fats in the body. Research suggests that the accumulation of very long-chain fatty acids is toxic to the adrenal cortex and the myelin membranes that surround many of the nerves in the brain and spinal cord.

How Do People Inherit X-Linked Adrenoleukodystrophy?

This condition is inherited in an X-linked recessive pattern. A condition is considered X-linked if the mutated gene that causes the disorder is located on the X chromosome, one of the two sex chromosomes. In males (who have only one X chromosome) one altered copy of the gene in each cell is sufficient to cause the condition. Males are affected by X-linked recessive disorders much more frequently than females. A striking characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

All of the daughters of a male with an X-linked disorder will inherit the gene mutation. These females are called carriers because they carry one copy of the altered gene. In females (who have two X chromosomes), a mutation must usually be present in both copies of the gene to cause the disorder. In some cases, however, females who are carriers of a gene mutation on the X chromosome will exhibit signs and symptoms of a disorder beginning in adulthood.

Where Can I Find Additional Information about X-Linked Adrenoleukodystrophy?

You may find the following resources about X-linked adrenoleukodystrophy helpful. These materials are written for the general public.

NIH Publications - National Institutes of Health

- National Center for Biotechnology Information: Genes and Disease:
  http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View.ShowSection&rid=gnd.section.226
- NINDS Adrenoleukodystrophy Information Page:
  http://www.ninds.nih.gov/disorders/adrenoleukodystrophy/adrenoleukodystrophy.ht

MedlinePlus - Health Informationm

- Encyclopedia: Adrenoleukodystrophy:
  http://www.nlm.nih.gov/medlineplus/ency/article/001182.htm
- Health Topic: Adrenal Gland Disorders:
  http://www.nlm.nih.gov/medlineplus/adrenalglanddisorders.html
- Health Topic: Endocrine Diseases:
  http://www.nlm.nih.gov/medlineplus/endocrinediseases.html
- Health Topic: Leukodystrophies:
  http://www.nlm.nih.gov/medlineplus/leukodystrophies.html

Educational Resources - Information Pages

- Kennedy Krieger Institute:
  http://www.kennedykrieger.org/kki_diag.jsp?pid=1069

- Madisons Foundation:
  http://www.madisonsfoundation.org/content/3/1/display.asp?did=281
- Orphanet:
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=43

Patient Support - for Patients and Families

- National Organization for Rare Disorders:
  http://www.rarediseases.org/search/rdbdetail_abstract.html?disname=Adrenoleukodystrophy
- The Adrenoleukodystrophy Foundation:
  http://www.aldfoundation.org/
- United Leukodystrophy Foundation:
  http://www.ulf.org/

Professional Resources

You may also be interested in these resources, which are designed for healthcare professionals and researchers.

- Gene Reviews - Clinical summary:
  http://www.genetests.org/query?dz=x-ald
- Gene Tests - DNA tests ordered by healthcare professionals:
  http://www.genetests.org/query?testid=2298
- ClinicalTrials.gov - Linking patients to medical research:
  http://clinicaltrials.gov/search/condition=%22x-linked+adrenoleukodystrophy%22?recruiting=false
- PubMed - Recent literature:
  http://ghr.nlm.nih.gov/condition=xlinkedadrenoleukodystrophy/show/PubMed;jsessionid=33A91175C386E8C89CB0C37834817780
- OMIM - Genetic disorder catalog:
  http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=300100

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These sources were used to develop the Genetics Home Reference condition summary on X-linked adrenoleukodystrophy.

- Dubey P, Raymond GV, Moser AB, Kharkar S, Bezman L, Moser HW. Adrenal insufficiency in asymptomatic adrenoleukodystrophy patients identified by very long-chain fatty acid screening. J Pediatr. 2005 Apr;146(4):528-32. PubMed citation
- Jia Z, Pei Z, Li Y, Wei L, Smith KD, Watkins PA. X-linked adrenoleukodystrophy: role of very long-chain acyl-CoA synthetases. Mol Genet Metab. 2004 Sep-Oct;83(1-2):117-27. PubMed citation

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- Moser H, Dubey P, Fatemi A. Progress in X-linked adrenoleukodystrophy. Curr Opin Neurol. 2004 Jun;17(3):263-9. Review. PubMed citation
- Moser HW, Raymond GV, Lu SE, Muenz LR, Moser AB, Xu J, Jones RO, Loes DJ, Melhem ER, Dubey P, Bezman L, Brereton NH, Odone A. Follow-up of 89 asymptomatic patients with adrenoleukodystrophy treated with Lorenzo's oil. Arch Neurol. 2005 Jul;62(7):1073-80. PubMed citation
- Pohl A, Devaux PF, Herrmann A. Function of prokaryotic and eukaryotic ABC proteins in lipid transport. Biochim Biophys Acta. 2005 Mar 21;1733(1):29-52. Epub 2004 Dec 31. Review. PubMed citation
- Wanders RJ, Waterham HR. Peroxisomal disorders I: biochemistry and genetics of peroxisome biogenesis disorders. Clin Genet. 2005 Feb;67(2):107-33. Review. PubMed citation

A summary of the gene related to X-linked adrenoleukodystrophy is provided below:

What Is the Official Name of the ABCD1 Gene?[4]

The official name of this gene is "ATP-binding cassette, sub-family D (ALD), member 1."

ABCD1 is the gene's official symbol. The ABCD1 gene is also known by other names, listed below.

What Is the Normal Function of the ABCD1 Gene?

The ABCD1 gene provides instructions for producing one component of a transport protein that is located in the membrane surrounding peroxisomes. Peroxisomes are small sacs in the cell that process many types of molecules. This transport protein, known as adrenoleukodystrophy protein, joins with another identical or closely related protein to form a complete, functional transporter. The exact function of the adrenoleukodystrophy protein has not been determined. It is thought that this protein transporter is a necessary component for the breakdown of very long-chain fatty acids (VLCFAs) in peroxisomes.

What Conditions Are Related to the ABCD1 Gene?

X-Linked Adrenoleukodystrophy - Caused by Mutations in the ABCD1 Gene

More than 400 mutations have been identified that cause X-linked adrenoleukodystrophy. These mutations prevent the production of any adrenoleukodystrophy protein in about 70

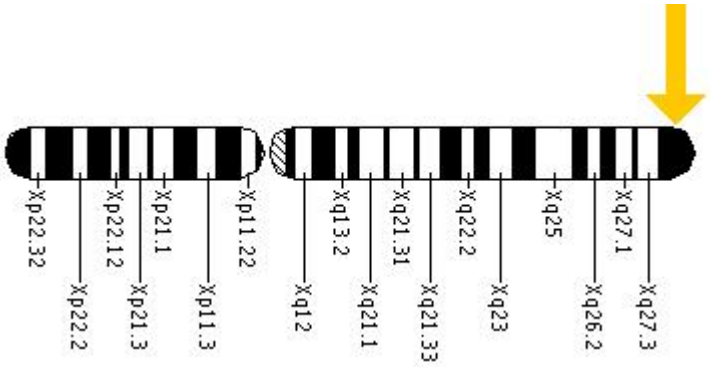
[4] Adapted from the Genetics Home Reference of the National Library of Medicine: **http://ghr.nlm.nih.gov/gene=abcd1;jsessionid=33A91175C386E8C89CB0C37834817780**.

percent of people with this disorder. Other people with this disorder have adrenoleukodystrophy protein present, but the protein is not able to perform its normal function. With little or no functional adrenoleukodystrophy protein, very long-chain fatty acids build up in the body. The accumulation of these fats is thought to be toxic to the adrenal glands (small glands on top of each kidney) and to the fatty layer of insulation (myelin) that surrounds many nerves in the body. The destruction of these tissues leads to the signs and symptoms of this disorder.

Where Is the ABCD1 Gene Located?

Cytogenetic Location: Xq28

Molecular Location on the X chromosome: base pairs 152,643,529 to 152,663,374



The ABCD1 gene is located on the long (q) arm of the X chromosome at position 28.

More precisely, the ABCD1 gene is located from base pair 152,643,529 to base pair 152,663,374 on the X chromosome.

References

These sources were used to develop the Genetics Home Reference gene summary on the ABCD1 gene.

- Entrez Gene
- Kemp S, Pujol A, Waterham HR, van Geel BM, Boehm CD, Raymond GV, Cutting GR, Wanders RJ, Moser HW. ABCD1 mutations and the X-linked adrenoleukodystrophy mutation database: role in diagnosis and clinical correlations. Hum Mutat. 2001 Dec;18(6):499-515. Review. PubMed citation
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- Pujol A, Ferrer I, Camps C, Metzger E, Hindelang C, Callizot N, Ruiz M, Pampols T, Giros M, Mandel JL. Functional overlap between ABCD1 (ALD) and ABCD2 (ALDR) transporters: a therapeutic target for X-adrenoleukodystrophy. Hum Mol Genet. 2004 Dec 1;13(23):2997-3006. Epub 2004 Oct 15. PubMed citation
- Wanders RJ, Waterham HR. Peroxisomal disorders I: biochemistry and genetics of peroxisome biogenesis disorders. Clin Genet. 2005 Feb;67(2):107-33. Review. PubMed citation
- X-linked Adrenoleukodystrophy Database

Federally Funded Research on X-Linked Adrenoleukodystrophy

The U.S. Government supports a variety of research studies relating to X-linked adrenoleukodystrophy. These studies are tracked by the Office of Extramural Research at the National Institutes of Health.[5]

CRISP (Computerized Retrieval of Information on Scientific Projects)

CRISP is a searchable database of federally funded biomedical research projects conducted at universities, hospitals, and other institutions. Search the CRISP Web site at **http://crisp.cit.nih.gov/crisp/crisp_query.generate_screen**. You will have the option to perform targeted searches by various criteria, including geography, date, and topics related to X-linked adrenoleukodystrophy.

For most of the studies, the agencies reporting into CRISP provide summaries or abstracts. As opposed to clinical trial research using patients, many federally funded studies use animals or simulated models to explore X-linked adrenoleukodystrophy. The following is typical of the type of information found when searching the CRISP database for X-linked adrenoleukodystrophy:

- **Project Title: FATTY ACID OXIDATION IN X-LINKED ADRENOLEUKODYSTROPHY**

  Principal Investigator & Institution: Singh, Inderjit; Scientific Director; Pediatrics; Medical University of South Carolina Charleston, Sc 29425

  Timing: Fiscal Year 2005; Project Start 09-SEP-1985; Project End 30-NOV-2006

  Summary: (provided by applicant): X-Adrenoleukodystrophy (X-ALD) is an inherited neurological disorder. Mutation/deletion of the ALD gene product (ALDP) results in deficient activity of lignoceroyl-CoA ligase, and 13-oxidation of VLC fatty acids which leads to the pathognomonic accumulation of VLC fatty acids with secondary inflammatory disease and loss o oligodendrocytes and dysmyelination/demyelination. The objective of this proposal is to determine the functional organization of ALDP/lignoceroyl-CoA ligase in peroxisomes, and to elucidate the molecular events responsible in VLC fatty acid-induced inflammatory disease leading to dysfunction/loss of oligodendrocytes. Studies are designed to determine the amino acid domains of

[5] Healthcare projects are funded by the National Institutes of Health (NIH), Substance Abuse and Mental Health Services (SAMHSA), Health Resources and Services Administration (HRSA), Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDCP), Agency for Healthcare Research and Quality (AHRQ), and Office of Assistant Secretary of Health (OASH).

ALDP that interact with lignoceroyl-CoA ligase for it's functional organization in the beta-oxidation of very long chain (VLC) fatty acids in peroxisomes and to elucidate the possible role of VLC fatty acid-induced derangements in the induction/propagation of neuroinflammatory disease and loss of oligodendrocytes in X-ALD. Studies are also designed to delineate the regulation of VLC fatty acid 13-oxidation and induction of expression of the ALD related gene product (ALDRP), an ALD related protein, for correction of the metabolic defect in X-ALD cultured skin fibroblasts and in tissues of ALD knockout mice. The proposed studies use state of the art techniques and will provide a better understanding of the regulation of VLC fatty acid metabolism in control and X-ALD and functional organization of ALDP/lignoceroyl-CoA ligase, and correction of the metabolic as well as the neuroinflammatory disease in X-ALD. We are very excited about the possibility that basic studies from our laboratory may become the basis for therapeutic approaches for X-ALD.

- **Project Title: GENETIC CAUSES OF MENTAL RETARDATION**

  Principal Investigator & Institution: Smith, Kirby D.; Associate Professor; Kennedy Krieger Research Institute, Inc. 707 North Broadway, Rm 614 Baltimore, Md 21205

  Timing: Fiscal Year 2005; Project Start 01-JAN-1978; Project End 31-DEC-2006

  Summary: For the past 15 years this Program has focused has focused on genetic disorders of peroxisome biogenesis and function. In recent years understanding of the biogenesis and metabolic functions of peroxisomes has expanded significantly. Thirteen of the known 16 peroxisomal genetic disorders manifest mental retardation but the connection between peroxisomal abnormality and mental retardation is still unknown. The peroxisome has been shown to have a much wider range of functions than has been recognized in the past. This Program Project has been characterized by a strong synergism between clinical and basic science and this interaction will continue. The projects and investigators of the proposed Program Project will interface with related basic research projects and with ongoing clinical trials (Moser). Our clinics have identified more than 5000 patients with peroxisomal disorders. While they continue to provide a framework for this proposal, new information will be derived from several mouse and yeast models of peroxisomal biogenesis, function and disease. The present proposal includes 4 projects in addition to administrative and clinical, biochemical, cell, and molecular cores. The first Project (Smith) will determine the function of the X-linked of the X-linked **adrenoleukodystrophy** (XALD) protein, explore causes of the marked clinical heterogeneity that typifies this disease and test therapeutic modalities in an ALD mouse model. The second Project (Watkins) will investigate the role of fatty acid activating enzymes in XALD and their role in the regulation of very long chain fatty acid homeostasis, particularly in the brain. The third Project (Gould) will resolve outstanding questions related to peroxisome biogenesis genetics and disorders and elucidate the biochemistry of a-oxidation and its disorders. The fourth Project (Valle) will use yeast and mouse models to investigate the role of peroxisomal membrane proteins in peroxisome biogenesis, function, and disease.

- **Project Title: MULTICENTER THERAPEUTIC TRIALS OF X-LINKED ALD**

  Principal Investigator & Institution: Moser, Hugo W.; Director; Kennedy Krieger Research Institute, Inc. 707 North Broadway, Rm 614 Baltimore, Md 21205

  Timing: Fiscal Year 2005; Project Start 18-SEP-2002; Project End 30-JUN-2007

  Summary: (provided by applicant): X-linked **adrenoleukodystrophy** (X-ALD) affects mainly the nervous system white matter and axons and the adrenal cortex. Its incidence is approximately 1:17,000. Phenotypic expression varies often within the same family

and in males ranges from the childhood cerebral form, which may lead to total disability and death by 10 years of age, to **adrenomyeloneuropathy** (AMN), which presents in the middle or late twenties as a paraparesis that is slowly progressive over decades. Women heterozygous for X-ALD may develop an AMN-like syndrome in middle age or later. Most males have primary adrenocortical insufficiency which responds to steroid replacement therapy. Accumulation of very long chain fatty acids (VLCFA) is the principal biochemical abnormality. The defective gene codes for a peroxisomal membrane protein (ALDP). There is no consistently effective therapy for the neurologic manifestations. Bone marrow transplantation benefits patients with early cerebral involvement but carries a high risk. The investigators propose a longitudinal cohort study and two Phase II therapeutic trials. Specific Aim 1 will establish a network of five clinical centers: The Kennedy Krieger Institute in Baltimore, the Texas Children's Hospital in Houston, the Massachusetts General Hospital in Boston, the University of Minnesota in Minneapolis, and the University of California at San Francisco. The Program will be coordinated by the Center for Clinical Trials at the Johns Hopkins Bloomberg School of Public Health. Specific Aim 2 will establish a cohort of 300 male X-ALD patients and 100 women heterozygous for X-ALD to permit a longitudinal study of natural history. Follow-up will utilize objective and validated measures of neurologic and neuropsychologic function, and quality of life. Neuroimaging studies have been shown to be valuable surrogate markers of the cerebral disease and will be scored independently by two neuroradiologists using an electronic transmission system developed for this purpose with the support from the National Library of Medicine. Newly developed quantitative tests will be used to aid assessment progression of AMN. Specific Aim 3 will conduct safety-efficacy studies of 4-phenylbutyrate therapy in patients with the cerebral forms of X-ALD, and a placebo controlled trial of insulin-like growth factor-1 in male patients with AMN and heterozygous women with an AMN like syndrome.

The National Library of Medicine: PubMed

One of the quickest and most comprehensive ways to find academic studies in both English and other languages is to use PubMed, maintained by the National Library of Medicine.[6] The advantage of PubMed over previously mentioned sources is that it covers a greater number of domestic and foreign references. It is also free to use. If the publisher has a Web site that offers full text of its journals, PubMed will provide links to that site, as well as to sites offering other related data. User registration, a subscription fee, or some other type of fee may be required to access the full text of articles in some journals.

To generate your own bibliography of studies dealing with X-linked adrenoleukodystrophy, simply go to the PubMed Web site at **http://www.ncbi.nlm.nih.gov/pubmed**. Type **X-linked adrenoleukodystrophy** (or synonyms) into the search box, and click **Go**. The following is the type of output you can expect from PubMed for X-linked adrenoleukodystrophy (hyperlinks lead to article summaries):

[6] PubMed was developed by the National Center for Biotechnology Information (NCBI) at the National Library of Medicine (NLM) at the National Institutes of Health (NIH). The PubMed database was developed in conjunction with publishers of biomedical literature as a search tool for accessing literature citations and linking to full-text journal articles at Web sites of participating publishers. Publishers that participate in PubMed supply NLM with their citations electronically prior to or at the time of publication.