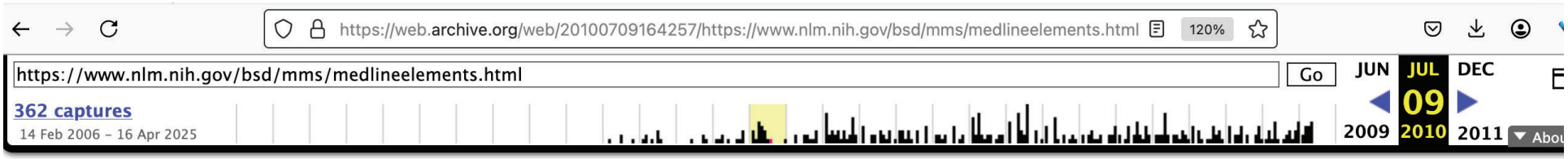
**EX-1005F** "MEDLINE/PubMed Data Element (Field) Descriptions" archived by Internet Archive on July 9, 2010, available at https://web.archive.org/web/20100709164257/https://www.nlm.nih.gov/bsd/mms/medlineelements.html.




United States
National Library of Medicine
National Institutes of Health

Search NLM Web Site

Go

NLM Home | Contact NLM | Site

Home > MEDLINE/PubMed Resources

# MEDLINE®/PubMed® Data Element (Field) Descriptions

Printer-friendly

This document describes the major elements (or fields) found on the MEDLINE display format for PubMed MEDLINE records. Some elements (e.g., Comment In) are not ma and will not appear in every record. Other elements (e.g., Author, MeSH term, Registry Number) may appear multiple times in one record. ***Some*** of the elements on this lis searchable fields in PubMed. For searching instructions, see the Search Field Tags section of PubMed Help. This document is supplementary information, to be used in conju with PubMed Help. MEDLINE/PubMed XML data element descriptions are also available.

PubMed MEDLINE display elements are presented in this section in alphabetical order, except in the case of certain elements that are closely related to one another.

| | | | | | |
|---|---|---|---|---|---|
| Abstract | (AB) | ISSN | (IS) | Full Personal Name as Subject | (FPS) |
| Copyright Information | (CI) | Issue | (IP) | Place of Publication | (PL) |
| Affiliation | (AD) | Journal Title Abbreviation | (TA) | Publication History Status | (PHST |
| Investigator Affiliation | (IRAD) | Journal Title | (JT) | Publication Status | (PST) |
| Article Identifier | (AID) | Language | (LA) | Publication Type | (PT) |
| Author | (AU) | Location Identifier | (LID) | Publishing Model | (PUBM |
| Full Author | (FAU) | Manuscript Identifier | (MID) | PubMed Central Identifier | (PMC) |
| Corporate Author | (CN) | MeSH Date | (MHDA) | PubMed Central Release | (PMCR |
| Comments/Corrections | | MeSH Terms | (MH) | PubMed Unique Identifier | (PMID |
| Date Completed | (DCOM) | NLM Unique ID | (JID) | Registry Number/EC Number | (RN) |
| Date Created | (DA) | Number of References | (RF) | Substance Name | (NM) |

Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000160

The Wayback Machine - https://web.archive.org/web/20100709164257/http://www.nlm.nih.gov:80/bsd/mms/medlineelem...



# MEDLINE®/PubMed® Data Element (Field) Descriptions

Printer-friendly Version

This document describes the major elements (or fields) found on the MEDLINE display format for PubMed MEDLINE records. Some elements (e.g., Comment In) are not mandatory and will not appear in every record. Other elements (e.g., Author, MeSH term, Registry Number) may appear multiple times in one record. ***Some*** of the elements on this list are searchable fields in PubMed. For searching instructions, see the Search Field Tags section of PubMed Help. This document is supplementary information, to be used in conjuction with PubMed Help. MEDLINE/PubMed XML data element descriptions are also available.

PubMed MEDLINE display elements are presented in this section in alphabetical order, except in the case of certain elements that are closely related to one another.

| | | | | | |
|---|---|---|---|---|---|
| Abstract | (AB) | ISSN | (IS) | Full Personal Name as Subject | (FPS) |
| Copyright Information | (CI) | Issue | (IP) | Place of Publication | (PL) |
| Affiliation | (AD) | Journal Title Abbreviation | (TA) | Publication History Status | (PHST) |
| Investigator Affiliation | (IRAD) | Journal Title | (JT) | Publication Status | (PST) |
| Article Identifier | (AID) | Language | (LA) | Publication Type | (PT) |
| Author | (AU) | Location Identifier | (LID) | Publishing Model | (PUBM) |
| Full Author | (FAU) | Manuscript Identifier | (MID) | PubMed Central Identifier | (PMC) |
| Corporate Author | (CN) | MeSH Date | (MHDA) | PubMed Central Release | (PMCR) |
| Comments/Corrections | | MeSH Terms | (MH) | PubMed Unique Identifier | (PMID) |
| Date Completed | (DCOM) | NLM Unique ID | (JID) | Registry Number/EC Number | (RN) |
| Date Created | (DA) | Number of References | (RF) | Substance Name | (NM) |
| Date Last Revised | (LR) | Other Abstract | (OAB) | Secondary Source ID | (SI) |
| Date of Electronic Publication | (DEP) | Other Copyright Information | (OCI) | Source | (SO) |
| Date of Publication | (DP) | Other ID | (OID) | Space Flight Mission | (SFM) |
| Entrez Date | (EDAT) | Other Term | (OT) | Status | (STAT) |
| Gene Symbol | (GS) | Other Term Owner | (OTO) | Subset | (SB) |
| General Note | (GN) | Owner | (OWN) | Title | (TI) |
| Grant Number | (GR) | Pagination | (PG) | Transliterated Title | (TT) |
| Investigator Name and Full Investigator Name | (IR) (FIR) | Personal Name as Subject | (PS) | Volume | (VI) |

## Abstract (AB)

English-language abstracts are taken directly from the published article. If the article does not have a published abstract, the National Library of Medicine does not create one, thus the record lacks the Abstract element. If a collaborating data producer has created an abstract, it will appear in the Other Abstract (OAB) field. This field may be used in addition to or instead of Abstract.

Publishers have given the National Library of Medicine permission to use abstracts for which they claim copyright. NLM does not hold copyright on the abstracts in MEDLINE. Users should obtain an opinion from their legal counsel for any use they plan for the abstracts in the database.

Generally, there are no abstracts for records created before 1975. However, starting in April 2007 NLM began to add abstracts from articles in PubMed Central (PMC) to the equivalent MEDLINE/PubMed citation record if that record does not already contain an abstract. The abstracts are derived from the PMC scanning project which is digitizing the back issues of participating PMC journals. As a result, additional records published prior to 1975 will contain abstracts.

All abstracts are in English. Because data entry policies at NLM have changed over the years, abstracts in some



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000161

records may be truncated, in which case one of the following phrases may appear at the end of the text enclosed in parentheses:

ABSTRACT TRUNCATED AT 250 WORDS
ABSTRACT TRUNCATED AT 400 WORDS
ABSTRACT TRUNCATED (This message occurred infrequently once the maximum length was raised to 4,096 characters in 1996.)

**Example:**

AB - Many disorders may result in delay of language. . . . . The reason for suggesting this diagnostic category is to stress that these children do initially behave in a similar way to those who are peripherally deaf. (ABSTRACT TRUNCATED AT 250 WORDS)

The maximum length of abstracts for records created after 2000 is 10,000 characters. Original policy on inclusion of abstracts set a limit of 250 words for acceptance. Effective with the January 1984 data (i.e., NLM's ELHILL legacy system 8401 Entry Month) two changes were made in this policy: 1) the word limit was expanded to 400 words for abstracts from articles ten pages or more in length or from articles in the cofre journals identified by the National Cancer Institute and 2) abstracts exceeding the 250- or 400-word limit are to be included in truncated form at the end of the sentence closest to the word limit. The percentage of records with abstracts has increased over the years as more publishers gave permission for NLM to include these data. A chart showing the number of MEDLINE records containing abstracts in various segments of MEDLINE is available at: http://www.nlm.nih.gov/bsd/medline_lang_distr.html.

Structured abstracts, describing key aspects of the purposes, methods, and results in a consistent way, are published in some journals. The key aspects of structured abstracts are capitalized to stand out, e.g., BACKGROUND, OBJECTIVES, METHOD, etc. The text is not broken into paragraphs. Structured abstracts were not truncated in the past, even if they surpassed the previous 250 or 400 word limit.

**Example:**

AB - BACKGROUND: Superantigens produced by Staphylococcus aureus and Streptococcus pyogenes are among the most lethal of toxins. Toxins in this family trigger an excessive cellular immune response leading to toxic shock. OBJECTIVES: To design an antagonist that is effective in vivo against a broad spectrum of superantigen toxins. METHODS: Short peptide antagonists were selected for their ability to inhibit superantigen-induced expression of human genes for cytokines that mediate shock. The ability of these peptides to protect mice against lethal toxin challenge was examined. RESULTS: Antagonist peptide protected mice against lethal challenge with staphylococcal enterotoxin B and toxic shock syndrome toxin-1, superantigens that share only 6% overall amino acid homology. Moreover, . . .

Table of Contents

## Copyright Information (CI)

Copyright Information (CI) associated with Abstract was introduced in 1999, and appears on a limited but increasing number of records. This singly-occurring element contains a copyright statement provided by the publisher of the journal and appears only on records supplied electronically to NLM by the publisher. This information is displayed at the end of the abstract.

**Example:**

AB - ... Copyright 1999 Academic Press.

See also the related Other Copyright Information (OCI) field.



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000162

Table of Contents

### Affiliation (AD)

The affiliation of the first author resides in this field. Starting in 1988, NLM began to include the address of the first author's affiliation on the record. Originally, the address was intended to help differentiate between two authors of the same name, not to provide detailed mailing information. It evolved that the institution, city, and state including zip code for U.S. addresses, and country for countries outside of the United States, were included if provided in the journal; sometimes the street address was also included if provided in the journal. In 1995, NLM began to add the designation USA at the end of this information where the first author's affiliation is in the fifty United States or the District of Columbia. Effective January 1, 1996, NLM includes the primary author's electronic mail (e-mail) address at the end of the Affiliation field, if present in the journal. Starting in 2003 the complete first author address is entered as it appears in the article with no words omitted.

**Examples:**

AD - Department of Anesthesiology, University of Virginia Health Sciences Center Charlottesville 22908, USA. med2p@virginia.edu

AD - Departamento de Farmacologia, Facultad de Medicina, Universidad Complutense de Madrid (UCM), 28040 Madrid, Spain.

AD - Center for Children With Special Needs, Children's Hospital, and the Department of Pediatrics, University of Washington School of Medicine, 4800 Sand Point Way NE, CM:09, Seattle, WA 98105-0371, USA. jneff@chmc.org

Table of Contents

### Investigator Affiliation (IRAD)

The Investigator Affiliation (IRAD) occurs only for data created by one of our former collaborating data producers, the National Aeronautics and Space Administration (NASA). It identifies the organization that the researcher was affiliated with at the time the article was written and as published in the journal. Unlike the Affiliation field associated with the Author field, this affiliation generally does not include detailed address information. This field is associated with the Investigator Name (IR) field, also created by NASA.

**Examples:**

IRAD - Marquette U, Milwaukee, WI
IRAD - VA Med Ctr, Richmond, VA

Table of Contents

### Article Identifier (AID)

This field is populated by the publisher. It may contain an identifier that links with records in the publisher's system. The article identifier values may include the controlled publisher identifier (PII) or the digital object identifier (DOI). It is most often used for LinkOut, and is not considered part of the citation source information.

**Examples:**

AID - S0272-7358(05)00023-1 [pii]
AID - 10.1016/j.cpr.2005.02.002 [doi]

Beginning in April 2008, DOI and PII data is included in the Location Identifier (LID) field. The information in the LID field is considered part of the citation source.

Table of Contents



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000163

## Author (AU)

NLM's author indexing policy is explained in the Fact Sheet: Authorship in MEDLINE.

Limitations to the number of author names included in MEDLINE are as follows:

| | |
|---|---|
| 1966 - 1983: | For records created during this time period, MEDLINE did not limit the number of authors. |
| 1984 - 1995: | For records created during this time period, NLM limited the number of authors to 10, with "et al." to indicate the existence of additional authors. This practice began with citations created on October 29, 1983. |
| 1996 - 1999: | For journal issues published during this time period, NLM increased the number of authors from 10 to 25. If there were more than 25 authors, the first 24 were listed, the last author was used as the 25th, and the 26th and beyond became "et al." |
| 2000 - Present: | Beginning with journal issues published in 2000, MEDLINE does not limit the number of listed authors. |

Beginning in mid-2005, the various policy restrictions on number of author names entered in past years were lifted so that on an individual basis, a record may be edited to include all author names present in the published article, regardless of the limitation in effect at the time the record was first created.

Effective with 1992 date of publication, letters are indexed individually with authors rather than as an anonymous group.

Note: Until 1990, NLM transliterated up to five authors' Cyrillic or Japanese names to the Roman alphabet. Since 1990, the first ten Cyrillic or Japanese names are transliterated. Chinese ideograms are not transliterated by NLM, but if transliterations of the authors names are available in the journal article or table of contents, they are included in the citation, even if that includes only one author in a multi-author article.

Format: last name followed by a space and up to the first two initials followed by a space and a suffix abbreviation, if applicable, all without periods or a comma after the last name.

**Examples:**

McCrary SV
Smith AB 3rd

See Full Author (FAU) for more information on initials.

See also Corporate Author (CN).

Table of Contents

## Full Author (FAU)

Beginning with articles with a publication year of 2002, PubMed records may include full names. BIOETHICSLINE citations converted to MEDLINE citations in late 2001 have full names on citations prior to publication year 2002; those data are found in the General Note (GN) field. Citations from the Kennedy Institute of Ethics (KIE) may have full names in the Full Author field for publication dates of prior to 2002.

Full author names are entered when they appear in the author position of an article, usually on the title page of an article. If only the last name and initials appear in the author position, then only the last name and initials will be entered, even if a form of the fuller name appears elsewhere in the article or in the Table of Contents for the journal.

Author Initials:
Initials data are generated from the Data Creation and Maintenance System (DCMS) ForeName data element using an algorithm. Here are the highlights of that algorithm:

- Only two initials are included. Initials are at the beginning of a name string or following a break (a space or hyphen). Only capital letters in the ForeName elements are candidates for initials, except for the letter following a hyphen. The letter following a hyphen is a candidate for an initial, unless the string following the hyphen is "ichi."
- When the ForeName data element consists of only initials, there are spaces between initials.



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000164

- An initial includes the following particles: da, de, del, do, dos, du, el, el-, and le. All particles except "el-" are followed by a space and are preceded by a space or are at the beginning of the name string. If found, all particles are converted to lower case when generated as part of the Initials data element.
- If the language of the article is Bulgarian, Russian, Serbo-Croatian (Roman), or Ukranian, then one initial may be a 2- or 4-character transliterated mixed-case initial. Current, mixed-case transliteration values are: Dj, Lj, Nj, Ch, Sh, Iu, Ia, Ie, Zh, Kh, Ts, Dz, Shch.

**Examples:**

| Last Name | Fore Name | Suffix | Initials |
|---|---|---|---|
| Melosh | H J | 3rd | HJ |
| Abrams | Judith | | J |
| Buncke | Gregory M | | GM |
| Gonzales-loza | Maria del R | | Mdel R |
| Dubuisson | Jean-Bernard | | JB |
| Amara | Mohamed el-Walid | | Mel-W |
| Shan | Yu-fei | | YF |
| Krylov | Ia K | | IaK |
| De Avila | Luiz Francisco Rodriguez | | LF |

Note that the end result of generating the Initials data is that the two initials are closed up with no space between, even though there may be spaces elsewhere in the Initials string if one or both of the initials has embedded spaces.

There are some author names that have no initials. These are mostly Malaysian names, for which the entire name is entered in the LastName DCMS data element.

The full name will display on the PubMed MEDLINE display format above the respective name field as in the following example:

**Example:**

FAU - Foa, Edna B
AU - Foa EB

Note: When an author's name has been corrected from a published erratum, the corrected name is placed in the Author field and the incorrect name that was originally published is retained in the last occurrence of the Author field. In this case, there will be an associated commentary linkage.

NLM expended much effort to parse the data converted from the legacy ELHILL format at the end of the 2000 production year accurately. Many citations from the 1966-1974 timeframe were changed to follow data entry conventions established later. For example, particles such as "van der" were moved from the suffix position to the beginning of the last name, and the abbreviations "2d" and "3d" were changed to "2nd" and "3rd". It is possible to have particles associated with initials, such as "Mdel R" for "María del R". It is also possible to have only a last name. Some occurrences of author data in this category are in error and will be corrected manually as time permits.

For OLDMEDLINE records, every published author name is included in the list of authors for citations from the 1951 - 1959 *Current List of Medical Literature* (CLML) and for citations from the 1960 - 1965 *Cumulated Index Medicus* (CIM). For citations from the 1950 CLML, a maximum of three author names were entered. OLDMEDLINE first and last name author elements are in all upper case letters, except in some cases the particle is in lower case letters. A suffix is in upper and lower case letters. OLDMEDLINE records do not contain collective or corporate names. A small percentage of OLDMEDLINE records contain the last name only, because that is the only Author data present in the abstracting and indexing tool used to create the record.

Table of Contents



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000165

### Corporate Author (CN)

This field identifies the corporate authorship of an article. Corporate Author (CN) was introduced in 2001. NLM's author indexing policy is explained in the Fact Sheet: Authorship in MEDLINE.

These names enter MEDLINE exactly as they appear in the journal (except to delete initial articles such as The, A or An). NLM will not edit the names to standardize them or translate them into English. NLM enters the Roman alphabet words (e.g., German, French) into the Corporate Author field. Transliterated Russian or other cyrillic names are also entered into the Corporate Author field, but for Japanese, Chinese, Hebrew, and Arabic, NLM puts the English translation of the name into this field.

**Example:**

CN - Centers for Disease Control and Prevention

From 2001 to April 2006, the corporate author name displayed in PubMed citations as the last occurrence in the author field, as a separate data element after any personal names. Effective May 2006, the collective author is retained in the order of all authors found in the byline of the published article. See the May-June 2006 Technical Bulletin article for details.

Citations prior to 1966, in general, have no indication of collective author unless they were created by NLM's data creation partners. Citations from 1966 to 2000 with collective author field data contain that data in the Title field. These records are generally those created by NLM's data creation partners, and are very few in number and typically in the population or ethics subject areas. As they are encountered, these retrospective records may be individually maintained to move the Corporate Author information from the Title field to the Corporate Author field.

---

Table of Contents

---

### Comments/Corrections (See fields and field tags listed below.)

The data in these fields, listed below, are citations to associated journal publications, e.g., comments, errata, or retractions. These data enable links between the record at hand and its associated citations.

MEDLINE records may contain one or more of the following. See more detailed information about the policy for each type of comment or correction. To search PubMed for records with comments or corrections, see PubMed Help.

| Comment or Correction Type | MEDLINE Display Field Tag | Description |
|---|---|---|
| **Comment on** | **(CON)** | cites the reference upon which the article comments; began use with journal issues published in 1989. |
| **Comment in** | **(CIN)** | cites the reference containing a commentary about the article (appears on citation for original article); began use with journal issues published in 1989. |
| **Erratum in** | **(EIN)** | cites a published erratum to the article (appears on citation for original article); began use in 1987. |
| **Erratum for** | **(EFR)** | cites the original article for which there is a published erratum. |
| **Corrected and Republished in** | **(CRI)** | cites the final, correct version of a corrected and republished article (appears on citation for original article). Began use in 1987 as Republished in (RPI); renamed in 2006. |
| **Corrected and Republished from** | **(CRF)** | cites the original article subsequently corrected and republished. Began use in 1987 as Republished from (RPF); renamed in 2006. |
| **Partial retraction in** | **(PRIN)** | cites the reference containing a partial retraction of the article (appears on citation for original article); began use in 2007. |
| **Partial retraction of** | **(PROF)** | cites the article being partially retracted; began use in 2007. |



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000166

| | | |
|---|---|---|
| **Republished in** | **(RPI)** | cites the subsequent (and possibly abridged) version of a republished article (appears on citation for original article); began use in 2006. |
| **Republished from** | **(RPF)** | cites the first, originally published article; began use in 2006. |
| **Retraction in** | **(RIN)** | cites the retraction of the article (appears on citation for original article); began use in August 1984. |
| **Retraction of** | **(ROF)** | cites the article(s) being retracted; began use in August 1984. |
| **Update in** | **(UIN)** | cites an updated version of the article (appears on citation for original article); began limited use in 2001. |
| **Update of** | **(UOF)** | cites the article being updated; limited use; began limited use in 2001. |
| **Summary for patients in** | **(SPIN)** | cites a patient summary article; began use in November 2001 (these records contain Publication Type, Patient Education Handout). See the article 'Patient Education Handouts in MEDLINE®/PubMed®' in the *NLM Technical Bulletin* at http://www.nlm.nih.gov/pubs/techbull/ma02/ma02_new_pt.html for more information. |
| **Original report in** | **(ORI)** | cites a scientific article associated with the patient summary. |

The PubMed Identifier (PMID) of the associated record in PubMed is provided (if available) to create a link between an article and its commentary.

**Examples:**

CIN - N Engl J Med. 2003 Jul 17;349(3):211-2. PMID: 12867604
CON - Dev Cell. 2002 Jul;3(1):85-97. PMID: 12110170
CRI - Orthop Nurs. 2003 May-Jun;22(3):232-9. PMID: 12872752
CRF - Biochemistry. 1994 May 10;33(18):5614-22. PMID: 8180186
EIN - Acta Obstet Gynecol Scand. 2003 Jan;82(1):102
EFR - J Arthroplasty. 2002 Jun;17(4):524-6. PMID: 12066289
RIN - J Biochem Mol Biol. 2002 Nov 30;35(6):642. PMID: 12476908
ROF - Ware FE, Lehrman MA. J Biol Chem. 1996 Jun 14;271(24):13935-8. PMID: 8663248
SPIN- Ann Intern Med. 2003 Jun 3;138(11):I60. PMID: 12779314
ORI - Ann Intern Med. 2003 Jun 3;138(11):907-16. PMID: 12779301
UIN - Cochrane Database Syst Rev. 2002;(3):CD003688. PMID: 12137706
UOF - Cochrane Database Syst Rev. 2002;(2):CD003680. PMID: 12076500

Occasionally, a note is added to the Comment or Correction. The note clarifies the data in the Comments or Correction element. It is most often used with **Erratum In** for corrected author names. The following are some possible notes:

- [added] is used when an author name is added to the citation as the result of a published erratum
- [removed] when an author name is removed
- [dosage error in published abstract; MEDLINE/PubMed abstract corrected] is used when there is a dosage error in a citation abstract. Within the abstract, then there is a bracketed phrase that indicates where the correction is: [DOSAGE ERROR CORRECTED]
- [dosage error in article text] when the dosage error is in the text portion of the article
- [abstract no. xxx only] for an erratum of a numbered abstract which is part of an overall citation
- [abstract by author names on page xxx only] when an erratum refers to an unnumbered abstract which is authored and part of an overall citation. The author names and page numbers of the abstract are included.
- [abstract abstract title on page xxx only] when an erratum refers to an unnumbered abstract which is not authored. In this case, the abstract title and page number are included.

In records from OLDMEDLINE, Comments In (CIN) is the only Comment or Correction found. Other comment or correction elements may be used in the future.

See the NLM Fact Sheet "Errata, Retraction, Partial Retraction, Corrected and Republished Articles, Duplicate Publication, Comment, Update, Patient Summary and Republished (Reprinted) Article Policy for MEDLINE®" at http://


Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000167

www.nlm.nih.gov/pubs/factsheets/errata.html for additional information.

Table of Contents

### Date Completed (DCOM)

Date Completed is the date processing of the record ends; i.e., MeSH® Headings have been added, quality assurance validations are completed, and the completed record subsequently is distributed to PubMed and licensees. This is contrasted with Date Created, which is the date processing begins.

Format: YYYYMMDD

**Example:**

DCOM - 20020207

In Process records lack the Date Completed field. For OLDMEDLINE records, the Date Completed is the approximate date the record entered PubMed, rather than the date processing ends. OLDMEDLINE records are created and processed differently than MEDLINE records.

Table of Contents

### Date Created (DA)

Date Created is the date that processing of the record begins.

Format: YYYYMMDD

**Example:**

DA - 20020516

This is contrasted with Date Completed, which is the date processing ends. Date Created is not the same as NLM's PubMed Entrez Date (EDAT), which is the date the record entered PubMed.

For citations up to about the year 2000, the Date Created (DA) and Date Completed (DCOM) data elements are identical. These dates were derived from NLM's legacy ELHILL system.

For OLDMEDLINE citations converted from the 1964 and 1965 *Index Medicus* (IM), Date Created represents the year and month the citations were printed in the monthly *Index Medicus*, and the day will always be "01". All other OLDMEDLINE records have a year based on the year of the printed index, the month is always "12" for December, and the day is always "01".

Table of Contents

### Date Last Revised (LR)

The Date Last Revised identifies the date a change is made to a record either as a result of individual or global maintenance. There is no indication of what the change is on the record. Only the latest revision date is displayed.

Format: YYYYMMDD

**Example:**

LR - 20020320

When the 10 million+ MEDLINE records through the 2000 production year were converted to XML from NLM's legacy



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000168

ELHILL system, all records were assigned a Last Revision Date of 20001218 (December 18, 2000). Subsequently, many of these records have been or will be maintained and given a later (LR) date.

Table of Contents

### Date of Electronic Publication (DEP)

The Electronic Publication Date is the date the publisher made an electronic version of the article available. In January 2003, global maintenance was performed to add this element retrospectively.

Format: YYYYMMDD

**Example:**

DEP - 20050513

Table of Contents

### Date of Publication (DP)

Date of Publication contains the full date on which the issue of the journal was published. The standardized format consists of elements for a 4-digit year, a 3-character abbreviated month, and a 1 or 2-digit day. Every record does not contain all of these elements; the data are taken as they are published in the journal issue, with minor alterations by NLM such as abbreviations.

**Examples:**

DP - 2001 Apr 15
DP - 2001 Apr
DP - 2000 Spring
DP - 2000 Nov-Dec
DP - 2001

Table of Contents

### Entrez Date (EDAT)

This field contains the date the citation was added to PubMed.

Format: YYYY/MM/DD HH:MM

**Example:**

EDAT- 2003/01/02 04:00

Table of Contents

### Gene Symbol (GS): not currently input

This field contains the "symbol" or abbreviated form of gene names as reported in the literature. This element resides in records processed at NLM from 1991 through 1995. Up to 25 occurrences per record may appear. NLM entered the symbols used by authors; there was no authority list or effort to standardize the data.

**Examples:**

GS - dyrA



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000169

GS - PYRE-F
GS - cpa2

Greek characters, superscripts, and subscripts may appear as part of the gene symbol. The code designations for the Greek characters may be found at http://www.nlm.nih.gov/bsd/licensee/greek_characters.html.

Table of Contents

## General Note (GN)

This field contains supplemental or descriptive information related to the document. The data in this field may be preceded by the acronym for the collaborator who provided this information.

The acronyms and names are:

| | |
|---|---|
| HMD | History of Medicine Division, National Library of Medicine |
| HSR | National Information Center on Health Services Research and Health Care Technology, National Library of Medicine |
| KIE | Kennedy Institute of Ethics, Georgetown University |
| NASA | National Aeronautics and Space Administration |
| PIP | Population Information Program; Johns Hopkins School of Health |

**Examples:**

GN - KIE: Article and commentaries
GN - KIE: KIE BoB Subject Heading: health care/economics

Note: BoB Subject Headings are controlled subject vocabulary terms found in the Kennedy Institute of Ethics' Bioethics Thesaurus under which citations print in their publication, Bibliography of Bioethics. The current format of these data in MEDLINE is reflected in the second example beginning with "KIE Bob" or "KIE Bib".

Table of Contents

## Grant Number (GR)

This field was introduced in 1981 and is comprised of four parts (modified from three in December 2007 and reordered in 2009):

1. **Number** contains the research grant or contract number (or both) that designates financial support by any agency of the United States Public Health Service, any institute of the National Institutes of Health, or other organization. The data are generally recorded exactly as they appear in the published article*; there is no attempt to standardize the numbers.
2. **Grant 2-letter code** contains the 2-letter grant code or acronym.
3. **Agency** includes the institute acronym or mnemonic in the case of US PHS institutes, or full organization name. As of 2009 this includes the agency's hierarchical structure from lower to higher entity, when known. For example NCI NIH HHS for National Cancer Institute, National Institutes of Health, Department of Health and Human Services.
4. **Country** contains the home country of the granting agency.

**Examples:**

GR - LM0577/LM/NLM NIH HHS/United States
GR - M0-1 RR07122/RR/NCRR NIH HHS/United States
GR - Wellcome Trust/United Kingdom
GR - 058423/Wellcome Trust/United Kingdom
GR - 067427/z/02/z/Wellcome Trust/United Kingdom

Grant numbers are added to the record only if the indexer has verified the grant information as published. The


Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000170

information is not based on the author's input in the author manuscript submission system.

A list of the possible values for the grant Acronym and Agency is available from: http://www.nlm.nih.gov/bsd/grant_acronym.html. Please be advised that while NLM enters the grant number, acronym and agency values are derived by using a machine algorithm against the grant number string. This may result in some inaccurate derivations, but the overall benefit of supplying the separate acronym and agency was considered to be worth the risk of some inaccuracies.

Effective for prospective citations indexed with MeSH as of June 2, 2005, the value Wellcome Trust is added if an author acknowledges that the research was supported financially by this organization. Effective March 24, 2006, Wellcome Trust grant numbers may also be added from data entered via PubMed Central, or from the published article. The grant number may appear in either six-digit (e.g., 069355) or expanded (e.g., 067427/Z/02/Z) format.

With the implementation of the United Kingdom Manuscript Submission System in August 2007, NLM began adding data for seven additional United Kingdom granting agencies. In early 2008, Howard Hughes Medical Institute was added as a designated funding organization. The typical data available for Howard Hughes Medical Institute is the name only; grant numbers are not generally part of the information.

Through 1999, NLM entered up to three grant numbers for each record. Beginning in 2000, NLM began to transition to an unlimited number of grant numbers or contract numbers. Some MEDLINE citations from 2000 and 2001 may still be limited to three grant numbers or contract numbers, but beginning in 2002, NLM does not limit the number of grant numbers or contract numbers. Some collaborating partners record grant numbers for agencies outside the U.S. Public Health Service in the General Notes field.

*In July 2006, NLM corrected a large number of NIH grant number prefixes which were entered with the letter O (e.g., RO1) rather than the number 0 (e.g., R01). This practice deviates with NLM's general policy that the data in the online citation match what is in the published article.

---

Table of Contents

---

## Investigator Name (IR) and Full Investigator Name (FIR)

Beginning in March of the 2008 production year, Investigator Name and Full Investigator Name fields are used to contain personal names of individuals (e.g., collaborators and investigators) who are not authors of a paper but rather are listed in the paper as members of a collective/corporate group that is an author of the paper. The same name listed multiple times will be repeated because NLM cannot make assumptions as to whether those names are the same person.

These fields also reside on MEDLINE citations created or maintained by one of our former collaborating data producers, the National Aeronautics and Space Administration (NASA). They identify the NASA-funded principal investigator(s) who conducted the research discussed in the article cited (but are not necessarily the authors). NASA Investigator Names are associated with the Investigator Affiliation field.

See Author field for details on format. NLM's author indexing policy is explained in the Fact Sheet: Authorship in MEDLINE.

**Examples:**

IR - Smith P
FIR - Smith, Paula

IR - Brody BA
FIR - Brody, B A

---

Table of Contents

---

## ISSN (IS)

ISSN (International Standard Serial Number) is an eight-character value that uniquely identifies the cited journal. It is nine characters long in the hyphenated form: XXXX-XXXX. The ISSN field has a qualifier that follows the ISSN data which will state whether it is for the print or the electronic version ISSN of the journal. For journals with multiple ISSNs (e.g., those with separate ISSNs for the print and electronic versions), the ISSN in the MEDLINE citation reflects the version used for MeSH indexing.



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000171

**Examples:**

IS - 0021-5252 (Print)
IS - 1471-2202 (Electronic)

Some records do not contain an ISSN value.

The complete title of the journal can be found in the Journal Title (JT) field. See more information about journals cited in MEDLINE.

See also NLM Unique ID (JID).

Table of Contents

### Issue (IP)

Issue identifies the issue, part or supplement of the journal in which the article was published.

**Examples:**

IP - 11
IP - 7 Pt 1
IP - First Half
IP - 3 Suppl 1

For records from OLDMEDLINE, some records contain Issue but lack Volume; some records contain Volume but lack Issue; and some records contain Volume and Issue data in the Volume element.

Table of Contents

### Title (TI)

The title field contains the entire title of the journal article. The title is always in English; those titles originally published in a non-English language and translated for the title field are enclosed in square brackets. All titles end with a period unless another punctuation mark such as a question mark or bracket is present. Explanatory information about the title itself is enclosed in parentheses, e.g.: (author's trans). Corporate/collective authors may appear at the end of the title field for citations up to about the year 2000. See also Corporate Author (CN) for more information about corporate or collective authors.

Records with (In Process Citation) in the title field are non-English language citations in In-Process status that do not yet have the article title translated into English.

**Examples:**

TI - The Kleine-Levin syndrome as a neuropsychiatric disorder: a case report.
TI - Why is xenon not more widely used for anaesthesia?
TI - [Biological rhythms and human disease]
TI - [In Process Citation]
TI - Prevalence of Helicobacter pylori resistance to antibiotics in Northeast Italy: a multicentre study. GISU. Interdisciplinary Group for the Study of Ulcer.

Table of Contents

### Journal Title Abbreviation (TA)

This field contains the standard abbreviation for the title of the journal in which an article appeared. See the NLM Fact Sheet "Construction of National Library of Medicine Title Abbreviations" at http://www.nlm.nih.gov/pubs/factsheets/constructitle.html, which discusses the rules currently used by the National Library of Medicine (NLM) to


Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000172

construct title abbreviations for journals cited in MEDLINE.

**Examples:**

TA - JAMA
TA - J Pediatr
TA - J Comp Physiol B
TA - Ann Biol Clin (Paris)

The complete title of the journal can be found in the Journal Title (JT) field. See more information about journals cited in MEDLINE.

All MEDLINE/PubMed records must be linked to a parent serial record in NLM's online catalog. In OLDMEDLINE records, the journal title abbreviation may differ from that found on the original citation in the printed index.

Table of Contents

### Journal Title (JT)

This field contains the full journal title, taken from NLM's cataloging data following NLM rules for how to compile a serial name. The NLM journal title abbreviation is in the (TA) element.

Examples are:

**Examples:**

JT - Molecular microbiology
JT - American journal of physiology. Cell physiology

Some characters that are not part of NLM's MEDLINE/PubMed Character Set reside in a relatively small number of full journal titles. These characters will display as the string 'inverted question mark.'

Table of Contents

### Language (LA)

The language in which an article was published is recorded in the Language field. All entries are three letter abbreviations stored in lower case, such as eng, fre, ger, jpn, etc. A record may contain more than one language value. Some records provided by collaborating data producers may contain the value "und" to identify articles whose language is undetermined.

**Examples:**

LA - eng
LA - rus

A table listing all languages found in MEDLINE is available at: http://www.nlm.nih.gov/bsd/language_table.html. A chart showing the number of English language MEDLINE articles in various segments of MEDLINE is available at: http://www.nlm.nih.gov/bsd/medline_lang_distr.html.

Table of Contents

### Location Identifier (LID)

In April 2008, NLM began accepting LocationID data from publishers for journal citations. This data consists of either a Digital Object Identifier (DOI) or another publisher ID that the publisher has determined serves the role of pagination in a citation in terms of locating the article (PII). This data will be submitted by the publisher in the LocationID field as part of the XML citation. If an LocationID is wrong or changed by the publisher, then the publisher



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000173

must publish an erratum notice in the journal with the incorrect and correct number in order for NLM to edit the data in the citation.

**Examples:**

LID - 8083
LID - s0212 16112008000100001

**Note:** PubMed records also include PIIs and DOIs in the Article ID field, if it is supplied by the publisher. This field is used to create links for the LinkOut program; it is not used to create citation source information.

Table of Contents

## Manuscript Identifier (MID)

A Manuscript ID is an identifier assigned to an author manuscript submitted to the NIH Manuscript Submission System. This may be in support of the NIH Public Access Policy, or another funding agency's policy. The following four types of MIDs currently exist in PubMed records:

NIH Manuscript System (NIHMS)
United Kingdom Manuscript System (UKMS)
Howard Hughes Medical Institute (HHMIMS)
Hyper Articles En Ligne (HAL) from the Centre pour la communication scientifique directe (CCSD)

**Examples:**

MID - NIHMS3373
MID - HHMIMS35653
MID - UKMS1522
MID - HALMS108756

Table of Contents

## MeSH Date (MHDA)

The date MeSH terms were added to the citation is recorded in the MeSH Date field. The MeSH date is the same as the Entrez date until MeSH are added.

Format: YYYYMMDD HH:MM

**Example:**

MHDA- 2005/08/03 09:00

Table of Contents

## MeSH Terms (MH)

NLM's controlled vocabulary, Medical Subject Headings (MeSH®), is used to characterize the content of the articles represented by MEDLINE citations.

Of the various MeSH headings assigned to a record, those representing the most significant points are identified with an asterisk (*) in the MeSH display. The remaining descriptors are used to identify concepts that have also been discussed in the item, but that are not the primary topics. In Process and publisher-supplied records lack MeSH terms. See the MeSH Fact Sheet (http://www.nlm.nih.gov/pubs/factsheets/mesh.html) or the MeSH home page


Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000174

(http://www.nlm.nih.gov/mesh/meshhome.html) for additional information about MeSH.

Subheadings (also known as Qualifiers) are often used with MeSH terms to help describe more completely a particular aspect of a subject. Subheadings are displayed after the MH and a slash (/). A major topic asterisk before a subheading indicates when the combination of that subheading with its associated MeSH term is a central concept of the article.

The presentation of MeSH terms is alphabetical. The Subheadings associated with a MeSH term are also in alphabetical order, without regard to the presence of the major topic asterisk (*).

**Example 1:**

MH - Adult
MH - Cardiovascular Diseases/etiology/*mortality
MH - Child Development/*physiology
MH - Embryo and Fetal Development/*physiology
MH - English Abstract
MH - Fetal Growth Retardation/complications/*physiopathology
MH - Human
MH - Infant, Newborn
MH - Nutrition
MH - Risk Factors
MH - Survival Rate

In the above example, the mortality aspect of cardiovascular diseases, the physiology of child development, as well as embryo and fetal development, and the physiopathology aspect of fetal growth retardation are the central concepts of the article. Note that the MeSH term English Abstract (also present in above example) means that a substantive English language abstract is present in the journal or was written by one of NLM's collaborating data producers. The abstract may or may not be present in the MEDLINE citation as the input policy changed over the years. There are many older non-English language citations without abstracts in MEDLINE but with the MeSH term English Abstract; this indicates that an English abstract is present in the journal, even if not a part of the online record.

**Example 2:**

MH - Animal
MH - Dogs
MH - *Myocardial Contraction
MH - Myocardium/*metabolism
MH - *Oxygen Consumption
MH - Surface Tension

In the above example, myocardial contraction, the metabolism aspect of myocardium, and oxygen consumption are the central concepts of the article.

The original subject headings assigned to OLDMEDLINE records were updated to current MeSH in December 2005 (with the exception of approximately 8% of OLDMEDLINE records, which will be updated as resources permit). All of the terms assigned to OLDMEDLINE citations are identified as the major topic of the article. The original subject headings have been placed in the Other Term (OT) field.

Table of Contents

## NLM Unique ID (JID)

This field is the alpha-numeric identifier for the cited journal. The element's value is the accession number for the journal's record assigned in the NLM Catalog, available at http://www.ncbi.nlm.nih.gov/nlmcatalog or via LocatorPlus at http://locatorplus.gov/. An NLM Unique ID may appear as seven, eight or nine characters.

Examples:

Citations from the *New England Journal of Medicine* will have the following JID field value:
JID - 0255562



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000175

Citations from the *Japanese Journal of Infectious Diseases* will have the following JID field value:
JID - 100893704

Table of Contents

## Number of References (RF)

This element appears on records indexed with Review as a Publication Type. This field contains the number of bibliographic references listed in the review article.

**Example:**

RF - 21

When collaborating data partners recorded the number of references for non-review articles, these data are found in the General Notes field.

Table of Contents

## Other Abstract (OAB)

NLM creates MEDLINE records without an Abstract field when the source journal article does not originally contain an abstract. In cases where a collaborating data partner provides an abstract, or an abstract is available following the journal publication, this abstract may appear in the Other Abstract field for that record. This field is associated with the Other Copyright Information (OCI) field, which displays beneath (OAB) if present. The abstract included in this field is not written by the authors of the article. The internal tracking number of the source document used by the collaborating partner resides in the Other ID field.

Acronyms used in the OAB field are:
**AAMC** - American Association of Medical Colleges; not currently used
**AIDS** - Special HIV/AIDS publications with abstracts written by someone other than the author
**KIE** - Kennedy Institute of Ethics, Georgetown University
**PIP** - Population Information Program, Johns Hopkins School of Public Health
**NASA** - National Aeronautics and Space Administration

Another value used in this field is **Publisher**.

**Example:**

OAB - NASA: The purpose of this review is to delineate the ubiquitous and pivotal role of Ca2+ in diverse physiological processes. Emphasis will be given to the role of Ca2+ in stimulus-response coupling. In addition to reviewing the present status of research, our intention is to critically evaluate the existing data and describe the newly developing areas of Ca2+ research in plants.

Table of Contents

## Other Copyright Information (OCI)

This field identifies the copyright owner. It appears on some records created by a collaborating data producer if that producer has written the abstract. The information for this field displays beneath the Other Abstract field.

**Example:**

OCI - NASA Edited

Table of Contents



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000176

### Other ID (OID)

This field may reside on a record owned by a collaborating partner or on an NLM-owned record to which a collaborating partner added additional information. The data identify: a) the organization responsible for the information on the citation or the document where the information originated, and b) a unique number for that citation or document.

The acronyms used in this field are listed below. Some of the values on this list currently are not in use at this time and some may never be used.

| | |
|---|---|
| **NASA** | National Aeronautics and Space Administration |
| **KIE** | Kennedy Institute of Ethics, Georgetown University |
| **PIP** | Population Information Program, Johns Hopkins School of Public Health; not currently used |
| **POP** | former NLM POPLINE database; not currently used |
| **ARPL** | Annual Review of Population Law; not currently used |
| **CPC** | Carolina Population Center; not currently used |
| **IND** | Population Index; not currently used |
| **CPFH** | Center for Population and Family Health Library/Information Program; not currently used |
| **NLM** | National Library of Medicine; used for PMCID and manuscript identifier data (NIHMS for NIH Manuscript System, UKMS for United Kingdom Manuscript System, HALMS for the French Manuscript System, or HHMIMS for the Howard Hughes Medical Institute Manuscript System) beginning in 2009. In some cases the data may contain a date in parentheses following the number. This date represents the embargo date after which the full text will be available in PubMed Central®. |
| **NRCBL** | National Reference Center for Biomedical Literature (for the KIE Reference Library shelving location) |
| **CLML** | Current List of Medical Literature; reserved for future use |
| **IM** | Index Medicus; reserved for future use (intended for pre-1966 publications) |
| **QCICL** | Quarterly Cumulative Index to Current Literature; reserved for future use (intended for pre-1966 publications) |
| **QCIM** | Quarterly Cumulated Index Medicus; reserved for future use (intended for pre-1966 publications) |
| **SGC** | Surgeon General's Catalog; reserved for future use |

For OLDMEDLINE records, this field occurs on records from 1950-1959 and is for internal use at NLM. CLML is currently the value for all OLDMEDLINE citations containing this field. The value IM may be used on a limited basis. Other values that may be defined for future use with OLDMEDLINE records are QCICL and QCIM.

**Examples:**

OID - KIE: 30206
OID - NRCBL: 18.2
OID - CLML: 5834:20412:395

Table of Contents

### Other Term (OT)

This field contains largely non-MeSH subject terms (also referred to as Keywords) that describe the content of the article. These are assigned by a collaborating data producer who is identified in the Other Term Owner field. This information is present on a small percentage of citations in the database. The Other Term data may be marked with an asterisk (*) to indicate a major concept. Asterisks are for display only.

**Examples:**



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000177

OT - Legal Approach
OT - Health Care and Public Health

Other Terms appear in addition to MeSH terms, with the exception of some OLDMEDLINE records which do not yet contain MeSH headings. OLDMEDLINE subject terms were mapped to current MeSH in preparation for NLM's 2006 production year. Both MeSH Headings and Other Terms are on all but approximately 8% of OLDMEDLINE records as of December, 2005. Additional mappings will occur as resources permit.

Table of Contents

### Other Term Owner (OTO)

This field contains an acronym that precedes the Other Term field. It identifies the organization that provided the Other Term data. The Other Term Owner acronyms and their respective organizations are:

| | |
|---|---|
| **KIE** | Kennedy Institute of Ethics, Georgetown University |
| **NASA** | National Aeronautics and Space Administration |
| **PIP** | Population Information Program, Johns Hopkins School of Public Health |
| **NLM** | National Library of Medicine (used for the OLDMEDLINE records) |

Table of Contents

### Owner (OWN)

The acronym for the organization that supplied the citation data is recorded in this field. Each citation has only one Owner and there are eight possible values in this field:

| | |
|---|---|
| **NLM** | National Library of Medicine, Index Section |
| **NASA** | National Aeronautics and Space Administration |
| **PIP** | Population Information Program, Johns Hopkins School of Public health (not a current value; only on older citations) |
| **KIE** | Kennedy Institute of Ethics, Georgetown University |
| **HSR** | National Information Center on Health Services Research and Health Care Technology, National Library of Medicine |
| **HMD** | History of Medicine Division, National Library of Medicine |
| **SIS** | Specialized Information Services Division, National Library of Medicine (not yet used; reserved for possible future use) |
| **NOTNLM** | For licensees' use. Not used by NLM. |

Table of Contents

### Pagination (PG)

Pagination indicates the inclusive pages for the article cited. The pagination can be entirely non-digit data. Redundant digits are omitted. Document numbers for electronic articles are also found here.

**Examples:**

PG - 12-9
PG - 304-10
PG - 335-6
PG - 1199-201
PG - 24-32, 64
PG - suppl 111-2
PG - 564
PG - E101-6
PG - 44; discussion 44-8



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000178

PG - 925; author reply 925-6
PG - e66
PG - XC-CIII
PG - 10.1-8

Beginning in December 2002, new rules are followed for pagination for letters to the editor that include text consisting of an author reply. If the reply is written by one or more of the authors of the original article, the words "author reply" are used in the pagination field rather than the word "discussion". "Discussion" continues to be used within pagination for other types of articles, such as an article presented at a meeting that is followed by the text of a separate discussion or verbal exchange by a panel or others attending the meeting. This new rule for pagination that includes "author reply" applies only to citations with Publication Type of Letter.

Table of Contents

### Personal Name as Subject (PS)

Individuals' names appear in this field for citations that contain a biographical note or obituary, or are entirely about the life or work of an individual or individuals. Data is entered in the same format as author names in the Author field. See Author (AU) field for details of format. See also the associated Full Personal Name as Subject (FPS) field description.

**Examples:**

PS - Koop CE
PS - Zerhouni EA

Table of Contents

### Full Personal Name as Subject (FPS)

This field contains the full name of the subject of the article for citations with a date of publication beginning with 2002. It is associated with the Personal Name as Subject (PS) field. See details on format in the Full Author (FAU) field description.

**Examples:**

FPS - Koop, C Everett
FPS - Zerhouni, Elias Adam

Table of Contents

### Place of Publication (PL)

This field indicates the cited journal's country of publication. Valid values are those country names found in the Z category of the Medical Subject Headings (MeSH) that may be displayed from the MeSH Browser at http://www.nlm.nih.gov/cgi/mesh/2010/MB_cgi?term=Geographic+Locations&field=entry#TreeZ01. Values may appear in all upper case or in mixed case. On older records, in cases where the place of publication is unknown, the (PL) value is Unknown.

**Examples:**

PL - United States
PL - FRANCE
PL - Nigeria

Place of Publication data are not maintained when names may change over time. These data indicate where the


Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000179

journal is published, not where the research was conducted.

Table of Contents

### Publication History Status (PHST)

This field contains information from the publisher regarding important events in the publishing process. It contains a date, and one of the following values for each date in the publication history:

| | |
|---|---|
| **[received]** | date manuscript received for review |
| **[accepted]** | accepted for publication |
| **[revised]** | article revised by publisher or author |
| **[aheadofprint]** | published electronically, to be followed by the print |

**Examples:**

PHST- 2004/06/01 [received]
PHST- 2004/09/01 [revised]
PHST- 2005/02/15 [accepted]

Table of Contents

### Publication Status (PST)

This field contains the current status of the publication, as submitted by the publisher. Possible values are:

**ppublish** - published in print (default value)
**epublish** - electronically published only, never published in print
**aheadofprint** - electronically published, but followed by print

**Examples:**

PST - aheadofprint
PST - ppublish

The date on which the current status took effect is submitted in the Date of Publication field.

Table of Contents

### Publication Type (PT)

This field describes the type of material that the article represents; it characterizes the nature of the information or the manner in which it is conveyed (e.g., Review, Letter, Retracted Publication, Clinical Trial). Records may contain more than one Publication Type, which are listed in alphabetical order.

**Examples:**

PT - Review
PT - Multicenter Study

Almost all citations have one of these four basic, most frequently used Publication Types applied to them: Journal Article, Letter, Editorial,
News. One of the above four Publication Types is applied to more than 99% of all citations indexed for MEDLINE.

A list of the Publication Types is available from PubMed Help at: http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=helppubmed.table.pubmedhelp.T42. A list with definitions is available at http://www.nlm.nih.gov/mesh/pubtypes.html. Publication Types are also available in the MeSH Database at http://www.ncbi.nlm.nih.gov/mesh.



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000180

Some Publication Types have similar main headings equivalents in MeSH. In 2008, the form of similar main headings was modified to include "AS TOPIC". For example, the Publication Type CLINICAL TRIAL has a similar MeSH heading CLINICAL TRIALS AS TOPIC.

Historical Notes:

Five citation types were used to describe various types of articles in MEDLARS before 1991. These were HISTORICAL ARTICLE, HISTORICAL BIOGRAPHY, CURRENT BIOGRAPHY-OBITUARY, MONOGRAPH and REVIEW. MONOGRAPHS were chosen for indexing in Index Medicus only from 1976 through 1981. Indexers were expected to identify each of these citation types during the indexing process.

In 1991 these citation types were replaced with a new MEDLARS data element called Publication Type (PT). The number of publication types was expanded to include types which are indexed for other NLM databases in addition to Index Medicus and MEDLINE.
All of the rubrics used to qualify titles have also become publication types.

At the request of the History of Medicine Division of NLM the list of publication types was expanded in 1997 to include 34 "genre terms" to describe the intellectual or literary type of presentation. These are used chiefly by catalogers and indexers for HISTLINE, rather than by indexers for Index Medicus and MEDLINE.

Every item indexed from 1991 forward is described by one or more of the Publication Types.

Table of Contents

### Publishing Model (PUBM)

This field was removed in the 2009 MEDLINE/PubMed production year.

This field described the medium/media in which the cited article is published. This information was derived from data submitted by the publishers.

**Examples:**

PUBM - Print
PUBM - Print-Electronic

Table of Contents

### PubMed Central Identifer (PMC)

This field contains the unique identifer for the cited article in PubMed Central. The identifier begins with the prefix PMC.

**Example:**

PMC - PMC1463022
PMC - PMC2271135

Table of Contents

### PubMed Central Release (PMCR)

This field contains the embargo date associated with the availability of the published article in PMC.

**Example:**

PMCR - 2009/08/01



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000181

Table of Contents

### PubMed Unique Identifier (PMID)

This field is a 1- to 8-digit accession number with no leading zeros. It is present on all records and is the accession number for managing and disseminating records. PMIDs are not reused after records are deleted.

**Examples:**

PMID - 10097079
PMID - 6012557

Prior to the 2004 version of PubMed (available December 3, 2003), many records contained a MEDLINE Unique Identifier in addition to the PMID. NLM no longer displays the MEDLINE Unique Identifier. The PMID has become the unique identifier for the MEDLINE record.

Table of Contents

### Registry Number/EC Number (RN)

This field contains the unique 5- to 9-digit number in hyphenated format assigned by the Chemical Abstracts Service (CAS) to specific chemical substances. For enzymes, the EC number derived from Enzyme Nomenclature is placed in this element. A zero (0) is a valid value when an actual number cannot be located or is not yet available.

Following the RN/EC field display is the Substance Name (NM) field value, enclosed in parentheses. Please see Substance Name (NM) field section for an explanation of that field.

**Examples:**

RN - 69-93-2 (Uric Acid)
RN - EC 3.1.1.34 (Lipoprotein Lipase)

Table of Contents

### Substance Name (NM)

This field contains the name of the substance that the registry number or the EC number identifies. The MeSH Database (http://www.ncbi.nlm.nih.gov/mesh) or MeSH Browser (http://www.nlm.nih.gov/mesh/MBrowser.html) contain the Substance Names. These records are of two types: 1) Supplementary Concept Records, which can be found in the MeSH Browser with a record type of C, or 2) MeSH Category D descriptors, identified in the MeSH Browser with a tree number that begins with D. The Substance Name follows the RN/EC field display, enclosed within parentheses.

**Examples:**

RN - 69-93-2 (Uric Acid)
RN - 6964-20-1 (tiadenol)

Table of Contents

### Secondary Source ID (SI)

The SI field contains information pertaining to the registration of several types of data discussed in MEDLINE articles: a) molecular sequence data; b) gene expression/molecular abundance data (beginning February 2006); c) clinical trial numbers (beginning summer 2005); and d) PubChem identifiers. The field is composed of the source followed by a slash followed by an accession number.



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000182

**Examples:**

SI - GENBANK/AF306859
SI - SWISSPROT/P13209
SI - ClinicalTrials.gov/NCT00000419
SI - GEO/GDS275
SI - PubChem-Substance/17424970

**Molecular Sequence Data**

NLM cooperates with international efforts to collect molecular sequence data. There are, at present, seven databanks that register molecular sequences deposited with them by researchers. In the journal literature, a reference to the databank and the accession number assigned to the sequence may accompany, or substitute for, a lengthy graphic representation of the sequence itself. NLM enters this data in the SI field if this information appears in the printed journal article. If the article lists a databank but no accession number, only the abbreviation for the databank will be entered. There is no attempt to edit or verify the databank accession numbers that appear in the journal. Since sequences may be deposited with more than one databank, there may be multiple occurrences of this field in a single citation. This information may appear on the article title page, in a footnote or in a statement such as:

> Sequence data from this article have been deposited with the EMBL, GenBank and DDBJ Data Libraries under Accession No. M16978.

The seven databanks registering molecular sequence data at the present time are:

| MEDLINE Abbreviation | Databank |
|---|---|
| **GDB** | Johns Hopkins University Genome Data Bank |
| **GENBANK** | GenBank Nucleic Acid Sequence Database |
| **OMIM** | Mendelian Inheritance in Man (McKusick) |
| **PDB** | Protein Data Bank |
| **PIR** | Protein Identification Resource |
| **RefSeq** | Reference Sequence |
| **SWISSPROT** | Protein Sequence Database |

NLM first began to include this information with the 1988 indexing year. Prior to 2000, NLM's policy was to enter up to 30 databank accession numbers for each record. Some global maintenance was done over the years to add databank names/accession numbers whether or not the article itself contained those references. From 2000 forward, NLM enters all databank accession numbers published in the journal. Data in this field are sorted first by databank name and then by the accession number.

Beginning in September 2006, accession numbers for sequences in NLM's Reference Sequence (RefSeq) database are included in the SI field. RefSeq is a curated, non-redundant set of sequences, including genomic DNA, transcript RNA and protein products.

The SI field and the Entrez sequence database links are not related. The PubMed links to these databases are created from the reference field of the GenBank or GenPept flatfile. These references include citations that discuss the specific sequence presented in these flatfiles.

**Gene Expression Data**

Beginning in February 2006, accession numbers for data deposited in NLM’s Gene Expression Omnibus (GEO) database are included in SI field. GEO is a gene expression/molecular abundance repository supporting data submissions, and a curated, online resource for gene expression data browsing, query and retrieval.

The databank abbreviation is GEO and the accession number is any one of four prefixes followed by a numeric string:

GDSxxxx (GEO Data Set)
GSExxxx (GEO SEries)
GPLxxxx (GEO PLatform)
GSMxxxx (GEO SaMple)

**Clinical Trial Numbers**

Beginning in the Summer of 2005, NLM includes the ClinicalTrials.gov identifier number in the SI field when the



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000183

article is devoted solely and entirely to announcing or reporting the results of the clinical trial. The ICMJE Web site (http://www.icmje.org/) contains an editorial and updates on the topic of registering clinical trials before publication of the results.

Beginning mid-2006, MEDLINE citations also carry the International Standard Randomised Controlled Trial Number (ISRCTN) when when the article is devoted solely and entirely to announcing or reporting the results of the clinical trial or other study that the Identifier Number represents. The ISRCTN Register (http://isrctn.org/) is a clinical trials deposit site based in the UK that meets the criteria set forth by the ICMJE (International Committee of Medical Journal Editors) for responsible disclosure of information to the public. The letters ISRCTN are a part of the trial number.

**PubChem Identifiers**

Beginning in January 2007, identifiers for records in the PubChem Substance database may be included in the SI field (but only if the data are included in the citation XML feeds from the publishers). The abbreviation is PubChem-Substance and the accession number is a numeric string, e.g. 10318689. In the distant future, identifiers for records in two additional databases, PubChem Compound and PubChem BioAssay, will likely also be added to MEDLINE/PubMed records.

Table of Contents

## Source (SO)

NLM concatenates the following elements to create the journal source:

Journal Title Abbreviation (TA)
Publication Date (DP)
Volume (VI)
Issue (IP)
Pagination (PG)

Elements of other date fields may be added to indicate an additional Epub or Print publication date.

**Examples:**

SO - Am J Med. 2005 May;118(5):567.
SO - Hepatology. 2004 Apr;39(4):915-23.
SO - Health Care Finance Rev. 2003 Winter;25(2):77-90.
SO - Eur Spine J. 2005 Nov;14(9):887-94. Epub 2005 Sep 8.

Table of Contents

## Space Flight Mission (SFM)

This field resides on citations created by one of our collaborating data producers, the National Aeronautics and Space Administration (NASA). It is the space flight/mission name and/or number when results of research conducted in space are covered in the cited publication. View a complete list of Space Flight Missions and their associated values (manned/unmanned; short/long duration) at http://www.nlm.nih.gov/bsd/space_flight.html.

**Examples:**

SFM - Flight Experiment
SFM - Mir Project
SFM - long duration
SFM - manned

Table of Contents

## Status (STAT)

The status field indicates the status of the record. There are seven possible values for this field:



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000184

- **In-Data-Review:** Records in this status have been submitted to NLM electronically by the publisher, and the journal title, date of publication and volume/issue (source data) have been checked. The source data have either been:
    1. matched to the print copy in NLM's collection and are correct;
    2. matched to the online version of the journal (when NLM assigns MeSH headings from the online version) and are correct; or
    3. compared to previously checked-in issues and appear to match the pattern or have been changed to match the established pattern. In these cases, the physical item has not yet been received for NLM's collection and the data have not been positively verified and may still change during NLM's processing cycle.

  While all three reviews are at the issue level, most citations fit into the last condition above. It is possible that the source information may be changed at a later point in the NLM quality assurance cycle once the hard copy issue is available for exact comparison.

  In-Data-Review records lack a Date Completed field. They are not yet MEDLINE records because they have not undergone complete quality review and MeSH indexing. The issue level review for In-Data-Review status is the first step in quality control. The records will typically either be reissued as In-process status records or go to PubMed-not-MEDLINE final record status.
- **In-Process:** Records in this status have undergone a citation level review; i.e., the author names, article title, and pagination are checked.

  In-process records do not have a Date Completed field, however, they do contain the Subset field. In-process records are not yet MEDLINE records because they have not undergone complete quality review and MeSH indexing.

  Most in-process records are eventually indexed with MeSH terms and are elevated to completed MEDLINE status. However, some are determined to be out of scope (e.g., articles on plate tectonics or astrophysics from certain MEDLINE journals, primarily general science and chemistry journals, for which the life sciences articles are indexed for MEDLINE) and are not elevated to MEDLINE status; instead they become PubMed-not-Medline final status records. In rare cases the records are deleted and do not become PubMed-not-MEDLINE records.
- **MEDLINE:** In-process records undergo rigorous quality assurance routines before they are elevated to MEDLINE status or to PubMed-not-MEDLINE status.

  Records in MEDLINE status are the only 'true' MEDLINE records in PubMed. They contain Date Completed and Subset fields and, in most cases, contain MeSH terms. MEDLINE records that are Retractions of Publications (see Publication Type element) are exceptions and do not contain MeSH terms.
- **OLDMEDLINE:** Citations from the OLDMEDLINE subset begin in OLDMEDLINE status. Once *all* of the original subject terms from the printed index have been mapped to current MeSH, the citation status is changed to MEDLINE. See more information about OLDMEDLINE.
- **PubMed-not-MEDLINE:** Records in this status are from journals included in MEDLINE and have undergone quality review but are not assigned MeSH headings because the cited item is not in scope for MEDLINE either by topic or by date of publication, or is from a non-MEDLINE journal. The categories of non-MEDLINE records in this status are:
    1. citations to articles that precede the date a journal was selected for MEDLINE indexing and are submitted for inclusion in PubMed after July 2003;
    2. out of scope citations to articles in journals covered by MEDLINE;
    3. analytical summaries of articles published elsewhere (see the article, "Linking MEDLINE Citations to Evidence-Based Medicine Assessments and Summaries", in the May-Jun 2002 *NLM Technical Bulletin*, page e2); and
    4. (starting in the Summer of 2005) prospective citations to articles from non-MEDLINE journals that submit full text to PubMed Central®, and are thus cited in PubMed.

  PubMed-not-MEDLINE records contain a Date Completed field and lack Subset and MeSH term fields.

- **Publisher:** The non-MEDLINE records in Publisher Status in PubMed contain the notation [PubMed - as supplied by publisher] in the PubMed display. At this time the records in Publisher Status are:
    1. the retrospective records (prior to July 2005) for the relatively few non-MEDLINE journals in PubMed;
    2. the retrospective records for MEDLINE journals prior to date of selection for MEDLINE and that were submitted electronically by the publishers before late July 2003;
    3. the prospective records for currently indexed journals when the publisher has submitted an issue's citation data electronically and NLM still awaits its print copy or access to the electronic copy to use for issue level review (i.e., the journal title, date of publication and volume/issue elements) AND the publisher-supplied record contains a validation error of some kind that prevents it from being exported from NLM's Data Creation and Maintenance System (DCMS) along with the records not containing errors from the same issue. If there were no errors, the record would move to In-Data-Review status right away and be exported. In these cases, however, NLM staff must take corrective action before the


Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000185

record can be elevated to In-Data-Review status for export; and
4. citations electronically submitted for articles that appear on the Web in advance of the journal issue's release (i.e., ahead of print citations). Following publication of the completed issue, the item will be queued for issue level review and released in In-Data-Review status.

---

Table of Contents

---

## Subset (SB)

This field identifies the subset for MEDLINE records from certain journal lists or records on specialized topics. Some of these values are found on extremely small numbers of records. Citations may contain more than one occurrence of this field. The value is true at the time the record was created. If the status of a journal changes, the value on the record does not change.

Subset field values and their definitions are as follows. Note that several are closed subsets no longer being assigned.

| | |
|---|---|
| **AIM** | citations from *Abridged Index Medicus* journals, a list of about 120 core clinical, English language journals. |
| **B** | citations from non-*Index Medicus* journals in the field of biotechnology (not currently used). |
| **C** | citations from non-*Index Medicus* journals in the field of communication disorders (not currently used). |
| **D** | citations from dental journals. See the current List of Journals Indexed for MEDLINE (LJI) under *Dentistry* and *Orthodontics*. |
| **E** | citations in the field of bioethics. (includes records from the former BIOETHICSLINE database) |
| **F** | older citations from one journal prior to its selection for *Index Medicus*. Used to augment the database for NLM's International MEDLARS Centers (not currently used). |
| **H** | citations from non-*Index Medicus* journals in the field of health administration. (includes records from the former HealthSTAR database) |
| **IM** | citations from *Index Medicus* journals. |
| **J** | citations in the field of population information. (not currently used; on records from the former POPLINE® database) |
| **K** | citations from non-*Index Medicus* journals relating to consumer health. |
| **N** | citations from nursing journals. See the current List of Journals Indexed for MEDLINE (LJI) under *Nursing*. |
| **OM** | citations from the OLDMEDLINE project that originated from the *Cumulated Index Medicus* and the *Current List of Medical Literature* (in 2008 this includes citations from the 1949-1965 print indexes). The ways they differ from other MEDLINE records are documented under the applicable element descriptions. The original MeSH Headings assigned at the time the citation was created in print reside in the Other Term field. Records in the OLDMEDLINE subset have a status of OLDMEDLINE until *all* of their original subject terms are mapped to current MeSH; then their status changes to MEDLINE. NLM makes available both new and revised OLDMEDLINE records on an irregular and infrequent basis. |
| **Q** | citations in the field of the history of medicine. (includes records from the former HISTLINE® database) |
| **QIS** | citations from non-*Index Medicus* journals in the field of the history of medicine. (For NLM use effective in late 2006 because they require special handling at NLM; not a subset of Q; some journals previously designated as Q are now QIS.) |
| **QO** | is subset of Q - indicates older history of medicine journal citations that were created before the former HISTLINE file was converted to a MEDLINE-like format. (For NLM use because they require special handling at NLM). |



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000186

| | |
|---|---|
| **R** | citations from non-*Index Medicus* journals in the field of population and reproduction (not currently used). |
| **S** | citations in the field of space life sciences. (includes records from the former SPACELINE™ database) |
| **T** | citations from non-*Index Medicus* journals in the field of health technology assessment. (includes records from the former HealthSTAR database) |
| **X** | citations in the field of AIDS/HIV. (includes records from the former AIDSLINE® database) |

**Examples:**

SB - AIM
SB - IM
SB - X

Do not confuse these journal/citation subsets with the Topics subsets available on PubMed's Limits screen, which are search strategies.

Table of Contents

### Transliterated Title (TT)

This field contains the title of each item originally published in a non-English language, in that language. Transliterations of article titles in some Cyrillic languages (Greek, Bulgarian, Russian, Serbian and Ukrainian) were added to this field through 2004.

**Examples:**

TT - Temoignages et lettres.
TT - Wplyw przebiegu rozwoju plodu i noworodka na ujawnienie sie niektórych chorób okresu doroslego.

For OLDMEDLINE records, the TT field for citations from the 1964 and 1965 *Cumulated Index Medicus* (CIM) is in all uppercase letters. Some OLDMEDLINE citations to articles originally published in a non-English language lack the TT field.

Table of Contents

### Volume (VI)

The volume number of the journal in which the article was published is recorded here.

**Examples:**

VI - 7
VI - 5 Spec No
VI - 49 Suppl 20

Some records (especially records from OLDMEDLINE) contain the Issue field but lack the Volume field; some contain the Volume field but lack the Issue field; and some records contain Volume and Issue data in the Volume element.

Table of Contents



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000187

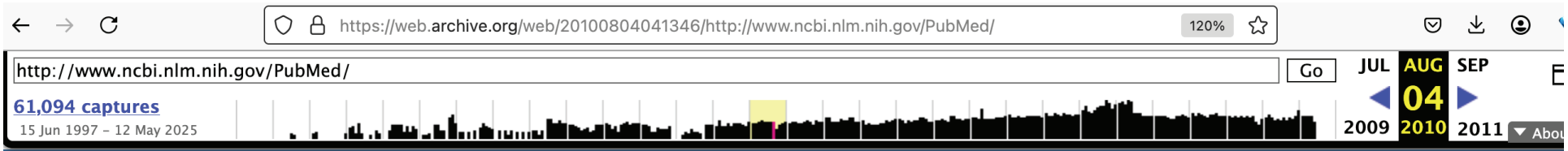
**Last reviewed:** 29 March 2010
**Last updated:** 29 March 2010
**First published:** 17 May 2005
**Metadata**| **Permanence level:** Permanent: Dynamic Content

Copyright, Privacy, Accessibility
U.S. National Library of Medicine, 8600 Rockville Pike, Bethesda, MD 20894
National Institutes of Health, Health & Human Services



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000188

**EX-1005G** PubMed home page archived by Internet Archive on August 4, 2010, available at https://web.archive.org/web/20100804041346/http://www.ncbi.nlm.nih.gov/PubMed/.




NCBI Resources How To

PubMed.gov
U.S. National Library of Medicine
National Institutes of Health

Search: PubMed Limits Advanced search Help

Search Clear

Your browser version may not work well with NCBI's Web applications. More information here...



# PubMed

PubMed comprises more than 19 million citations for biomedical literature from MEDLINE, life science journals, and online Citations may include links to full-text content from PubMed Central and publisher web sites.

## Using PubMed

- PubMed Quick Start Guide
- Full Text Articles
- PubMed FAQs
- PubMed Tutorials
- New and Noteworthy

## PubMed Tools

- Single Citation Matcher
- Batch Citation Matcher
- Clinical Queries
- Topic-Specific Queries

## More Resources

- MeSH Database
- Journals Database
- Clinical Trials
- E-Utilities
- LinkOut

Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000190

The Wayback Machine - https://web.archive.org/web/20100804041346/http://www.ncbi.nlm.nih.gov:80/PubMed/

# PubMed

U.S. National Library of Medicine
National Institutes of Health

Your browser version may not work well with NCBI's Web applications. More information here...

## PubMed

PubMed comprises more than 19 million citations for biomedical literature from MEDLINE, life science journals, and online books. Citations may include links to full-text content from PubMed Central and publisher web sites.

### Using PubMed

- PubMed Quick Start Guide
- Full Text Articles
- PubMed FAQs
- PubMed Tutorials
- New and Noteworthy

### PubMed Tools

- Single Citation Matcher
- Batch Citation Matcher
- Clinical Queries
- Topic-Specific Queries

### More Resources

- MeSH Database
- Journals Database
- Clinical Trials
- E-Utilities
- LinkOut



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000191

**EX-1005H** Publisher webpage for *Nature Biotechnology*, *28*(6), archived by Internet Archive on June 28, 2010, available at https://web.archive.org/web/20100628153945/http://www.nature.com/nbt/journal/v28/n6/index.html.

https://web.archive.org/web/20100628153945/http://www.nature.com/nbt/journal/v28/n6/i
133%
http://www.nature.com/nbt/journal/v28/n6/index.html
Go
32 captures
11 Jun 2010 - 15 Jun 2017
MAY JUN AUG
2009 28 2010 2011
About this capture



# nature biotechnology



## Current issue



**June 2010, Volume 28 No 6 pp529-628**

In This Issue
Editorial
News News Features
Bioentrepreneur
Opinion and Comment Correspondence
Features Patents
News and Views
Research Highlights

SciBX
From the makers of *Nature* and BioCentury
Subscribe today

Language selector
Japanese table of contents

Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000193

The Wayback Machine - https://web.archive.org/web/20100628153945/http://www.natur...

# Current issue




ISSUE

**June 2010, Volume 28 No 6 pp529-628**

**In This Issue**
**Editorial**
**News** News Features
**Bioentrepreneur**
**Opinion and Comment** Correspondence
**Features** Patents
**News and Views**
**Research Highlights**
**Computational Biology** Analysis
**Research** Review Brief Communications Article Letters Resources
**Errata**
**Careers and Recruitment** People

**About the cover**

## In This Issue

**PDF**

## Editorial

### An empiric victory p529

doi:10.1038/nbt0610-529

Provenge already looks like the product of a bygone era.

**Abstract** | **Full Text** | **PDF (98 KB)**

## News

### Landmark approval for Dendreon's cancer vaccine pp531 - 532

Laura DeFrancesco

doi:10.1038/nbt0610-531

**Full Text** | **PDF (263 KB)**

### Firms chase diabetic inflammation with anti-IL-1β antibodies pp533 - 534

Cormac Sheridan

doi:10.1038/nbt0610-533

**Full Text** | **PDF (188 KB)**



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000194

**African GM safety drill p534**
Lucas Laursen
doi:10.1038/nbt0610-534
**Full Text** | **PDF (107 KB)**

**Burgeoning stem cell product market lures major suppliers pp535 - 536**
Sarah Webb
doi:10.1038/nbt0610-535
**Full Text** | **PDF (228 KB)**

**GMP cell lines to order p536**
Susan Aldridge
doi:10.1038/nbt0610-536a
**Full Text** | **PDF (78 KB)**

**Open-access fermenter p536**
Asher Mullard
doi:10.1038/nbt0610-536b
**Full Text** | **PDF (78 KB)**

**Glyphosate resistance threatens Roundup hegemony pp537 - 538**
Emily Waltz
doi:10.1038/nbt0610-537
**Full Text** | **PDF (346 KB)**

**SBIR grants wax p538**
Emma Dorey
doi:10.1038/nbt0610-538a
**Full Text** | **PDF (133 KB)**

**Relief over stem cell lines p538**
Jeffrey L Fox
doi:10.1038/nbt0610-538b
**Full Text** | **PDF (133 KB)**


Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000195

**Obama appoints bioethics panel to offer practical advice p539**
Jeffrey L Fox
doi:10.1038/nbt0610-539a
**Full Text** | **PDF (126 KB)**

**GSK's RNA splash p539**
Janelle Weaver
doi:10.1038/nbt0610-539b
**Full Text** | **PDF (126 KB)**

**Germany caps drug prices p539**
Suzanne Elvidge
doi:10.1038/nbt0610-539c
**Full Text** | **PDF (126 KB)**

### News Features

**Biotech breeding goes bovine pp540 - 543**
Stephen Strauss
doi:10.1038/nbt0610-540

Dairy farmers are rapidly adopting molecular profiling to accelerate the process of siring cows. But this seismic shift in breeding practices is raising new questions and translating more slowly to the beef industry. Stephen Strauss reports.

**Abstract** | **Full Text** | **PDF (227 KB)**

**Up for grabs pp544 - 546**
Michael Eisenstein
doi:10.1038/nbt0610-544

As issued patents on induced pluripotent stem (iPS) cells stack up, the specter of a patent thicket looms. Michael Eisenstein investigates.

**Abstract** | **Full Text** | **PDF (187 KB)** | **Supplementary information**

## Bioentrepreneur

**Beyond venture capital pp547 - 549**


Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000196

John Hollway
doi:10.1038/bioe.2010.4
**PDF (208 KB)**

## Opinion and Comment

### Correspondence

**1 out of 27—European politicians score poorly in agbiotech pp551 - 552**
Atanas Atanassov, Godelieve Gheysen, Denis J Murphy, Olivier Sanvido, Joachim Schiemann, Charles Spillane & Roberto Tuberosa
doi:10.1038/nbt0610-551
**Full Text** | **PDF (237 KB)**

**Split approvals and hot potatoes pp552 - 553**
Henry I Miller
doi:10.1038/nbt0610-552
**Full Text** | **PDF (157 KB)**

**Why drought tolerance is not the new *Bt* pp553 - 554**
Travis J Lybbert & Adrian Bell
doi:10.1038/nbt0610-553
**Full Text** | **PDF (193 KB)**

**Health impact in China of folate-biofortified rice pp554 - 556**
Hans De Steur, Xavier Gellynck, Sergei Storozhenko, Ge Liqun, Willy Lambert, Dominique Van Der Straeten & Jacques Viaene
doi:10.1038/nbt0610-554
**Full Text** | **PDF (296 KB)** | **Supplementary information**

**Alive and kicking p556**
Lance Stewart
doi:10.1038/nbt0610-556
**Full Text** | **PDF (171 KB)**


Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000197

## Features

### Patents

**Pluripotent patents make prime time: an analysis of the emerging landscape pp557 - 559**
Brenda M Simon, Charles E Murdoch & Christopher T Scott
doi:10.1038/nbt0610-557

An examination of three patents in the fast-moving iPS space may help determine their ultimate value.

**Abstract** | **Full Text** | **PDF (130 KB)**

**Recent patent applications in epigenetics p560**
doi:10.1038/nbt0610-560
**Full Text** | **PDF (41 KB)**

## News and Views

**Raising the bar for cancer therapy models pp561 - 562**
Giulio Francia & Robert S Kerbel
doi:10.1038/nbt0610-561

Can mouse cancer models predict the results of phase 3 clinical trials?

**Full Text** | **PDF (1,755 KB)**
**See also:** **Research by Singh *et al.***

**Scalable pluripotent stem cell culture pp562 - 563**
Larry A Couture
doi:10.1038/nbt0610-562

Large-scale production of human embryonic stem cells will require improved culture methods.

**Full Text** | **PDF (707 KB)**
**See also:** **Research by Villa-Diaz *et al.*** | **Research by Melkoumian *et al.*** | **Research by Rodin *et al.***

**Complex molecular dynamics in the spotlight pp564 - 565**
Lois Pollack & Watt W Webb
doi:10.1038/nbt0610-564


Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000198

Zero-mode waveguides illuminate the process of translation.

**Full Text** | **PDF (907 KB)**

### Detecting methylated bases in real time p565

Markus Elsner

doi:10.1038/nbt0610-565

**Full Text** | **PDF (570 KB)**

## Research Highlights

### Research highlights p566

doi:10.1038/nbt0610-566

**Full Text** | **PDF (97 KB)**

## Computational Biology

**Analysis**

### Comparative assessment of methods for aligning multiple genome sequences pp567 - 572

Xiaoyu Chen & Martin Tompa

doi:10.1038/nbt.1637

Mining information from genomes often begins by aligning the sequences to identify evolutionarily conserved regions. Chen *et al.* assess the performance of four commonly used multiple sequence alignment tools.

**Abstract** | **Full Text** | **PDF (647 KB)** | **Supplementary information**

## Research

**Review**

### Rationalizing the development of live attenuated virus vaccines pp573 - 579

Adam S Lauring, Jeremy O Jones & Raul Andino

doi:10.1038/nbt.1635

**Abstract** | **Full Text** | **PDF (484 KB)**



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000199

## Brief Communications

### Synthetic polymer coatings for long-term growth of human embryonic stem cells pp581 - 583

Luis G Villa-Diaz, Himabindu Nandivada, Jun Ding, Naiara C Nogueira-de-Souza, Paul H Krebsbach, K Sue O'Shea, Joerg Lahann & Gary D Smith

doi:10.1038/nbt.1631

The development of fully defined culture conditions for human embryonic stem cells (hESCs) should enhance experimental reproducibility, reduce unwanted contaminants and facilitate scale-up production. Villa-Diaz *et al.* show that a substrate made of the synthetic polymer PMEDSAH supports long-term culture of hESCs.

**First Paragraph** | **Full Text** | **PDF (471 KB)** | **Supplementary information**

**See also:** **News and Views by Couture**

## Article

### Assessing therapeutic responses in *Kras* mutant cancers using genetically engineered mouse models pp585 - 593

Mallika Singh, Anthony Lima, Rafael Molina, Patricia Hamilton, Anne C Clermont, Vidusha Devasthali, Jennifer D Thompson, Jason H Cheng, Hani Bou Reslan, Calvin C K Ho, Timothy C Cao, Chingwei V Lee, Michelle A Nannini, Germaine Fuh, Richard A D Carano, Hartmut Koeppen, Ron X Yu, William F Forrest, Gregory D Plowman & Leisa Johnson

doi:10.1038/nbt.1640

Genetically engineered mouse models of cancer simulate the spontaneous development of tumors in their native tissue environment. Singh *et al.* establish their ability to predict the efficacy of different treatment regimens by comparing clinical trial results to equivalent experiments in mutated KRAS-driven mouse models of pancreatic and lung cancer.

**Abstract** | **Full Text** | **PDF (1,979 KB)** | **Supplementary information**

**See also:** **News and Views by Francia & Kerbel**

## Letters

### Single-molecule enzyme-linked immunosorbent assay detects serum proteins at subfemtomolar concentrations pp595 - 599

David M Rissin, Cheuk W Kan, Todd G Campbell, Stuart C Howes, David R Fournier, Linan Song, Tomasz Piech, Purvish P Patel, Lei Chang, Andrew J Rivnak, Evan P Ferrell, Jeffrey D Randall, Gail K Provuncher, David R Walt & David C Duffy

doi:10.1038/nbt.1641

Rissin *et al.* increase the sensitivity of sandwich ELISA by segregating beads bearing a single enzyme-labeled immunoconjugate into femtoliter-volume reaction chambers. As the small volume of each well permits detection of extremely low levels of fluorescence, protein abundance is determined by counting the number of



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000200

fluorescent wells as a percentage of the number of wells containing beads.

**First Paragraph** | **Full Text** | **PDF (511 KB)** | **Supplementary information**

### Identification of influenza A nucleoprotein as an antiviral target pp600 - 605

Richard Y Kao, Dan Yang, Lai-Shan Lau, Wayne H W Tsui, Lihong Hu, Jun Dai, Mei-Po Chan, Che-Man Chan, Pui Wang, Bo-Jian Zheng, Jian Sun, Jian-Dong Huang, Jason Madar, Guanhua Chen, Honglin Chen, Yi Guan & Kwok-Yung Yuen

doi:10.1038/nbt.1638

The spread of influenza virus strains resistant to the current generation of anti-viral drugs makes the identification of new druggable targets and lead compounds of prime importance. Kao *et al.* show that the influenza A nucleoprotein can be targeted by a small molecule that protects mice from lethal viral challenges.

**First Paragraph** | **Full Text** | **PDF (839 KB)** | **Supplementary information**

### Synthetic peptide-acrylate surfaces for long-term self-renewal and cardiomyocyte differentiation of human embryonic stem cells pp606 - 610

Zara Melkoumian, Jennifer L Weber, David M Weber, Andrei G Fadeev, Yue Zhou, Paula Dolley-Sonneville, Jiwei Yang, Liqun Qiu, Catherine A Priest, Christopher Shogbon, Arthur W Martin, Jodelle Nelson, Peter West, James P Beltzer, Santona Pal & Ralph Brandenberger

doi:10.1038/nbt.1629

The development of fully defined culture conditions for human embryonic stem cells (hESCs) should enhance experimental reproducibility, reduce unwanted contaminants and facilitate scale-up production. Melkoumian *et al.* show that a substrate made of peptides derived from extracellular matrix proteins supports long-term culture of hESCs and differentiation to cardiomyocytes.

**First Paragraph** | **Full Text** | **PDF (1,187 KB)** | **Supplementary information**

**See also:** **News and Views by Couture**

### Long-term self-renewal of human pluripotent stem cells on human recombinant laminin-511 pp611 - 615

Sergey Rodin, Anna Domogatskaya, Susanne Ström, Emil M Hansson, Kenneth R Chien, José Inzunza, Outi Hovatta & Karl Tryggvason

doi:10.1038/nbt.1620

The development of fully defined culture conditions for human embryonic stem cells (hESCs) should enhance experimental reproducibility, reduce unwanted contaminants and facilitate scale-up production. Rodin *et al.* show that a substrate made of human recombinant laminin-511 supports long-term culture of hESCs and human induced pluripotent stem cells.

**First Paragraph** | **Full Text** | **PDF (1,728 KB)** | **Supplementary information**

**See also:** **News and Views by Couture**



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000201

**Resources**

### Analysis of a genome-wide set of gene deletions in the fission yeast *Schizosaccharomyces pombe* pp617 - 623

Dong-Uk Kim, Jacqueline Hayles, Dongsup Kim, Valerie Wood, Han-Oh Park, Misun Won, Hyang-Sook Yoo, Trevor Duhig, Miyoung Nam, Georgia Palmer, Sangjo Han, Linda Jeffery, Seung-Tae Baek, Hyemi Lee, Young Sam Shim, Minho Lee, Lila Kim, Kyung-Sun Heo, Eun Joo Noh, Ah-Reum Lee, Young-Joo Jang, Kyung-Sook Chung, Shin-Jung Choi, Jo-Young Park, Youngwoo Park, Hwan Mook Kim, Song-Kyu Park, Hae-Joon Park, Eun-Jung Kang, Hyong Bai Kim, Hyun-Sam Kang, Hee-Moon Park, Kyunghoon Kim, Kiwon Song, Kyung Bin Song, Paul Nurse & Kwang-Lae Hoe

doi:10.1038/nbt.1628

Genome-wide single-gene deletion libraries can be important tools for understanding the molecular workings of an organism, but have only been created for a single eukaryotic species, *Saccharomyces cerevisiae*. Now, Kim *et al.* present a second collection of deletion mutants that covers 98.4% of the genes of *Schizosaccharomyces pombe*, allowing a systematic comparison of gene essentiality and knockout phenotypes between two eukaryotic species.

**Abstract** | **Full Text** | **PDF (569 KB)** | **Supplementary information**

## Errata

### Erratum: The cancer vaccine roller coaster p624

Bruce Goldman & Laura DeFrancesco

doi:10.1038/nbt0610-624a

**Full Text** | **PDF (56 KB)**

### Erratum: Irish bioethics council axed p624

Cormac Sheridan

doi:10.1038/nbt0610-624b

**Full Text** | **PDF (56 KB)**

### Erratum: Never again p624

Chris Scott

doi:10.1038/nbt0610-624c

**Full Text** | **PDF (56 KB)**

### Erratum: Resuscitated deCODE refocuses on diagnostics p624

Mark Ratner

doi:10.1038/nbt0610-624d



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000202

**Full Text** | **PDF (56 KB)**

### Erratum: Biotech in a blink p624

Ken Garber

doi:10.1038/nbt0610-624e

**Full Text** | **PDF (56 KB)**

## Careers and Recruitment

### The ABC's of industry: a postdoc program provides a sneak peek into industry careers pp625 - 626

Adnan O Abu-Yousif, Erik C Hett, Ann M Skoczenski & Tayyaba Hasan

doi:10.1038/nbt0610-625

An innovative partnership allows local companies to educate postdocs about careers in industry.

**Abstract** | **Full Text** | **PDF (94 KB)**

## People

### People p628

doi:10.1038/nbt0610-628

**Full Text** | **PDF (93 KB)**

*Nature Biotechnology* ISSN 1087-0156 EISSN 1546-1696



© 2010 Nature Publishing Group, a division of Macmillan Publishers Limited. All Rights Reserved.

partner of AGORA, HINARI, OARE, INASP, CrossRef and COUNTER



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000203

**EX-1005I** Publisher webpage on how to access *Rissin* online, archived by Internet Archive on June 11, 2010, available at https://web.archive.org/web/20100611073455/http://www.nature.com/nbt/journal/v28/n6/full/nbt.1641.html.

https://web.archive.org/web/20100611073455/http://www.nature.com/nbt/journal/v28/n6/f
133%
http://www.nature.com/nbt/journal/v28/n6/full/nbt.1641.html
Go
MAY JUN JUL
11
2009 2010 2011
About this capture
36 captures
11 Jun 2010 – 21 Feb 2018



## Access

**To read this article in full you may need to log in, make a payment or gain access through a site license (see right).**



Research

*Nature Biotechnology* **28**, 595–599 (1 June 2010) | doi:10.1038/nbt.1641

# Single-molecule enzyme-linked immunosorbent assay detects serum proteins at subfemtomolar

ARTICLE TOOLS

Personal subscribers to *Nature Biotechnology* can view this article. To do this, associate your subscription with your registration via the My Account page. If you already have an active subscription, login here to your nature.com account.

If you do not have access to the article you require, you can purchase the article (see below) or access it through a site license. Institutions can add additional archived content to their license at any time. Recommend site license access to your institution.

Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000205

The Wayback Machine - https://web.archive.org/web/20100611073455/http://www.nature...

## Access

**To read this article in full you may need to log in, make a payment or gain access through a site license (see right).**

Research

*Nature Biotechnology* **28**, 595–599 (1 June 2010) | doi:10.1038/nbt.1641

# Single-molecule enzyme-linked immunosorbent assay detects serum proteins at subfemtomolar concentrations

David M Rissin , Cheuk W Kan , Todd G Campbell , Stuart C Howes , David R Fournier , Linan Song , Tomasz Piech , Purvish P Patel , Lei Chang , Andrew J Rivnak , Evan P Ferrell , Jeffrey D Randall , Gail K Provuncher , David R Walt & David C Duffy

**The ability to detect single protein molecules in blood could accelerate the discovery and use of more sensitive diagnostic biomarkers. To detect low-abundance proteins in blood, we captured them on microscopic beads decorated with specific antibodies and then labeled the immunocomplexes (one or zero labeled target protein molecules per bead) with an enzymatic reporter capable of generating a fluorescent product.**

**To read this article in full you may need to log in, make a payment or gain access through a site license (see right).**

**ARTICLE TOOLS**

- **Send to a Friend**
- **Rights & Permissions**
- **Order commercial reprints**

**SEARCH PUBMED FOR**

- **David M Rissin**
- **Cheuk W Kan**
- **Todd G Campbell**
- **Stuart C Howes**
- **David R Fournier**
- **Linan Song**
- **Tomasz Piech**
- **Purvish P Patel**
- **Lei Chang**
- **Andrew J Rivnak**
- **Evan P Ferrell**
- **Jeffrey D Randall**
- **Gail K Provuncher**
- **David R Walt**
- **David C Duffy**

***Nature Biotechnology*** ISSN 1087-0156 EISSN 1546-1696

**About NPG** **Privacy policy** **Nature News**
**Contact NPG** **Legal notice** **Naturejobs**
**RSS web feeds** **Accessibility statement** **Nature Asia**
**Help** **Terms** **Nature Education**



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000206

Search: go

© 2010 Nature Publishing Group, a division of Macmillan Publishers Limited. All Rights Reserved.

partner of AGORA, HINARI, OARE, INASP, CrossRef and COUNTER



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000207

**EX-1005J** Quanterix announcement of the publication of *Rissin*, issued on May 23, 2010, and archived by Internet Archive on June 1, 2010, available at https://web.archive.org/web/20100601142509/http://quanterix.com/news/pdfs/natureBiotech.pdf.

https://web.archive.org/web/20100601142509/http://quanterix.com/news/pdfs/natureBiotech.pdf 120%
http://quanterix.com/news/pdfs/natureBiotech.pdf Go MAY JUN JAN
3 captures 01
1 Jun 2010 – 19 Apr 2011 2009 2010 2011



Quanterix

One Kendall Square, Building 1400
Cambridge, MA 02139
617.301.9400 877.786.8749

**Groundbreaking Study Published in *Nature Biotechnology* Demonstrates Sensitivity of Single Molecule Test for Detection of Prostate Cancer**

*Quanterix Technology Shown To Be More Than 1,000 Times More Sensitive Than Standard Methods With Potential For Broad Application To Measure Biomarkers In Cancer, Autoimmune, and Neurological Diseases*

Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000209

The Wayback Machine - https://web.archive.org/web/20100601142509/http://www.quanterix.com:80/news/pdfs/natureBi…

Quanterix

One Kendall Square, Building 1400
Cambridge, MA 02139
617.301.9400 877.786.8749

**Groundbreaking Study Published in *Nature Biotechnology* Demonstrates Sensitivity of Single Molecule Test for Detection of Prostate Cancer**

*Quanterix Technology Shown To Be More Than 1,000 Times More Sensitive Than Standard Methods With Potential For Broad Application To Measure Biomarkers In Cancer, Autoimmune, and Neurological Diseases*

**CAMBRIDGE, MA – May 23, 2010** – Quanterix Corporation, the single molecule diagnostics company focused on developing and commercializing high sensitivity tests, announced the publication of a breakthrough study of the company's proprietary technology that demonstrates an unprecedented sensitivity for measuring a biomarker for prostate cancer recurrence. The research article, featured on the cover of the June issue (Volume 28, No. 6) of *Nature Biotechnology*, describes how researchers developed a simple blood test using Quanterix's Single Molecule Array (SiMoA™) technology to selectively capture and measure individual Prostate Specific Antigen (PSA) molecules in prostate cancer patients. The study showed that SiMoA was 1,700 times more sensitive than standard hospital tests, potentially allowing for detection of prostate cancer recurrence years earlier than current tests.

To demonstrate the clinical potential of SiMoA, PSA was measured in serum from men who had undergone radical prostatectomy for prostate cancer. For the majority of these patients PSA is initially reported as undetectable following surgery, but may be present at very low levels that predict the likelihood of disease recurrence. The Quanterix test was so sensitive that it was able to measure residual PSA levels in all samples tested. The PSA levels had been reported to be undetectable in these samples by standard tests, highlighting the sensitivity and precision of the SiMoA technology.

"This paper demonstrates the extraordinary sensitivity provided by our SiMoA platform. Its single molecule resolution has allowed us to measure PSA at extremely low levels, rather than having to wait until the cancer is more advanced," said Dr. David C. Duffy, Senior Director of Platform Research, Quanterix and corresponding author of the study. "By using Quanterix's high density arrays, we were able to hone in on individual molecules rather than looking at the average response of thousands of molecules. SiMoA provides the resolution for the proteome that the Hubble telescope did for the cosmos."

"A diagnostic test with this sensitivity may eliminate unnecessary secondary treatment while also providing significant peace of mind for the over 100,000 American men who annually undergo radical prostatectomy for the treatment of prostate cancer and who will ultimately remain disease-free," said Dr. Herbert Lepor, a prostate cancer expert and Chairman of the Department of Urology at the New York University School of Medicine. "New York University Langone Medical Center is looking forward to investigating the Quanterix test to determine its potential for identifying patients who require more or less vigilant follow-up after surgery and, identifying earlier those men who require secondary treatment, thereby optimizing postoperative management."

"The implications of this technology are far reaching," noted David Walt, Ph.D., scientific founder of both Quanterix and Illumina (NASDAQ: ILMN). "In analytical chemistry, single molecule counting is the ultimate goal for sensitivity. This report shows the applicability of SiMoA in measuring an important cancer marker and opens the door for its application in many other areas including neurological, cardiovascular and autoimmune diseases."



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000210

**EX-1005K** Citation history of *Rissin* obtained from Google Scholar.

**EX1005K**
Citations to Rissin

**Source Document**

Rissin, D. M., Kan, C. W., Campbell, T. G., Howes, S. C., Fournier, D. R., Song, L., ... & Duffy, D. C. (2010, May). Single-molecule enzyme-linked immunosorbent assay detects serum proteins at subfemtomolar concentrations, *Nature Biotechnology*, *28*(6), 595-599.

**2010 Citations** (in chronological order)

Brody, E. N., Gold, L., Lawn, R. M., Walker, J. J., & Zichi, D. (2010, November). High-content affinity-based proteomics: unlocking protein biomarker discovery. *Expert review of molecular diagnostics*, *10*(8), 1013-1022.

Sanavio, B., Scaini, D., Grunwald, C., Legname, G., Scoles, G., & Casalis, L. (2010, November). Oriented immobilization of prion protein demonstrated via precise interfacial nanostructure measurements. *Acs Nano*, *4*(11), 6607-6616.

Schwenk, J. M., Igel, U., Neiman, M., Langen, H., Becker, C., Bjartell, A., ... & Uhlen, M. (2010, November). Toward next generation plasma profiling via heat-induced epitope retrieval and array-based assays. *Molecular & Cellular Proteomics*, *9*(11), 2497-2507.

Krishnan, S., Mani, V., Wasalathanthri, D., Kumar, C. V., & Rusling, J. F. (2010, December). Attomolar detection of a cancer biomarker protein in serum by surface plasmon resonance using superparamagnetic particle labels. *Angewandte Chemie (International ed. in English)*, *50*(5), 1175.

Sakakihara, S., Araki, S., Iino, R., & Noji, H. (2010). A single-molecule enzymatic assay in a directly accessible femtoliter droplet array. *Lab on a Chip*, *10*(24), 3355-3362.

**EX-1006A** Copy of *Todd* obtained from the fall 2008 archive of *Drug Discovery World* at https://www.ddw-online.com/media/32/2304/fall-08-immunoassay-systems.pdf.

DRUG DISCOVERY WORLD
DDW
turning science into business

## 2008 ARCHIVE

DDW Spring 2008 | DDW Summer 2008 | DDW Fall 2008 | DDW Winter 2008/09

Prediction versus Attrition in Drug Discovery & Development
DOWNLOAD PDF I GO TO ARTICLE

Treating Rheumatoid Arthritis with Disease-Modifying Antirheumatic Drugs (DMARDs) and Biologics
DOWNLOAD PDF I GO TO ARTICLE

Challenges in Transferring Bioanalytical Methods
DOWNLOAD PDF I GO TO ARTICLE

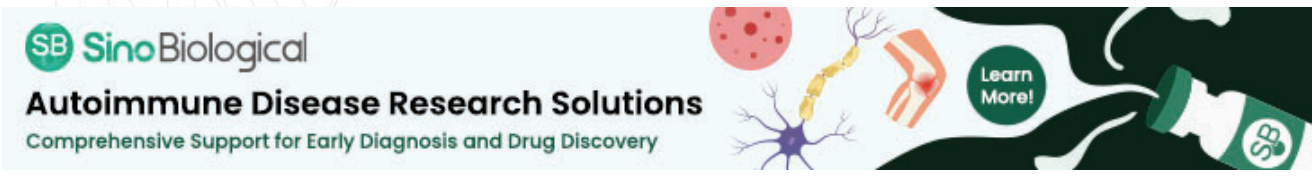
Next Generation Immunoassay Systems and the Revival of Protein Biomarkers
DOWNLOAD PDF I GO TO ARTICLE

High Throughput Screening in Academia – Drug discovery initiatives at the University of Kansas
DOWNLOAD PDF I GO TO ARTICLE

A Bronchoscopically Administered Therapeutic Approach to Advanced Emphysema
DOWNLOAD PDF I GO TO ARTICLE

Microwave-Assisted Organic Synthesis – An enabling technology with disruptive potential
DOWNLOAD PDF I GO TO ARTICLE

Contact Us






Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000214

Media Info

Log In

Terms and Conditions

Privacy Policy

Cookie Policy

## Follow our social accounts

Copyright 2025 © Drug Discovery World (DDW). All Rights Reserved

Designed & Developed with ❤ for digital by Inbound FinTech






Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000215

Immunoassay systems:Layout 1 6/10/08 12:54 Page 51



# HOW LOW CAN YOU GO?

## next generation immunoassay systems and the revival of protein biomarkers

Proteins are the machinery that drive most biological processes; however, measuring their concentrations at low levels has been historically impeded by a lack of appropriately sensitive technology. Advances in immunoassay technology, such as single molecule counting, have provided orders of magnitude of increased sensitivity. These novel technologies are enabling new discoveries and a clearer understanding of previously intractable biology. Here we discuss how single molecule counting technology can brighten the future of translational research, drug discovery and personalised medicine.

**By Dr John Todd and Dr Sara J. Agee**

There is a great paradox facing drug developers: get the most innovative and effective new drugs from bench to bedside as quickly as possible while meeting stringent regulatory demands that demonstrate robust safety and efficacy. This leaves quite a dilemma. Pressure to drive innovative drug candidates through the pharmaceutical pipeline into clinical trials leads to a high level of attrition, where even the most promising drug candidates can fail. This keeps promising therapies from needy patients and leaves pharma footing the bill. The key to solving this puzzle is to effectively rule-in or rule-out drug candidates early in the pipeline, before they enter into costly late phase clinical trials.

### Biomarkers – the beacon of translational biology

One can view classic biochemistry as the original drug discovery machine, beginning with discovery and purification of insulin from pancreatic islet cells in dogs. The medicinal application of this discovery led to a Nobel Prize in 1923 and paved the way for the first pharmaceutical giant: Eli Lilly & Sons. The biology around protein analysis remained the mainstay of big pharma until the molecular revolution of the 90s led into the genomics era. The difficulties of specific and sensitive protein detection helped set the stage for the molecular revolution, where genomics-based approaches have taken centre stage. However, this does not change the central dogma of biology, that our pathopysiology is ultimately determined at the protein level. Therefore we must continue to develop advanced protein detection systems, even for protein biomarkers with previously intractable biology.

The strength of the biomarker movement has been its promise to provide a standardised metric for evaluating new therapies across disease states. In this way biomarkers have become inseparable from the drug development process, and may combine physiological and molecular biomarkers for disease. However, molecular and protein biomarkers (ie



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000216

Immunoassay systems:Layout 1 6/10/08 12:54 Page 52



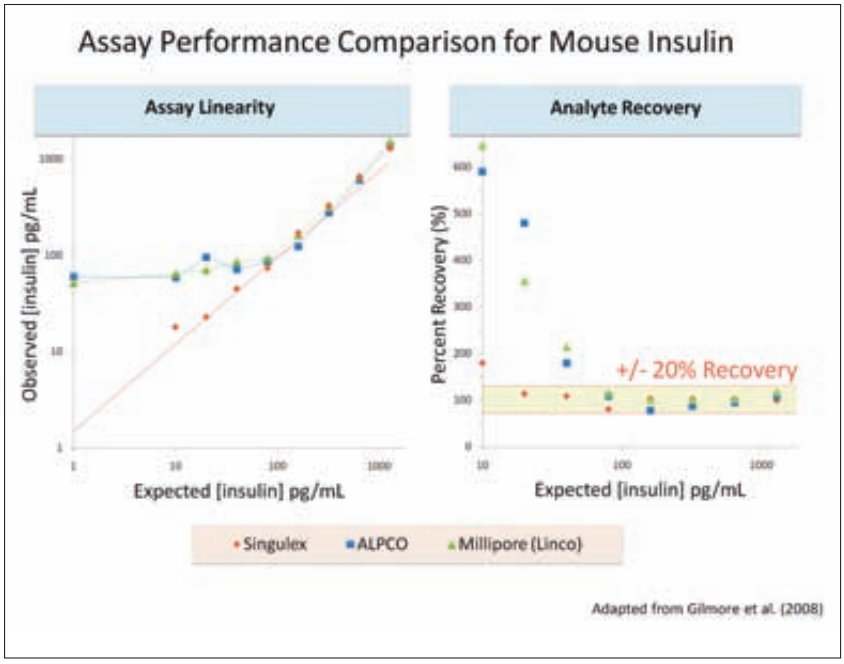



**Figure 1**
Comparison of mouse insulin assay performance

cTnI, insulin) have a strong advantage over physiological biomarkers (ie electrocardiogram, BMI) because they are more quantitative and less subjective. A desired approach is to use protein biomarkers for the targeted disease in early phase I/II studies to understand if a candidate drug exerts a dose-dependent pharmacodynamic (PD) effect on biomarkers that are either in the disease pathway or that are a direct target of the drug. If a drug candidate does not impact the concentration of a relevant biomarker in a dose dependent fashion, this will halt development of the compound. The earlier a problem drug can be screened out the better, saving the expense of costly late phase clinical trials. However, in many cases technology to do this effectively has been a limiting factor, especially for measuring protein biomarkers in readily available specimens such as blood plasma or serum.

Systems biology ushers in a new paradigm, and shifts attitudes from scepticism towards early adoption and implementation of cutting edge technology. We have seen the fields of genomics and bioinformatics grow under this strategy, which can now be applied towards validation of these discoveries at the protein level. In order for this to work requires the successful deployment of several approaches: biomarker discovery, target validation, assay development, instrumentation and clinical trial management. There has been an attempt to unify these approaches under the umbrella of translational research, which has become a hot buzz word even though few people seem to agree on how it is defined or executed. One thing most researchers agree on is that this integrative approach is the future of pharmaceutical development, as evidenced by investments by both the NIH and the European Commission towards funding translational research centres and consortiums[1,2]. The point of confusion usually concerns where and how researchers fit into the very broad 'bench-to-bedside' model. Diagnostics is unique in that it can play a supporting role across the entire bench-to-bedside spectrum, since there is something to be measured every step of the way.

## The disease continuum – a full spectrum of disease states

In a general sense, current diagnostic guidelines based on quantification of protein-based biomarkers suffer from three distinct challenges. First, assay sensitivity is often what determines the lower limit of the threshold and the diagnostic cut-off value. Second, the threshold system only reveals the tip of the iceberg when it comes



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000217

Immunoassay systems:Layout 1 6/10/08 12:54 Page 53



to disease states. As in cTnI, a potential gold mine of information resides beneath the 99th percentile threshold value for a clinically relevant biomarker. This valuable information, quantifiable by single molecule counting (SMC) technology in particular, could be used to diagnose, stratify, determine risk, or aid in disease prevention. Third, development of a disease state is not an on/off proposition. Rather, there is a continuum of disease development which makes disease onset and diagnosis difficult to mark. When does a patient cross the line to a full-fledged disease state? The fuzzy line marking disease onset is a common cause of diagnostic failures.

An excellent example of prolonged disease onset leading towards diagnostic failure is Alzheimer's Disease (AD). Right now, the only definitive diagnosis of AD is a post-mortem examination of brain tissue for amyloid plaques and neurofibrillary tangles. Currently, clinical diagnosis of this disease is diagnosed by ruling out other probable causes for the symptoms of AD, which are usually only apparent after significant disease progression has occurred. Thus there is no reliable way at this time to clinically define when this complex disease officially starts, and an FDA approved molecular diagnostic for AD is desperately needed.

The need for an early diagnosis for AD is especially important as new therapies for AD are developed, which provide better patient outcomes when administered early in the course of the disease. Currently, there is no FDA approved protein biomarker for clinical diagnosis of Alzheimer's disease, though there are some hopeful candidates: beta-amyloid and tau proteins.

However, further clinical validation of this new diagnostic information will be necessary to define the disease state and set the guidelines for early diagnosis and onset of AD.

In this way, protein biomarker programmes in AD and other disease areas can benefit immensely from the application of novel immunoassay technologies with ultra-sensitive detection.

## The solution – integrating novel technology into next generation immunoassay systems

**Fluorosphere immunoassays (Luminex) –** xMAP technology integrates flow cytometry, microspheres, lasers, digital signal processing and traditional chemistry to feature a flexible immunoassay system that can be configured to perform a wide variety of bioassays. Luminex uses colour-coded microspheres, which can be combined into 100 distinct sets. Each bead set can be coated with a reagent specific to a particular bioassay, allowing the capture and detection of specific analytes from a sample. Within the Luminex compact analyser, lasers excite the internal dyes that identify each microsphere particle, and also any reporter dye captured during the assay. In this way, xMAP technology allows multiplexing of up to 100 unique assays within a single sample, both rapidly and precisely. However, multiplexing can come at the expense of assay sensitivity and this technology generally does not provide sensitive measurements beyond what has been historically obtained with 96-well enzymatic assays (eg ELISA).

**Gold nanoparticle probes (Nanosphere) –** Nanoparticles can be used as the solid phase for protein capture by attaching specific capture antibodies for specific analytes. Detection is achieved by attaching bio-barcode nucleic acid probes, which are specifically amplified and quantified. Sequence tagged barcodes are then correlated with specific analyte capture. Multiplexing is accomplished by changing the bio-barcode tags on a set of gold microparticles, providing a method for differential readout. However, the amplification step and multiplexing can increase background and can impact assay precision.

**Single Molecule Counting (SMC)=based systems (Singulex) –** Singulex has developed a proprietary immunoassay technology, which leads the next generation of molecular diagnostic technologies capable of quantifying biomarkers at the sub-picogram level. The proprietary Singulex immunoassay technology utilises paramagnetic microparticles (MPs) as the solid phase for immune-capture and detection of analyte from a complex biological sample, providing enhanced specificity, sensitivity and precision by 1-3 logs over existing plate-based methods. The incorporation of SMC technology into next generation immunoassays, like the Singulex Erenna System, is already having an impact by quantifying proteins at sub-picogram levels[3,4].

## The impact of next generation immunoassay systems

Each of these new immunoassay systems adds value by increasing sensitivity to unprecedented levels of detection, some to below the femtomolar range. The benefit of this new limit of diagnostic sensitivity is the availability of a new tool kit for solving intractable problems in the biology of disease and to embark upon clinical investigations which were

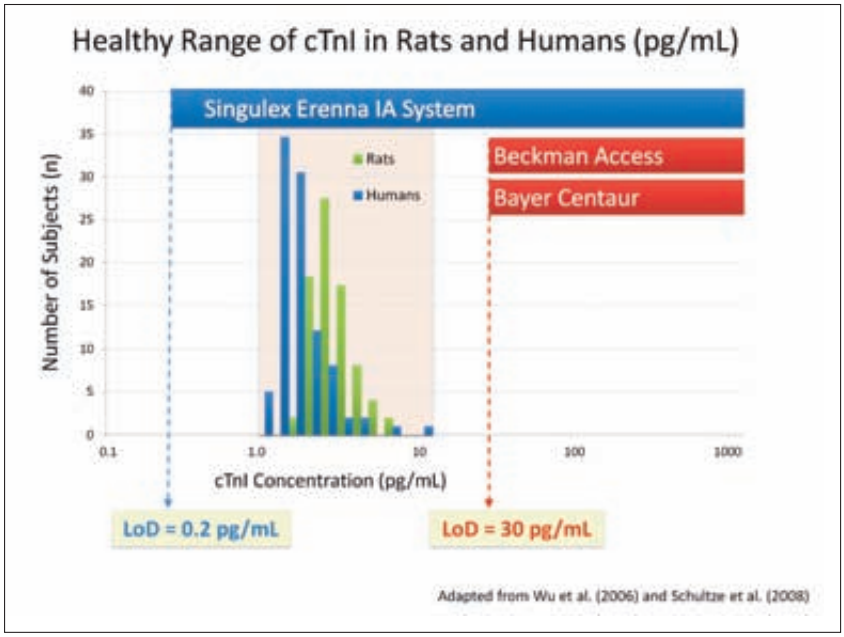


Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000218

Immunoassay systems:Layout 1 6/10/08 12:54 Page 54



**Figure 2**
Range of cTnI in humans and rats compared to assay LoD




previously considered untenable. There are several strategic applications of these new technologies towards key issues facing drug development.

**Making new biological discoveries**

Fundamental to drug discovery is the understanding and manipulation of how biological pathways are altered during disease. These fundamental questions are tackled during preclinical stages of discovery and development, often times in cell culture or small animal model systems for which sensitivity and precision of measurements is an issue. For example, there are several genetic mouse models for diabetes, however accurate insulin measurements in fasted female mice are notoriously difficult. Recently the Singulex proprietary immunoassay has been shown to make accurate quantifications from only 5uL mouse plasma samples, allowing long-term monitoring of insulin over time[5]. In this model, the accuracy of the Erenna System has been shown to provide superior precision over currently available commercial assays (**Figure 1**). Long-term monitoring is also an issue for studies of cardiotoxicity studies in small animals, and the same immunoassay system has shown the ability to accurately quantify cTnI levels from 15uL samples of healthy rat serum[6]. Interestingly, the healthy range of cTnI levels in rats is consistent with measurements in other animals, including humans[7] and is far below the LoD of other currently available commercial assays (**Figure 2**). Lastly, another factor important during the discovery phase is the ability to quantify multiple targets, which also benefits from small volume assays due to increased sensitivity. For example, a recent diagnostic test for diabetes was released that calculates risk based upon the quantification of a panel of biomarkers from samples as small as1.3 uL[8].

**Early disease detection**

The ultimate diagnostic challenge is to detect the onset of disease as early as possible. In terms of patient risk, earlier diagnoses are correlated with better patient outcomes, assuming that efficiacious therapeutic modalities can be employed. The development of clinically relevant molecular biomarkers has already had a huge impact on diagnosis of disease, however a continuing problem is that current guidelines rely on the establishment of cut-off values and thresholds for making a diagnosis. These requisite guidelines were set because technologies at that time could not provide the requisite sensitivity. Now we can measure the complete spectrum from healthy to disease state and hence need to think differently. For example, cardiac troponin-I (cTnI) is considered the gold standard for



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000219

Immunoassay systems:Layout 1 6/10/08 12:54 Page 55



diagnosis of acute myocardial infarction (AMI), and recent guidelines recommended using a diagnostic cut-point set at a cTnI concentration where the assay imprecision exceeds 10%CV. These cut-points are far removed from the reference range of healthy volunteers and hence small increases in cTnI in the population or within individuals cannot be measured. The Singulex immunoassay technology offers a solution by achieving the sensitivity and precision with which to quantify cTnI to levels below those found in healthy patients[3,4], allowing accurate investigation into the clinical relevance of values below the threshold compared to other leading immunoassays (**Figure 2**). Additionally, quantifying acute changes in analyte may provide diagnostic information in the form of biomarker velocity. For example, cTnI velocity before and after stress testing has been shown to be a promising indicator to detect transient myocardial ischaemia[9], diagnostic information which can be used for risk stratification and prediction of adverse cardiac events (**Figure 3**). Similarly, this concept is currently used for prostate cancer management, whereby a rapid increase in PSA levels after surgical intervention is associated with unfavourable outcomes. This new diagnostic information may allow earlier disease detection and therapeutic intervention, ultimately saving lives.

**Targeting baseline levels in healthy states**

The issue still remains once 'official' guidelines are set, what diagnostic information resides below the threshold? Are we throwing away data that could have an impact on diagnosis, basic research and therapeutic development? The diagnostic goal should not be to merely capture the tip of the iceberg, but to gather all of the relevant data below the threshold – ultimately including baseline measurements of biomarkers in healthy subjects. After all, if you measure the sick and dying, then you will know when patients are sick and dying. If you measure the healthy, then you will know when patients are not healthy – which is a much better proposition. Development criteria for diagnostic sensitivity of immunoassay systems should be redefined in terms of quantifying biomarkers in easily collected, routine samples like serum from healthy individuals. By integrating SMC technology into immunoassay systems, the next generation of molecular diagnostics will have a large impact on translational research by the routine establishment of biomarker baseline profiles from healthy subjects. For example, recently a panel of pro-inflammatory cytokines was quantified in serum samples from normal healthy blood donors using the Erenna System (Singulex), a new IA system based on SMC technology[10]. As more ultra-sensitive

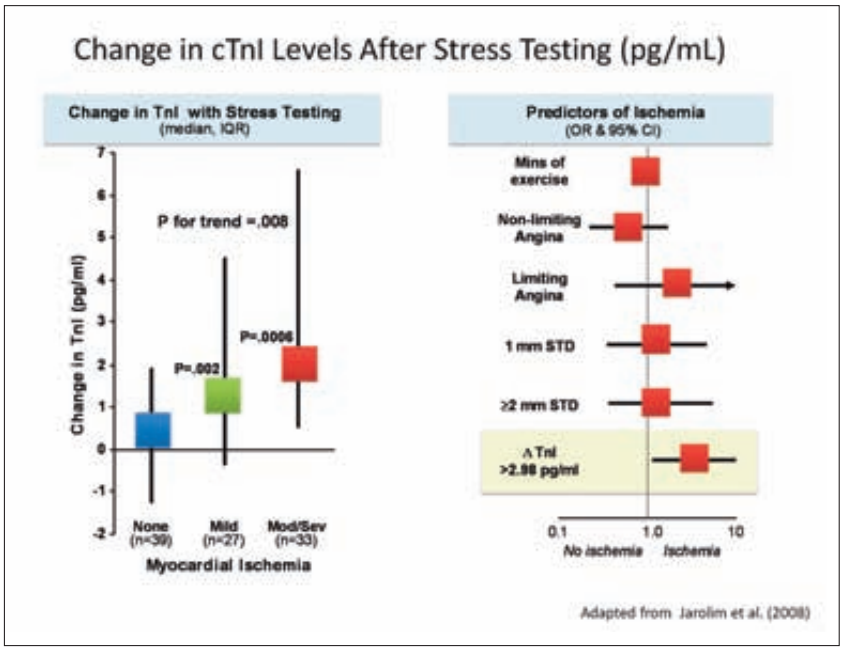



**Figure 3**
Use of cTnI for detecting cardiac risk and stratification



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000220

Immunoassay systems:Layout 1 6/10/08 12:54 Page 56



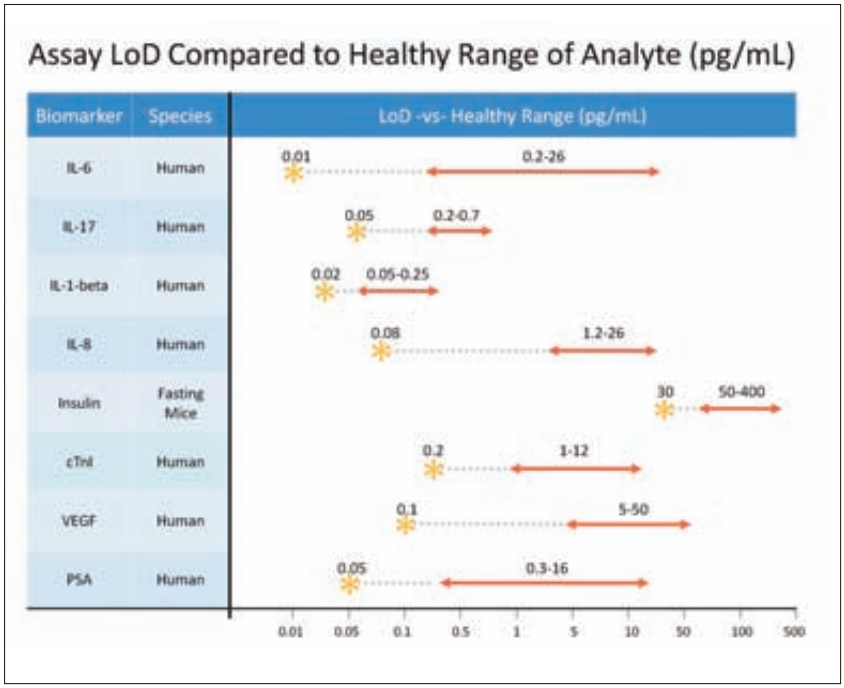



**Figure 4**
Erenna immunoassay system LoD compared to the measured range of analyte quantified in healthy human subjects

immunoassay systems are used for this type of research, healthy reference ranges can be determined that define baseline levels of clinically important biomarkers (**Figure 4**). This brings immediate benefit to current research and development programmes, and brings future benefits in clinical settings to improve patient outcomes.

**Better efficacy and safety**

Evidence-based medicine is pushing pharmaceutical developers to prove that the clinical benefit outweighs risk of administering a drug. Next generation IA systems can immediately benefit pharmaceutical developers by increasing the sensitivity of assays for biomarkers used as surrogate endpoints and safety biomarkers. SMC technology strengthens this application of biomarkers by quantifying a reference range of baseline biomarker levels in healthy subjects, providing a necessary comparison for determining the efficacy and safety of new therapies. For showing drug efficacy, the return of a companion diagnostic biomarker to levels at or below those in healthy subjects builds a strong case for clinical benefit. During drug safety studies, biomarkers indicative of adverse events can be measured with SMC systems to be sure they are not substantially elevated above healthy levels. Also, with SMC technology a panel of safety biomarkers can be detected in small animal model systems, allowing safety studies to be integrated very early in the product pipeline. A good example is the use of IA systems based on SMC to quantify cTnI in small volume samples from rats, dogs and monkeys[7] allowing for pre-clinical time-lapse studies of cardiotoxicity.

**Early rule in/rule out decisions**

Shifting drug efficacy and safety studies earlier into the product pipeline allows rule-in/rule-out decisions to be made earlier in the development cycle to avoid costly late-phase attrition and market failures. SMC-based systems enhance this process by providing ultra-sensitive detection of biomarkers with high precision, providing a larger set of discreet data points with which to make quality decisions. SMC systems can be used to test very small volumes – as low as 1-5ul of serum[5] – without compromising assay sensitivity. This enables greater sampling from individual small animals, time-course study design, capability to test a panel of biomarkers in each sample, and better discrimination between samples. The ability to



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000221

Immunoassay systems:Layout 1 6/10/08 12:54 Page 57



conduct timed trials through serial testing allows for the measurement of biomarker velocity. The use of small volumes allows for efficient sample acquisition and conservation, enabling the use of valuable bio-repository samples (including plasma, CSF, interstitial fluids, sputum, etc) in order to determine the clinical relevance of a biomarker. All of these benefit the researcher by expanding opportunities for robust early phase clinical study design. In a similar fashion, SMC technology can be applied to reposition drugs at market, improve allocation of development resources, and decrease time to market, all of which ultimately bring benefit to the patient.

**Enabling personalised medicine**

We are in a post-omics era, and we are now seeing regular demonstrations of the clinical relevance of genomic and proteomic data. We know that individuals with the same disease can have unique risks, presentations and responses to therapy. How can new diagnostic technology add value to translational researchers in the post-omics era? One way SMC technology is bringing value to researchers is by enabling the translation of biomarker discovery into the determination of risk for disease development. For example, SMC technology has been used recently to discover and validate a panel of protein biomarkers constituting a new diagnostic assay, the PreDx Diabetes Risk Test, which predicts a patient's risk of developing Type 2 Diabetes within five years[8]. This new diagnostic assay quantifies a risk score from the measurement of a panel of relevant biomarkers identified through the discovery process. From studies like these, we continue to learn that different patients may have different pre-dispositions for disease, different disease pathologies, and require different therapies. With SMC technology, biomarker panels can be utilised to pre-screen patient cohorts for contra-indications, to administer targeted therapies for different disease presentations or patient profiles, or to avoid contra-indications for administering drugs to subsets of patients. In this way SMC diagnostic systems will evolve personalised medicine into more than just a buzz word, and into an approach which is implemented at the bedside.

## Summary

SMC-based diagnostic technologies are continuing to increase the sensitivity of molecular diagnostic platforms, benefiting a broad spectrum of translational researchers. These new diagnostic systems should strive to meet the changing needs of translational researchers by playing a supporting role throughout the entire bench to bedside spectrum. This expanded role for diagnostics will require continued clinical evaluation of SMC-based diagnostic systems with the flexibility to provide a broad range of clinical utility. Looking to the future of molecular medicine, this kind of partnership will be invaluable. DDW

***Dr John Todd*** *is currently Vice-President of Research & Development at Singulex, Inc based in Alameda, CA. He is a seasoned biotech executive, with previous appointments at Chiron, NuGen, Protogene Laboratories, Baxter Healthcare and Enzo Biochem. John earned his PhD in Biochemistry from the University of Southern California Medical Center, and performed his post-doctoral training in Cell & Molecular Biology in the Sabatini Lab at the New York University Medical Center.*

***Dr Sara J. Agee*** *earned her PhD in Molecular & Cell Biology from the University of California, Berkeley with funding from the Department of Defense. Sara worked for several years as a scientist and educator in the non-profit sector before joining Singulex as a Research Scientist.*

## References

**1** National Institutes of Health. http://nihroadmap.nih.gov/clinicalresearch/overview-translational.asp [Accessed June 2, 2008].
**2** European Commission. http://ec.europa.eu/research/fp7/index_en.cfm?pg=health [Accessed June 2, 2008].
**3** Todd et al. Ultrasensitive Flow-based Immunoassays by Use of Single-Molecule Counting. Clin Chem 2007 Nov; 53(11):1990-5. Epub 2007 Sep 21.doi:10.1373/clinchem. 2007.091181 [PMID: 17890441].
**4** Wu et al. (2006) Development and preliminary clinical validation of a high sensitivity assay for cardiac troponin using a capillary flow (single molecule) fluorescence detector. Clin Chem 2006 Nov; 52(11): 2157-9. doi:10.1373/clinchem.2006.073163 [PMID: 18061987].
**5** Gilmore et al. (2008) Development of a High Sensitivity Assay for Mouse Plasma Insulin using Single Molecule Counting. [abstract] ADA 68th Scientific Sessions, San Francisco, CA.
**6** Schultze et al. (2008) Temporal Variability of Cardiac Troponin-I Concentration in Rats Under Standard Laboratory Conditions. [abstract] AACC Annual Meeting, Washington, DC.
**7** Schultze et al. (2008) Ultrasensitive Cross-species Measurement of Cardiac Troponin-I Using the Erenna Immunoassay System. Tox Path, in press. doi:10.1177/0192623308322016.
**8** Tansey, B. (2008) Emeryville firm devises diabetes risk test. *San Francisco Chronicle* Tuesday, May 27, 2008.
**9** Jarolim et al. (2008) Detection of Transient Myocardial Ischemia Using a Novel, Highly Sensitive, Single Molecule, Troponin I Assay. [abstract] AACC Annual Meeting, Washington, DC.
**10** Lu et al. (2008) Use of single-molecule counting technology to determine the concentration of cytokines IL-6, IL-8, IL-17, and IL-1B in plasma from healthy subjects. [abstract] AACC Annual Oak Ridge Conference, April 2008, San Jose, CA.



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000222

**EX-1006B** Copy of *Todd* obtained from the National Library of Medicine.

Drug discovery world : DDW.
v. 9, no. 4 (Autumn 2008)
General Collection
W1 DR514BM
2008-11-20 10:07:26

orld

FALL 2008

# DDW

he quarterly business review of drug discovery & development

PROPERTY OF THE
NATIONAL
LIBRARY OF
MEDICINE



## treating rheumatoid arthritis

www.ddw-online.com

Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000224

drug discovery world
DDW
the quarterly business review of drug discovery & development

# contents

**Publisher and Editor-in-Chief**
Robert Jordan
Robert@rjcoms.com

**Consultant Editor**
Dr Roger Brimblecombe

**Contributing Author**
Dr John Comley

**Publishing Manager**
Damian Doherty
Damian@rjcoms.com

**Design & Production**
Melissa Chadderton
melissa@rhubarbcreative.demon.co.uk

**Circulation & Production Controller**
Charles Davenport
CD@rjcoms.com

**Editorial Advisors**
Dr Steve Arlington
Dr Nigel Brown
Graham Cameron
Dr David Clough
Dr Gregory Lennon
Dr Keith Mansford
Professor Stephen Naylor
Dr George Poste
Dr Amber Salzman
Dr David U'Prichard
Dr Timothy Wells
Dr Rene Ziegler

*Drug Discovery World* (USPS 018-892) is published four times a year by RJ Communications & Media Ltd, 39 Vineyard Path, London SW14 8ET, United Kingdom.
Tel: +44 (0)20 8487 5656
Fax: +44 (0)20 8487 5666
E-mail: Robert@rjcoms.com

**Subscription Rates**
Annual Subscription (four Issues):
£89 UK & Europe; $175 USA & Canada; £99 Rest of World

Airfreight and mailing in the USA by Agent Air Business, C/O Priority Airfreight NY Ltd, 147-29 182nd Street, Jamaica, NY11413. Periodical postage paid at Jamaica, NY 11413. US Postmaster: Send address changes to Drug Discovery World, C/O Air Business Ltd/Priority Airfreight NY Ltd, 147-29 182nd Street, Jamaica, NY 11413. Subscription records are maintained at RJ Communications & Media Ltd, 39 Vineyard Path, London SW14 8ET, UK. Air Business Ltd is acting as our mailing agent.

© 2008 RJ Communications & Media Ltd
All rights reserved. ISSN 1469-4344

No part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means electronic, mechanical, photocopying, recording or otherwise without the prior written permission of the copyright holder. While the publishers believe that all information contained in this publication was correct at the time of going to press, they can accept no liability for any inaccuracies that may appear or loss suffered directly or indirectly by any reader as a result of any advertisement, editorial, photographs or other material published in Drug Discovery World.

VOLUME 9 ISSUE 4 ● FALL 2008

**Introduction** 7
*Dr Roger Brimblecombe*
*Consultant Editor*

**Business** 9
Prediction v Attrition
*Prof Malcolm Young*

**Therapeutics** 15
Treating Rheumatoid Arthritis with DMARDs and Biologics
*Dr William E. Fogler*

**Drug Development** 21
Challenges in Transferring Bioanalytical Methods
*Dr Chris Beaver*

**Lead Discovery** 28
Progress in the Implementation of Label-Free Detection – Part 2: Binding Analysis Assays
*Dr John Comley*

**Immunoassays** 51
How Low Can You Go? – Next Generation Immunoassay Systems and the Revival of Protein Biomarkers
*Dr John Todd and Dr Sara J. Agee*

**Screening** 59
High Throughput Screening in Academia – Drug Discovery Initiatives at the University of Kansas
*Dr Peter R. McDonald, Dr Anuradha Roy, Byron Taylor, Ashleigh Price, Dr Sitta Sittampalam, Dr Scott Weir and Dr Rathnam Chaguturu*

**Therapeutics** 77
Targeted Remodelling of the Diseased Lung with Biopharmaceutical Agents – A Bronchoscopically Administered Therapeutic Approach to Advanced Emphysema
*Dr Edward E. Berger*

**Organic Synthesis** 83
Microwave-Assisted Organic Synthesis – An Enabling Technology With Disruptive Potential
*Dr Anil Vasudevan*

*Front cover illustration courtesy of David Gifford/Science Photo Library*



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000225

This material may be protected by Copyright law (Title 17 U.S. Code)



# HOW LOW CAN YOU GO?
## next generation immunoassay systems and the revival of protein biomarkers

Proteins are the machinery that drive most biological processes; however, measuring their concentrations at low levels has been historically impeded by a lack of appropriately sensitive technology. Advances in immunoassay technology, such as single molecule counting, have provided orders of magnitude of increased sensitivity. These novel technologies are enabling new discoveries and a clearer understanding of previously intractable biology. Here we discuss how single molecule counting technology can brighten the future of translational research, drug discovery and personalised medicine.

By Dr John Todd and Dr Sara J. Agee

There is a great paradox facing drug developers: get the most innovative and effective new drugs from bench to bedside as quickly as possible while meeting stringent regulatory demands that demonstrate robust safety and efficacy. This leaves quite a dilemma. Pressure to drive innovative drug candidates through the pharmaceutical pipeline into clinical trials leads to a high level of attrition, where even the most promising drug candidates can fail. This keeps promising therapies from needy patients and leaves pharma footing the bill. The key to solving this puzzle is to effectively rule-in or rule-out drug candidates early in the pipeline, before they enter into costly late phase clinical trials.

### Biomarkers – the beacon of translational biology

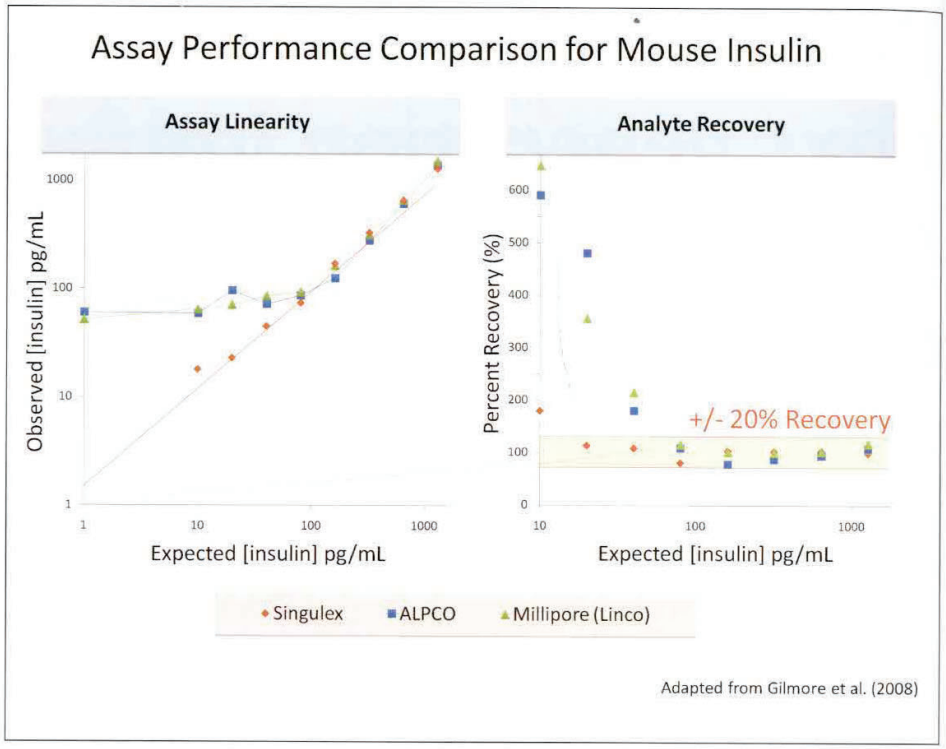
One can view classic biochemistry as the original drug discovery machine, beginning with discovery and purification of insulin from pancreatic islet cells in dogs. The medicinal application of this discovery led to a Nobel Prize in 1923 and paved the way for the first pharmaceutical giant: Eli Lilly & Sons. The biology around protein analysis remained the mainstay of big pharma until the molecular revolution of the 90s led into the genomics era. The difficulties of specific and sensitive protein detection helped set the stage for the molecular revolution, where genomics-based approaches have taken centre stage. However, this does not change the central dogma of biology, that our pathopysiology is ultimately determined at the protein level. Therefore we must continue to develop advanced protein detection systems, even for protein biomarkers with previously intractable biology.

The strength of the biomarker movement has been its promise to provide a standardised metric for evaluating new therapies across disease states. In this way biomarkers have become inseparable from the drug development process, and may combine physiological and molecular biomarkers for disease. However, molecular and protein biomarkers (ie



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000226

**Figure 1**
Comparison of mouse insulin assay performance




cTnI, insulin) have a strong advantage over physiological biomarkers (ie electrocardiogram, BMI) because they are more quantitative and less subjective. A desired approach is to use protein biomarkers for the targeted disease in early phase I/II studies to understand if a candidate drug exerts a dose-dependent pharmacodynamic (PD) effect on biomarkers that are either in the disease pathway or that are a direct target of the drug. If a drug candidate does not impact the concentration of a relevant biomarker in a dose dependent fashion, this will halt development of the compound. The earlier a problem drug can be screened out the better, saving the expense of costly late phase clinical trials. However, in many cases technology to do this effectively has been a limiting factor, especially for measuring protein biomarkers in readily available specimens such as blood plasma or serum.

Systems biology ushers in a new paradigm, and shifts attitudes from scepticism towards early adoption and implementation of cutting edge technology. We have seen the fields of genomics and bioinformatics grow under this strategy, which can now be applied towards validation of these discoveries at the protein level. In order for this to work requires the successful deployment of several approaches: biomarker discovery, target validation, assay development, instrumentation and clinical trial management. There has been an attempt to unify these approaches under the umbrella of translational research, which has become a hot buzz word even though few people seem to agree on how it is defined or executed. One thing most researchers agree on is that this integrative approach is the future of pharmaceutical development, as evidenced by investments by both the NIH and the European Commission towards funding translational research centres and consortiums[1,2]. The point of confusion usually concerns where and how researchers fit into the very broad 'bench-to-bedside' model. Diagnostics is unique in that it can play a supporting role across the entire bench-to-bedside spectrum, since there is something to be measured every step of the way.

## The disease continuum – a full spectrum of disease states

In a general sense, current diagnostic guidelines based on quantification of protein-based biomarkers suffer from three distinct challenges. First, assay sensitivity is often what determines the lower limit of the threshold and the diagnostic cut-off value. Second, the threshold system only reveals the tip of the iceberg when it comes



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000227

to disease states. As in cTnI, a potential gold mine of information resides beneath the 99th percentile threshold value for a clinically relevant biomarker. This valuable information, quantifiable by single molecule counting (SMC) technology in particular, could be used to diagnose, stratify, determine risk, or aid in disease prevention. Third, development of a disease state is not an on/off proposition. Rather, there is a continuum of disease development which makes disease onset and diagnosis difficult to mark. When does a patient cross the line to a full-fledged disease state? The fuzzy line marking disease onset is a common cause of diagnostic failures.

An excellent example of prolonged disease onset leading towards diagnostic failure is Alzheimer's Disease (AD). Right now, the only definitive diagnosis of AD is a post-mortem examination of brain tissue for amyloid plaques and neurofibrillary tangles. Currently, clinical diagnosis of this disease is diagnosed by ruling out other probable causes for the symptoms of AD, which are usually only apparent after significant disease progression has occurred. Thus there is no reliable way at this time to clinically define when this complex disease officially starts, and an FDA approved molecular diagnostic for AD is desperately needed.

The need for an early diagnosis for AD is especially important as new therapies for AD are developed, which provide better patient outcomes when administered early in the course of the disease. Currently, there is no FDA approved protein biomarker for clinical diagnosis of Alzheimer's disease, though there are some hopeful candidates: beta-amyloid and tau proteins.

However, further clinical validation of this new diagnostic information will be necessary to define the disease state and set the guidelines for early diagnosis and onset of AD.

In this way, protein biomarker programmes in AD and other disease areas can benefit immensely from the application of novel immunoassay technologies with ultra-sensitive detection.

## The solution – integrating novel technology into next generation immunoassay systems

**Fluorosphere immunoassays (Luminex)** – xMAP technology integrates flow cytometry, microspheres, lasers, digital signal processing and traditional chemistry to feature a flexible immunoassay system that can be configured to perform a wide variety of bioassays. Luminex uses colour-coded microspheres, which can be combined into 100 distinct sets. Each bead set can be coated with a reagent specific to a particular bioassay, allowing the capture and detection of specific analytes from a sample. Within the Luminex compact analyser, lasers excite the internal dyes that identify each microsphere particle, and also any reporter dye captured during the assay. In this way, xMAP technology allows multiplexing of up to 100 unique assays within a single sample, both rapidly and precisely. However, multiplexing can come at the expense of assay sensitivity and this technology generally does not provide sensitive measurements beyond what has been historically obtained with 96-well enzymatic assays (eg ELISA).

**Gold nanoparticle probes (Nanosphere)** – Nanoparticles can be used as the solid phase for protein capture by attaching specific capture antibodies for specific analytes. Detection is achieved by attaching bio-barcode nucleic acid probes, which are specifically amplified and quantified. Sequence tagged barcodes are then correlated with specific analyte capture. Multiplexing is accomplished by changing the bio-barcode tags on a set of gold microparticles, providing a method for differential readout. However, the amplification step and multiplexing can increase background and can impact assay precision.

**Single Molecule Counting (SMC)=based systems (Singulex)** – Singulex has developed a proprietary immunoassay technology, which leads the next generation of molecular diagnostic technologies capable of quantifying biomarkers at the sub-picogram level. The proprietary Singulex immunoassay technology utilises paramagnetic microparticles (MPs) as the solid phase for immune-capture and detection of analyte from a complex biological sample, providing enhanced specificity, sensitivity and precision by 1-3 logs over existing plate-based methods. The incorporation of SMC technology into next generation immunoassays, like the Singulex Erenna System, is already having an impact by quantifying proteins at sub-picogram levels[3,4].

## The impact of next generation immunoassay systems

Each of these new immunoassay systems adds value by increasing sensitivity to unprecedented levels of detection, some to below the femtomolar range. The benefit of this new limit of diagnostic sensitivity is the availability of a new tool kit for solving intractable problems in the biology of disease and to embark upon clinical investigations which were



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000228

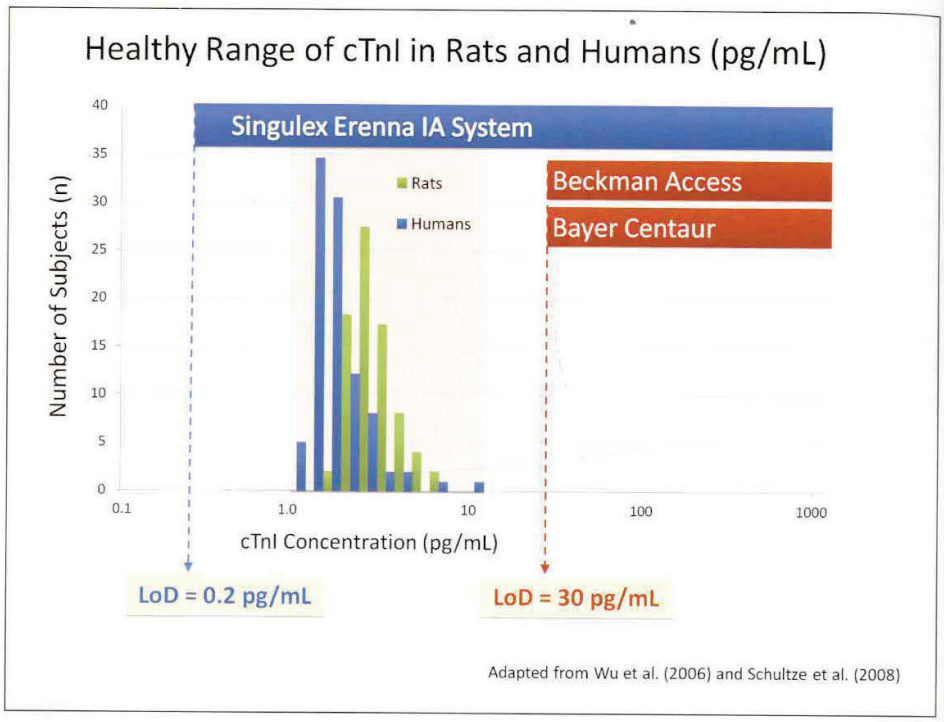



**Figure 2**
Range of cTnI in humans and rats compared to assay LoD

previously considered untenable. There are several strategic applications of these new technologies towards key issues facing drug development.

### Making new biological discoveries

Fundamental to drug discovery is the understanding and manipulation of how biological pathways are altered during disease. These fundamental questions are tackled during preclinical stages of discovery and development, often times in cell culture or small animal model systems for which sensitivity and precision of measurements is an issue. For example, there are several genetic mouse models for diabetes, however accurate insulin measurements in fasted female mice are notoriously difficult. Recently the Singulex proprietary immunoassay has been shown to make accurate quantifications from only 5uL mouse plasma samples, allowing long-term monitoring of insulin over time[5]. In this model, the accuracy of the Erenna System has been shown to provide superior precision over currently available commercial assays (**Figure 1**). Long-term monitoring is also an issue for studies of cardiotoxicity studies in small animals, and the same immunoassay system has shown the ability to accurately quantify cTnI levels from 15uL samples of healthy rat serum[6]. Interestingly, the healthy range of cTnI levels in rats is consistent with measurements in other animals, including humans[7] and is far below the LoD of other currently available commercial assays (**Figure 2**). Lastly, another factor important during the discovery phase is the ability to quantify multiple targets, which also benefits from small volume assays due to increased sensitivity. For example, a recent diagnostic test for diabetes was released that calculates risk based upon the quantification of a panel of biomarkers from samples as small as1.3 uL[8].

### Early disease detection

The ultimate diagnostic challenge is to detect the onset of disease as early as possible. In terms of patient risk, earlier diagnoses are correlated with better patient outcomes, assuming that efficiacious therapeutic modalities can be employed. The development of clinically relevant molecular biomarkers has already had a huge impact on diagnosis of disease, however a continuing problem is that current guidelines rely on the establishment of cut-off values and thresholds for making a diagnosis. These requisite guidelines were set because technologies at that time could not provide the requisite sensitivity. Now we can measure the complete spectrum from healthy to disease state and hence need to think differently. For example, cardiac troponin-I (cTnI) is considered the gold standard for



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000229

diagnosis of acute myocardial infarction (AMI), and recent guidelines recommended using a diagnostic cut-point set at a cTnI concentration where the assay imprecision exceeds 10%CV. These cut-points are far removed from the reference range of healthy volunteers and hence small increases in cTnI in the population or within individuals cannot be measured. The Singulex immunoassay technology offers a solution by achieving the sensitivity and precision with which to quantify cTnI to levels below those found in healthy patients[3,4], allowing accurate investigation into the clinical relevance of values below the threshold compared to other leading immunoassays (**Figure 2**). Additionally, quantifying acute changes in analyte may provide diagnostic information in the form of biomarker velocity. For example, cTnI velocity before and after stress testing has been shown to be a promising indicator to detect transient myocardial ischaemia[9], diagnostic information which can be used for risk stratification and prediction of adverse cardiac events (**Figure 3**). Similarly, this concept is currently used for prostate cancer management, whereby a rapid increase in PSA levels after surgical intervention is associated with unfavourable outcomes. This new diagnostic information may allow earlier disease detection and therapeutic intervention, ultimately saving lives.

### Targeting baseline levels in healthy states

The issue still remains once 'official' guidelines are set, what diagnostic information resides below the threshold? Are we throwing away data that could have an impact on diagnosis, basic research and therapeutic development? The diagnostic goal should not be to merely capture the tip of the iceberg, but to gather all of the relevant data below the threshold – ultimately including baseline measurements of biomarkers in healthy subjects. After all, if you measure the sick and dying, then you will know when patients are sick and dying. If you measure the healthy, then you will know when patients are not healthy – which is a much better proposition. Development criteria for diagnostic sensitivity of immunoassay systems should be redefined in terms of quantifying biomarkers in easily collected, routine samples like serum from healthy individuals. By integrating SMC technology into immunoassay systems, the next generation of molecular diagnostics will have a large impact on translational research by the routine establishment of biomarker baseline profiles from healthy subjects. For example, recently a panel of pro-inflammatory cytokines was quantified in serum samples from normal healthy blood donors using the Erenna System (Singulex), a new IA system based on SMC technology[10]. As more ultra-sensitive

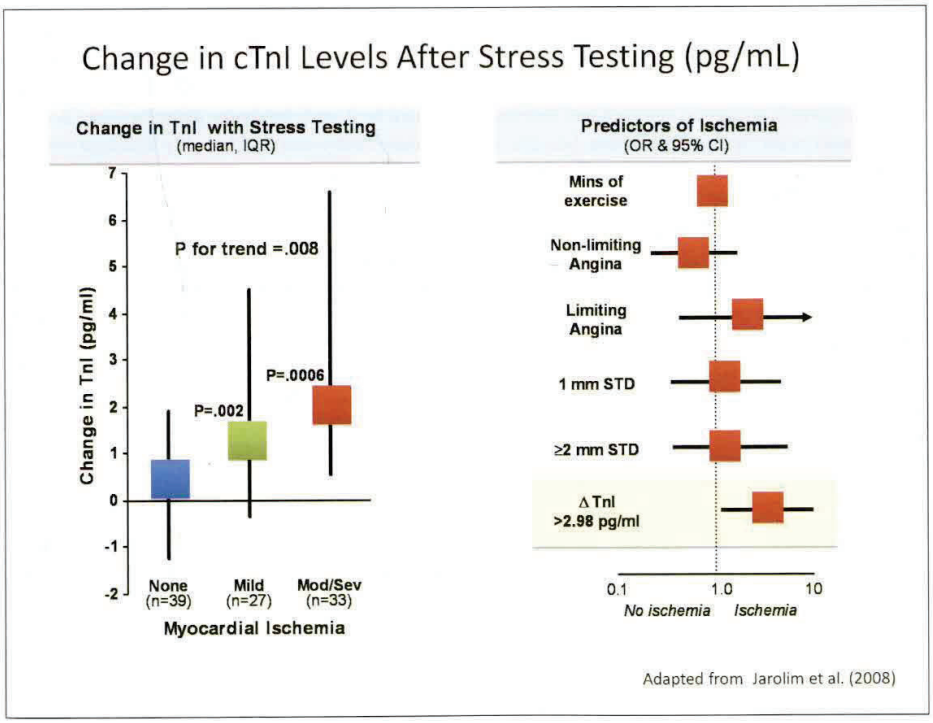



**Figure 3**
Use of cTnI for detecting cardiac risk and stratification



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000230

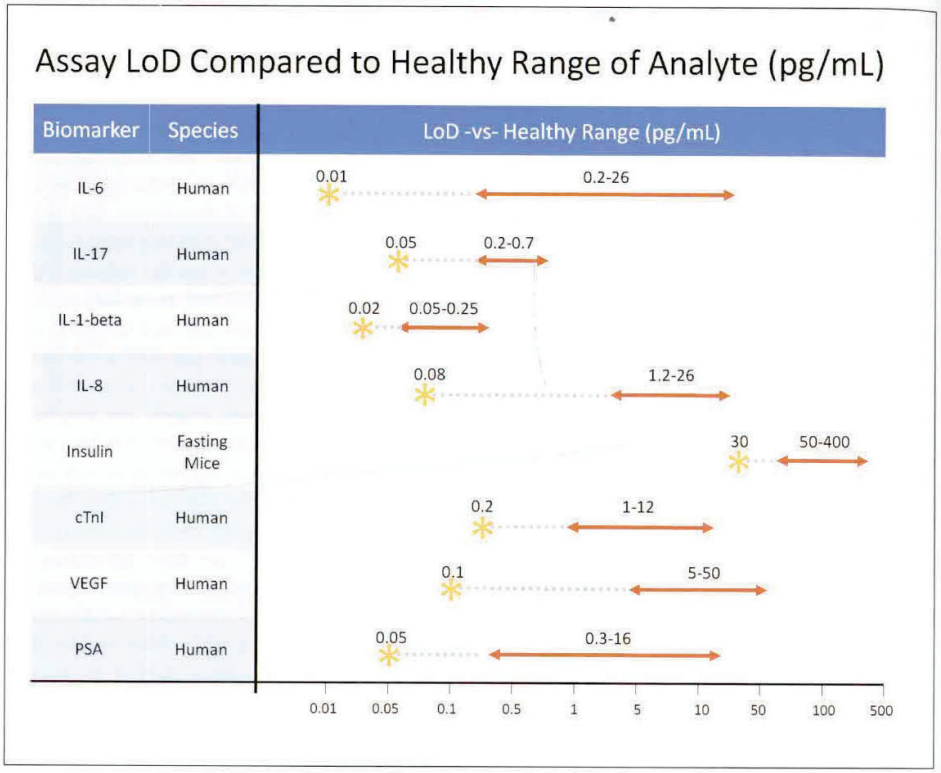



**Figure 4**
Erenna immunoassay system LoD compared to the measured range of analyte quantified in healthy human subjects

immunoassay systems are used for this type of research, healthy reference ranges can be determined that define baseline levels of clinically important biomarkers (**Figure 4**). This brings immediate benefit to current research and development programmes, and brings future benefits in clinical settings to improve patient outcomes.

### Better efficacy and safety

Evidence-based medicine is pushing pharmaceutical developers to prove that the clinical benefit outweighs risk of administering a drug. Next generation IA systems can immediately benefit pharmaceutical developers by increasing the sensitivity of assays for biomarkers used as surrogate endpoints and safety biomarkers. SMC technology strengthens this application of biomarkers by quantifying a reference range of baseline biomarker levels in healthy subjects, providing a necessary comparison for determining the efficacy and safety of new therapies. For showing drug efficacy, the return of a companion diagnostic biomarker to levels at or below those in healthy subjects builds a strong case for clinical benefit. During drug safety studies, biomarkers indicative of adverse events can be measured with SMC systems to be sure they are not substantially elevated above healthy levels. Also, with SMC technology a panel of safety biomarkers can be detected in small animal model systems, allowing safety studies to be integrated very early in the product pipeline. A good example is the use of IA systems based on SMC to quantify cTnI in small volume samples from rats, dogs and monkeys[7] allowing for pre-clinical time-lapse studies of cardiotoxicity.

### Early rule in/rule out decisions

Shifting drug efficacy and safety studies earlier into the product pipeline allows rule-in/rule-out decisions to be made earlier in the development cycle to avoid costly late-phase attrition and market failures. SMC-based systems enhance this process by providing ultra-sensitive detection of biomarkers with high precision, providing a larger set of discreet data points with which to make quality decisions. SMC systems can be used to test very small volumes – as low as 1-5ul of serum[5] – without compromising assay sensitivity. This enables greater sampling from individual small animals, time-course study design, capability to test a panel of biomarkers in each sample, and better discrimination between samples. The ability to



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000231

conduct timed trials through serial testing allows for the measurement of biomarker velocity. The use of small volumes allows for efficient sample acquisition and conservation, enabling the use of valuable bio-repository samples (including plasma, CSF, interstitial fluids, sputum, etc) in order to determine the clinical relevance of a biomarker. All of these benefit the researcher by expanding opportunities for robust early phase clinical study design. In a similar fashion, SMC technology can be applied to reposition drugs at market, improve allocation of development resources, and decrease time to market, all of which ultimately bring benefit to the patient.

### Enabling personalised medicine

We are in a post-omics era, and we are now seeing regular demonstrations of the clinical relevance of genomic and proteomic data. We know that individuals with the same disease can have unique risks, presentations and responses to therapy. How can new diagnostic technology add value to translational researchers in the post-omics era? One way SMC technology is bringing value to researchers is by enabling the translation of biomarker discovery into the determination of risk for disease development. For example, SMC technology has been used recently to discover and validate a panel of protein biomarkers constituting a new diagnostic assay, the PreDx Diabetes Risk Test, which predicts a patient's risk of developing Type 2 Diabetes within five years[8]. This new diagnostic assay quantifies a risk score from the measurement of a panel of relevant biomarkers identified through the discovery process. From studies like these, we continue to learn that different patients may have different pre-dispositions for disease, different disease pathologies, and require different therapies. With SMC technology, biomarker panels can be utilised to pre-screen patient cohorts for contra-indications, to administer targeted therapies for different disease presentations or patient profiles, or to avoid contra-indications for administering drugs to subsets of patients. In this way SMC diagnostic systems will evolve personalised medicine into more than just a buzz word, and into an approach which is implemented at the bedside.

## Summary

SMC-based diagnostic technologies are continuing to increase the sensitivity of molecular diagnostic platforms, benefiting a broad spectrum of translational researchers. These new diagnostic systems should strive to meet the changing needs of translational researchers by playing a supporting role throughout the entire bench to bedside spectrum. This expanded role for diagnostics will require continued clinical evaluation of SMC-based diagnostic systems with the flexibility to provide a broad range of clinical utility. Looking to the future of molecular medicine, this kind of partnership will be invaluable. DDW

***Dr John Todd*** *is currently Vice-President of Research & Development at Singulex, Inc based in Alameda, CA. He is a seasoned biotech executive, with previous appointments at Chiron, NuGen, Protogene Laboratories, Baxter Healthcare and Enzo Biochem. John earned his PhD in Biochemistry from the University of Southern California Medical Center, and performed his post-doctoral training in Cell & Molecular Biology in the Sabatini Lab at the New York University Medical Center.*

***Dr Sara J. Agee*** *earned her PhD in Molecular & Cell Biology from the University of California, Berkeley with funding from the Department of Defense. Sara worked for several years as a scientist and educator in the non-profit sector before joining Singulex as a Research Scientist.*

## References

1 National Institutes of Health. http://nihroadmap.nih.gov/clinicalresearch/overview-translational.asp [Accessed June 2, 2008].
2 European Commission. http://ec.europa.eu/research/fp7/index_en.cfm?pg=health [Accessed June 2, 2008].
3 Todd et al. Ultrasensitive Flow-based Immunoassays by Use of Single-Molecule Counting. Clin Chem 2007 Nov; 53(11):1990-5. Epub 2007 Sep 21.doi:10.1373/clinchem. 2007.091181 [PMID: 17890441].
4 Wu et al. (2006) Development and preliminary clinical validation of a high sensitivity assay for cardiac troponin using a capillary flow (single molecule) fluorescence detector. Clin Chem 2006 Nov; 52(11): 2157-9. doi:10.1373/clinchem.2006.073163 [PMID: 18061987].
5 Gilmore et al. (2008) Development of a High Sensitivity Assay for Mouse Plasma Insulin using Single Molecule Counting. [abstract] ADA 68th Scientific Sessions, San Francisco, CA.
6 Schultze et al. (2008) Temporal Variability of Cardiac Troponin-I Concentration in Rats Under Standard Laboratory Conditions. [abstract] AACC Annual Meeting, Washington, DC.
7 Schultze et al. (2008) Ultrasensitive Cross-species Measurement of Cardiac Troponin-I Using the Erenna Immunoassay System. Tox Path, in press. doi:10.1177/0192623308322016.
8 Tansey, B. (2008) Emeryville firm devises diabetes risk test. *San Francisco Chronicle* Tuesday, May 27, 2008.
9 Jarolim et al. (2008) Detection of Transient Myocardial Ischemia Using a Novel, Highly Sensitive, Single Molecule, Troponin I Assay. [abstract] AACC Annual Meeting, Washington, DC.
10 Lu et al. (2008) Use of single-molecule counting technology to determine the concentration of cytokines IL-6, IL-8, IL-17, and IL-1B in plasma from healthy subjects. [abstract] AACC Annual Oak Ridge Conference, April 2008, San Jose, CA.

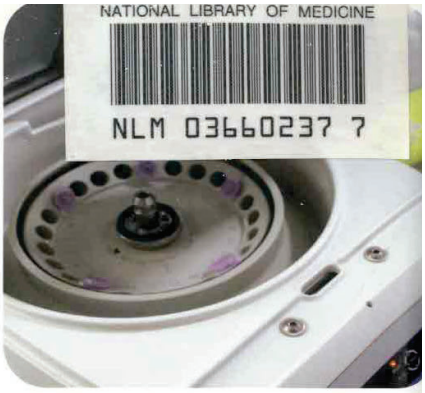


Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000232

NATIONAL LIBRARY OF MEDICINE
NLM 03660237 7







Thermo
SCIENTIFIC











## Moving science forward.

Thermo Scientific stands for superior analytical instruments and workflow solutions spanning sample preparation, sample analysis and data interpretation.

Learn more at www.thermo.com

- Lab Equipment
- Reagents & Consumables
- Analytical Instruments
- LIMS & Lab Software
- Services & Support

DFA387 PR 101
06-23-11 13:27:0 XI

Part of Thermo Fisher Scientific

Thermo
SCIENTIFIC

Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000233

**EX-1006C** Bibliographic and MARC serial records for *Drug Discovery World* that contains *Todd*, available at https://catalog.nlm.nih.gov/permalink/01NLM_INST/1o1phhn/alma9912756903406676 from the online catalog of the National Library of Medicine.

JOURNAL

# Drug discovery world : DDW

London : RJ Communications & Media; Began in 2000. Cf. ISSN Portal.; 2000

Library Catalog ; MMS ID 9912756903406676; ISSN 1469-4344; NLM Unique ID 101275690

Available at NLM General Collection (W1 DR514BM) >

Available Online >

TOP
SEND TO
VIEW ONLINE
GET IT
DETAILS
LINKS

## Send to

DOWNLOAD MARC | EMAIL | SHARE | PERMALINK | CITATION

ENDNOTE | EXPORT RIS | QR | EXPORT TO EXCEL | PRINT

## View Online

**Full text availability**

Free E- Journals

Available from 2000.

*This journal is freely available. Access is not guaranteed.*

## Get It

Please sign in to check if there are other options. Sign in



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000235

BACK TO LOCATIONS

LOCATION ITEMS

NLM
Available , General Collection ; W1 DR514BM
Summary holdings: v.7(2006)-14(2012/2013),19(2017/2018)-v.21:no.2(2020)

v. 21, no. 2 (Spring 2020)
v. 21, no. 1 (Winter 2019-2020)
v. 20 (2018/2019)
v. 19 (2017/2018)
v. 14 (2012/2013)
v. 13 (2012)

SHOW MORE ITEMS

## Details

| | |
|---|---|
| **Title(s)** | Drug discovery world : DDW |
| **Other Title(s)** | DDW |
| **Publisher** | London : RJ Communications & Media<br>Began in 2000. Cf. ISSN Portal.<br>2000 |
| **Country** | England |
| **Language(s)** | English |
| **Description** | v. |
| **Frequency** | Four no. a year |
| **Identifier(s)** | LC : 2014243669<br>ISSN : 1469-4344<br>OCLC : (OCoLC)894657237 |
| **Medical Subject Headings (MeSH)** | Drug Industry ><br>Technology, Pharmaceutical ><br>Periodical > |
| **Notes** | Description based on: Vol. 7, issue 1 (winter 2005/6); title from cover.<br>Latest issue consulted: Vol. 7, issue 2 (spring 2006).<br>Print issues ceased with 2022.<br>Also issued online. |
| **NLM Unique ID** | 101275690 |
| **MMS ID** | 9912756903406676 |
| **Source** | Library Catalog |



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000236

## Links

Link to resource >
Find other libraries that own this >
View and download the MARC record >
Display Source Record >

Connect with NLM

National Library of Medicine
8600 Rockville Pike
Bethesda, MD 20894

Web Policies
FOIA
HHS Vulnerability Disclosure

NLM Support Center
Accessibility
Careers

NLM | NIH | HHS | USA.gov



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000237

```
leader  01457cas a22004934a 4500
001     9912756903406676
005     20240609160255.0
007     cr||||||||||||
008     060501c20009999enk x p       0    0eng
010     ##$a  2014243669
022     ##$a1469-4344 $l1469-4344
035     ##$9101275690
040     ##$aDNLM $cDNLM
041     0#$aeng
042     ##$alcd
044     ##$9England
060     00$aW1 $bDR514BM
245     00$aDrug discovery world : $bDDW.
246     30$aDDW
260     ##$aLondon : $bRJ Communications & Media
300     ##$av.
310     ##$aFour no. a year
336     ##$atext $btxt $2rdacontent
337     ##$aunmediated $bn $2rdamedia
338     ##$avolume $bnc $2rdacarrier
362     1#$aBegan in 2000. $zCf. ISSN Portal.
500     ##$aDescription based on: Vol. 7, issue 1 (winter 2005/6); title from cover.
500     ##$aLatest issue consulted: Vol. 7, issue 2 (spring 2006).
500     ##$aPrint issues ceased with 2022.
530     ##$aAlso issued online.
650     12$aDrug Industry
650     22$aTechnology, Pharmaceutical
655     #2$aPeriodical
856     4#$uhttp://www.ddw-online.com
911     ##$aElectronic only, print ceased 2022. Confirmed 20220919
935     ##$a(DNLM)1275690-nlmdb
992     ##$pP2 $eE4 $a20060711
993     ##$aKSS $b20060711
994     ##$aCDN $b20060711
995     ##$aAUTH $b20060724 $cREV $d20220921
996     ##$aCONSER $b20141105
998     ##$aFER $b20181108
999     ##$aAUTH
035     ##$a(OCoLC)894657237
```



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000238

Connect with NLM



National Library of Medicine
8600 Rockville Pike
Bethesda, MD 20894

Web Policies
FOIA
HHS Vulnerability Disclosure

NLM Support Center
Accessibility
Careers

NLM | NIH | HHS | USA.gov



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000239

**EX-1006D** Profile of the National Library of Medicine, available at https://librarytechnology.org/library/2297.

# libraries.org

## A directory of libraries throughout the world



found **3** items where the item contains **National Library of Medicine**. Showing item **2** of **3**.



## National Library of Medicine

**United States -- National Library of Medicine**

**Address:** 8600 Rockville Pike
**Bethesda**, **Maryland**
20894
United States

**Connect to:** Library Web Site✔ Online Catalog

**Library details:** **National Library of Medicine** is a **National** library.
This library is affiliated with **National Library of Medicine** (**view map**) .

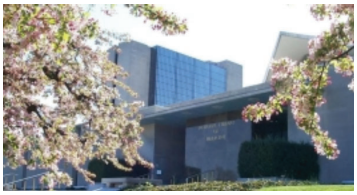
**Other Info:** The National Library of Medicine (NLM), on the campus of the National Institutes of Health in Bethesda, Maryland, has been a center of information innovation since its founding in 1836. The world's largest biomedical library, NLM maintains and makes available a vast print collection and produces electronic information resources on a wide range of topics that are searched billions of times each year by millions of people around the globe. It also supports and conducts research, development, and training in biomedical informatics and health information technology. In addition, the Library coordinates a 6,000-member National Network of Libraries of Medicine that promotes and provides access to health information in communities across the United States.

**Permalink:** **https://librarytechnology.org/library/2297**
(Use this link to refer back to this listing.)

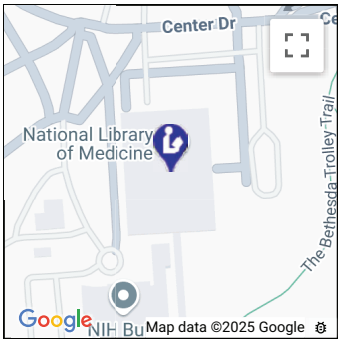
**Administration:** The director of the library is **Dr. Stephen Sherry (Acting)** .

**Affiliations:** The library is a member of the **Association of Research Libraries**

| Technology Profile | | |
|---|---|---|
| | **Product Name** | **Year Contracted** |
| **Current Automation System** | **Alma** | **2020** |
| **Previous Automation System** | **Voyager** | 1998 |
| **Discovery Interface** | **Primo** | **2020** |
| **Digital Collection Management** | **Fedora** | |
| **Interlibrary Loan or Resource Sharing** | **ILLiad**<br>**Relias ILL** | |
| This library is responsible for the procurement of the library automation system. | | |



National Library of Medicine




map location✔

**Related Libraries**

- All members of the **Association of Research Libraries** members
- **Directory of ARL Member Libraries**
- Libraries located in **Bethesda** (Maryland)
- **all National libs in Maryland**

**About libraries.org**

**libraries.org** is a free directory of libraries throughout the world.

This directory is a component of **Library Technology Guides**.



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000241

View Privacy and Security Report

| Identifiers | |
|---|---|
| libraries.org ID | 2297 |

Please **contact Marshall Breeding** to report corrections about information listed for this library.

**Record History:** This listing was created on Aug 11, 1998 and was last modified on Jan 14, 2025.

**Updates:** Corrections or Updates? Registered members of Library Technology Guides can submit updates to library listings in libraries.org. **Registration** is free and easy. Already registered? **login**. Or, you can report corrections just by sending a message to **Marshall Breeding**.

libraries.org | Update this Entry | Library Technology Guides

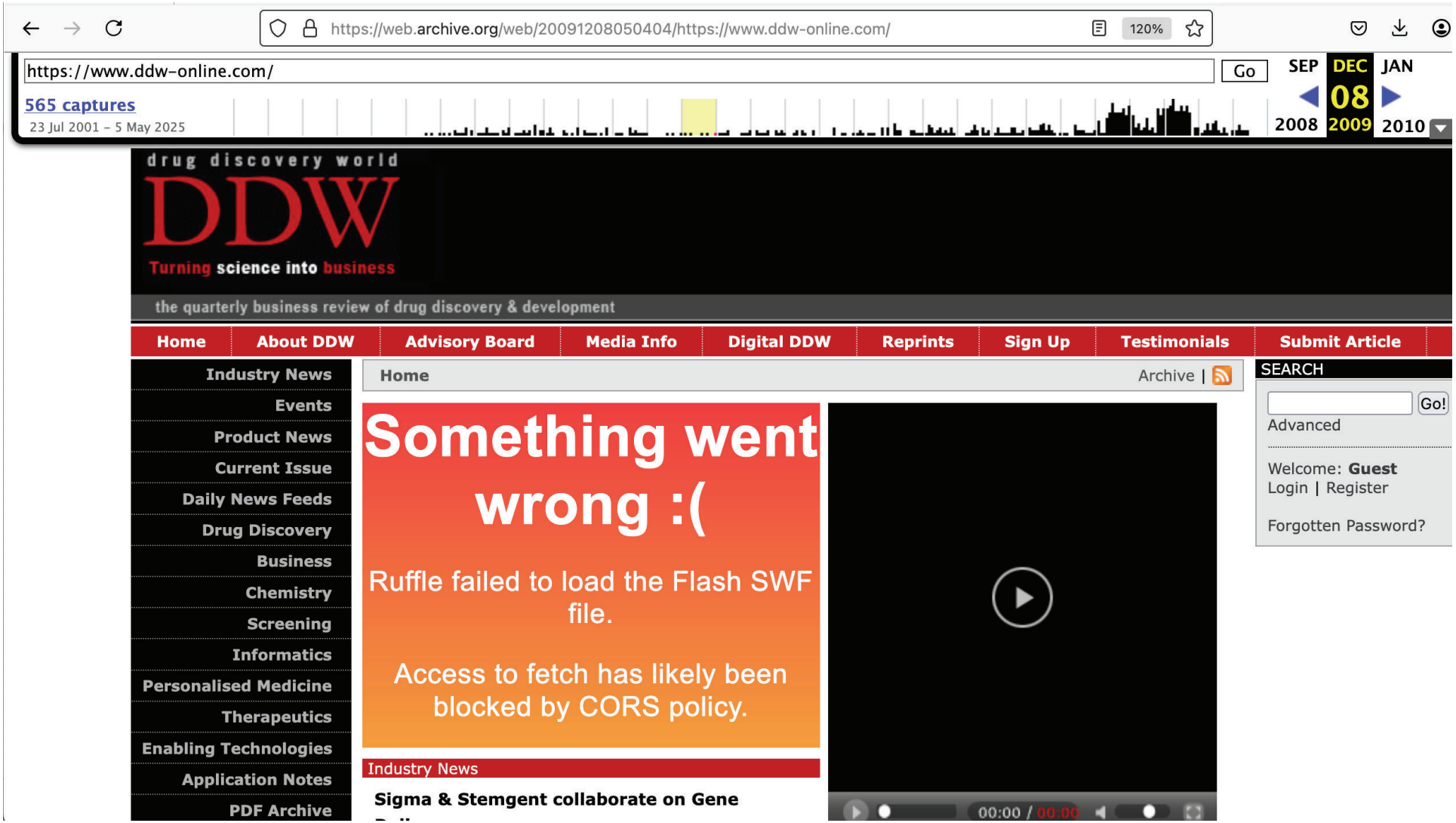
Maintained by **Marshall Breeding**

terms of service
Copyright 1994-2024

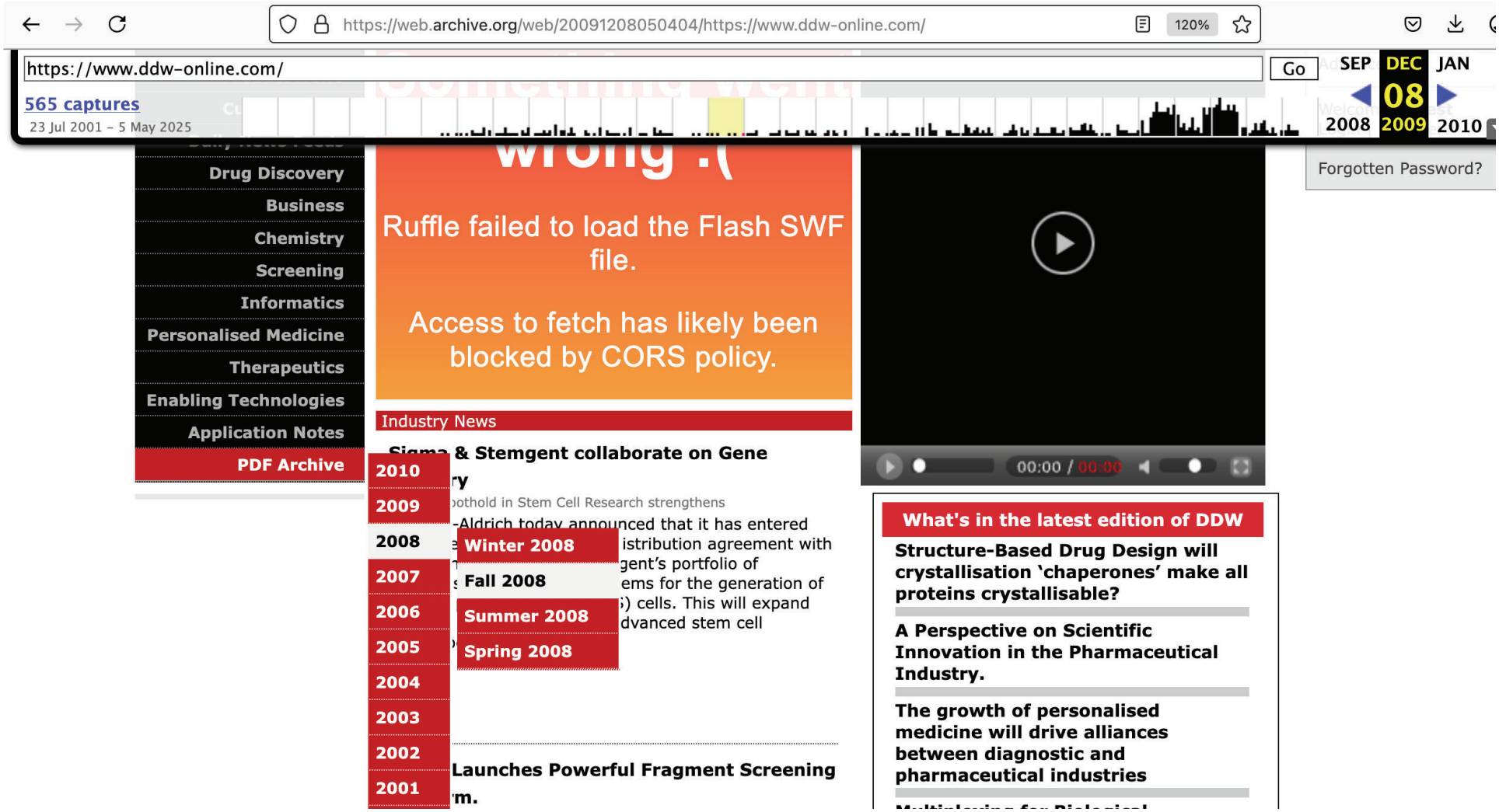


Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000242

**EX-1006E** Webpage of *Drug Discovery World* archived by Internet Archive on December 8, 2009, available at https://web.archive.org/web/20091208050404/https://www.ddw-online.com/.




Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000244




Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000245

**EX-1024A** Webpage of *INNOTEST* archived by Internet Archive on September 14, 2004, available at https://web.archive.org/web/20040914040003fw_/http://www.innogenetics.be/site/prodview.asp?id=38&lang=E&print=true.

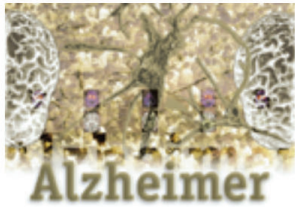
https://web.archive.org/web/20040914040003/www.innogenetics.be/site/prodview.asp?id
133%
http://www.innogenetics.be/site/prodview.asp?id=38&lang=E&print=true
Go
MAR SEP DEC
14
7 captures
27 Feb 2003 - 29 Dec 2004
2003 2004 2005
About this capture

# INNOTEST™ hTAU Ag

INNOTEST™ hTAU Ag is an ELISA micro plate assay for the quantitative determination of human tau antigen in human cerebrospinal fluid (CSF).

Combined use of CSF-tau and CSF-Aß42 markers results in a high sensitivity and specificity for Alzheimer's disease versus normal aging and other neurological disorders (1, 2, 3, 4, 5)

**Article number:** 80005
**Number of tests:** 1 plate of 96 tests (8-well strips)




**Easy, reliable and specific quantification of CSF-tau. The combined use of CSF-tau and CSF-Aß42 markers allows differentiation between AD and normal aging/other neurologic disorders.**

Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000247

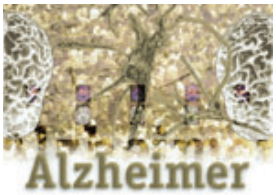
The Wayback Machine - https://web.archive.org/web/20040914040003/http://www.innogenetics.be:80/site/prodview.asp?id…

# INNOTEST™ hTAU Ag

INNOTEST™ hTAU Ag is an ELISA micro plate assay for the quantitative determination of human tau antigen in human cerebrospinal fluid (CSF).

Combined use of CSF-tau and CSF-Aß42 markers results in a high sensitivity and specificity for Alzheimer's disease versus normal aging and other neurological disorders (1, 2, 3, 4, 5)

**Article number:** 80005
**Number of tests:** 1 plate of 96 tests (8-well strips)




**Easy, reliable and specific quantification of CSF-tau. The combined use of CSF-tau and CSF-Aß42 markers allows differentiation between AD and normal aging/ other neurologic disorders.**

## Features & Benefits:

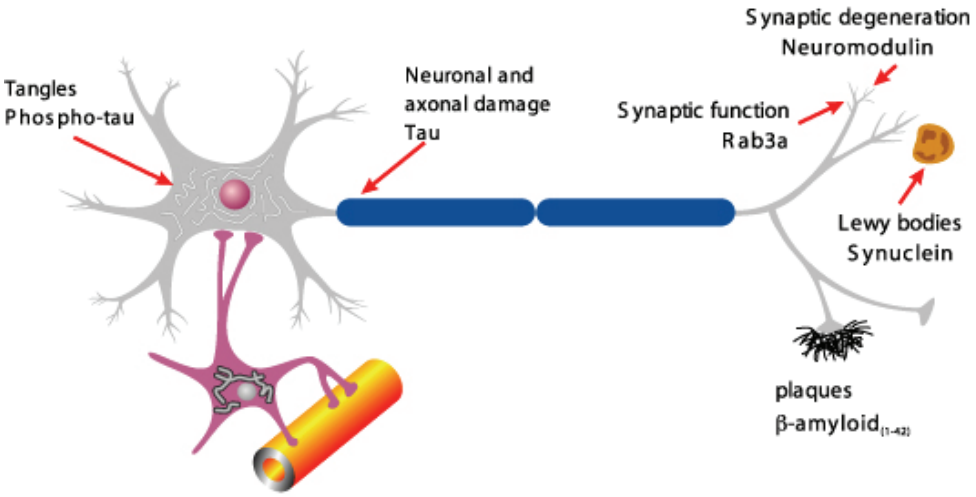



- **Convenient**
  User-friendly enzyme immunoassay
- **Easy**
  Minimum of handling steps
  25 µl of CSF, duplo testing is strongly recommended and requires 2x25 µl of CSF
- **Reliable**
  Reproducible results within the standards range
- **Broad assay range**
  Lowest detection limit: 60 pg/ml
  Standards range: 75 to 1200 pg/ml
- **Clinical utility:**
  High sensitivity and specificity for the differentiation of Alzheimer's disease from normal aging or other neurological disorders such as depression, when used in combination with CSF-Aß42 (1, 2, 3, 4, 5).

## Background:



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000248




Alzheimer's disease (AD) can be considered as being the most important of all neuronal degenerative diseases because of its frequent occurrence (accounting for 60% of all senile dementias) (6) and devastating consequences. Given the gradual aging of the population and an exponential increase in the prevalence of AD after the age of 65 (from 5% at age 75-79 to 19% at age 85-89) (6, 7), the detection of AD is one of today's major challenges for healthcare. AD diagnosis is based on the presence of characteristic clinical features, the exclusion of other causes of dementia, and post-mortem confirmation. Current diagnostic criteria for probable AD, such as the NINCDS-ADRDA (8) or DSM-IV (9), lack the necessary specificity and sensitivity to discriminate AD from other causes of dementia such as vascular dementia (VAD), dementia with Lewy bodies (DLB), or co-existing Parkinson's disease (PD). Clinico-pathological studies reveal accuracy rates between 63% and 90% at academic medical centers (10, 11). As specific therapeutic options are currently emerging, there is a definite need to seek means of improving diagnostic approaches.

The two most widely recognized pathological features of AD, although not 100% specific, are senile plaques and neurofibrillary tangles in the brain (12, 13). These features also seem to correlate with the degree of dementia. Since biochemical changes in the brain are known to alter the composition of cerebrospinal fluid (CSF), tests based on the quantitative detection of these features in CSF may be helpful in the diagnosis of Alzheimer's disease.

Senile plaques consist largely of an insoluble peptide called ß-amyloid (Aß).
The main type of ß-amyloid is Aß 42, a sticky protein fragment abnormally cleaved from a larger precursor protein called amyloid precursor protein or APP. Amyloid deposits are sparsely found in different regions of the normal aging brain, between the brain's nerve cells, but become increasingly more abundant in the initial and subsequent stages of AD. As a result, ß-amyloid(1-42) concentrations in the CSF of AD patients are significantly lower compared to age-matched controls (14).

Tangles are mainly composed of abnormal aggregations of tau protein. Normally, this protein is abundantly present in neurons where it serves to stabilize the microtubular network in the axons (15). In Alzheimer's disease, and particularly in those brain regions affected, the tau protein becomes abnormally phosphorylated, and this hyperphosphorylated form twists itself into paired helical filaments. These filaments aggregate to form the neurofibrillary tangles. When this happens, tau can no longer fulfil its stabilizing function, resulting in a collapse of the cell's internal transport, communication malfunction between nerve cells, and neuronal loss.
Since tau is normally an intracellular protein, the amount found in cerebrospinal fluid (CSF) is low. However, in Alzheimer's disease, the slow neurodegenerative process leads to increased neuronal loss which may give rise to increased tau levels in CSF.

The development of high affinity monoclonal antibodies highly specific for tau, tau phosphorylated at threonine 181, and specifically recognizing well-defined epitopes of Aß has led to simple tests for the quantification of tau (INNOTEST™ hTAU Ag) (16), phosphorylated tau (INNOTEST™ PHOSPHO-TAU(181P)) (17) and Aß 42 (INNOTEST™ ß- AMYLOID(1-42)) (18) in CSF.

Reference values for both CSF-tau and CSF-Aß42 have been established (19). Multi-center studies


Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000249

and meta-analysis in the United States (2, 5) and Japan (3), as well as an international multi-center study (1), consistently found that the combined use of CSF-tau and CSF-Aß42 marker quantification results in a high sensitivity and specificity (> 80%) to distinguish AD patients from healthy controls and other neurological disorders like depression. These results confirm the added value of biomarkers, especially in the light of the Consensus guidelines, established by the Working Group on Molecular and Biochemical Markers for AD (20) stating that a useful biomarker should have a sensitivity of more than 80% for detecting AD and a specificity of more than 80% for distinguishing other dementias. The value of CSF-tau, CSF-Aß42, and CSF-phospho-tau in differential and early diagnosis has been described in several studies (21, 22, 23, 24, 25).

These tests may also prove to be of value in monitoring long-term effects of disease-modifying therapies.

References:


1. Hulstaert F, Blennow K, Ivanoiu A, et al. Improved discrimination of AD patients using ß-Amyloid(1-42)) and tau levels in CSF. Neurology 1999;52:1555-1562.
2. Galasko D, Chang L, Motter R, et al. High cerebrospinal fluid tau and low amyloid ß42 levels in the clinical diagnosis of Alzheimer's disease and relation to apolipoprotein E genotype. Arch Neurol 1998;55:937-945.
3. Shoji M, Kanai M, Matsubara E, Ikeda M, Harigaya Y, Okamoto K, Hirai S, Taps to Alzheimer's patients: a continuous Japanese study of cerebrospinal fluid markers. Ann Neurol 2000;48:402.
4. Andreasen N, Minthon L, Davidsson P, et al. Evaluation of CSF-tau and CSF- Aß42 as diagnostic markers for Alzheimer's disease in clinical practice. Arch Neurol 2001;58:373-379.
5. Sunderland T, Linker G, Mirza N, et al. Decreased b-amyloid1-42 and Increased Tau Levels in Cerebrospinal Fluid of Patients With Alzheimer disease. Journal of the American Medical Association 2003;289:2094-2103.
6. Knopman D, Ritchie K, Polge C, Alafuzoff I, Soininen H. Alzheimer's disease. In: Qizilbash N, ed. Evidence-based Dementia Practice. Oxford: Blackwell Science;2002. p. 228-259.
7. McDowell I. Alzheimer's disease: Insights from epidemiology. Agin Clin Exp Res 2001;13:143-162.
8. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984; 34:939-944.
9. APA (American Psychiatric Association): Diagnostic and statistical manual of mental disorders, Fourth Edition. Washington, DC, American Psychiatric Association, 1994
10. Morris JC. Clinical presentation and course of Alzheimer's disease. In: Terry RD, Katzman R, Bick KL, et al., eds. Alzheimer's disease. 2nd Ed. Philadelphia: Lippincott, Williams & Wilkins; 1999. p. 11. 11. Boller F, Lopez OL, Moossy J. Diagnosis of dementia: clinicopathologic correlations. Neurology 1989;39:76-79.
11. Selkoe DJ. The molecular pathology of Alzheimer's disease. Neuron 1991;6:487-498.
12. Braak H and Braak. Staging of Alzheimer's disease-related neurofibrillary changes. Neurobiol Aging 1995 May-Jun; 16(3):271-8; discussion 278-84.
13. Motter R, Vigo-Pelfrey C, Kholodenko D, et al. Reduction of beta-amyloid peptide42 in the cerebrospinal fluid of patients with Alzheimer's disease. Ann Neurol 1995;38(4):643-8. 15. Goedert M. Tau protein and the neurofibrillary pathology of Alzheimer's disease. Ann N Y Acad Sci 1996;777:121-131
14. Vandermeeren M, Mercken M, Vanmechelen E, et al. Detection of tau proteins in normal and Alzheimer's disease cerebrospinal fluid with a sensitive sandwich enzyme linked immunosorbent assay. J Neurochem 1993;61:1828-1834.
15. Vanmechelen E, Vanderstichele H, Davidsson P, et al. Quantification of tau phosphorylated at threonine 181 in human cerebrospinal fluid: a sandwich ELISA with a synthetic phosphopeptide for standardization. Neuroscience Letters 2000;285:49-52.
16. Vanderstichele H, Van Kerschaver E, Hesse C, et al. Standardization of measurement of b-amyloid(1-42) in cerebrospinal fluid and plasma. Int. J. Exp. Clin. Invest. 2000;7:245-258.
17. Sjögren M, Vanderstichele H, Agren H, et al. Tau and Ab42 in Cerebrospinal Fluid from Healthy Adults 21-93 Years of Age: Establishment of Reference Values. Clinical Chemistry 2001;47:1776-1781.
18. The Ronald and Nancy Reagen Research Institute of the Alzheimer's Association and the National Institute on Aging Working Group. Neurobiol Aging 1998;19:109-116.
19. Hesse C, Rosengren L, Andreasen N, et al. Transient increase in total tau but not phospho-tau in human cerebrospinal fluid after acute stroke. Neurosci Lett 2001;297:187-190.
20. Otto M, Wiltfang J, Tumani H, et al. Elevated levels of tau-protein in cerebrospinal fluid of patients with Creutzfeldt-Jakob disease. Neurosci Lett 1997;225:210-212.
21. Otto M, Wiltfang J, Cepek L, et al. Tau protein and 14-3-3 protein in the differential diagnosis of Creutzfeldt-Jakob disease. Neurology 2002;58:192-197.
22. Riemenschneider M, Lautenschlager N, Wagenpfeil S, Diehl J, Drzezga A, Kurz A. Cerebrospinal fluid tau and ß-amyloid 42 proteins identify Alzheimer disease in subjects with mild cognitive impairment. Arch Neurol 2002;59:1729-1734.
23. Andreasen N, Vanmechelen E, Vanderstichele H, Davidsson P, Blennow K. Cerebrospinal fluid levels of total-tau, phospho-tau and Aß42 predicts development of Alzheimer disease in patients with mild cognitive impairment. Acta Neurol Scand 2003;107(suppl 179):1-5.


## Publications

- Basic and Clinical Studies on the Measurement of Tau Protein in Cerebrospinal Fluid as a Biological Marker for Alzheimer's Disease and Related Disorders: Multi center Study in Japan.
- Cerebrospinal fluid tau and Aß42 as predictors of development of Alzheimer's disease in patients with mild cognitive impairment.
- Improved discrimination of AD patients using ß-amyloid(1-42) and tau levels in CSF.
- Levels of TAU protein in cerebrospinal fluid are correlated with neuronal loss in Alzheimer's disease.
- Are elevated CSF tau levels in Alzheimer patients related to clinical parameters?



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000250

- CSF tau is related to apolipoprotein E genotype in early Alzheimer's disease.
- Phosphorylated tau in cerebrospinal fluid as marker for Creutzfeldt-Jacob disease
- CSF-phospho-tau (181P) as a promising marker for discriminating Alzheimer's disease from dementia with Lewy bodies.
- Highly increased CSF tau protein and decreased ß-amyloid (1-42) in sporadic CJD: a discrimination from Alzheimer's disease?
- CSF markers for the diagnosis of Alzheimer's disease.
- Effects of cholinesterase inhibitors on Alzheimer's disease biomarkers.

## Customer support

For all inquiries regarding Innogenetics products and instrumentation we offer the service of our customer support team. This team of technical experts is commited to dealing with

- General inquiries
- Technical assistance
- Complaint resolution

To conserve your time and eliminate the need to navigate through the company structure, the customer support team is designed to be your principle point of contact. They will ensure that all product-related inquiries are handled by the appropriate person. For this service please contact us.



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000251

**EX-1030A** Webpage for *AD* from Quanterix, archived by Internet Archive on May 29, 2010, available at https://web.archive.org/web/20100529185326/www.quanterix.com/applications/ad.html.




Quanterix

The Leader in Single Molecule Analysis

Applications

Company | Technology | Applications | Partnering | News & Events | Careers | Contact & Directions

## Applications:

High-Sensitivity Immunodiagnostics (Digital ELISA)

Prostate Cancer Recurrence Monitoring

Alzheimer's Disease (AD)

# Alzheimer's Disease (AD)

It is estimated that 5.3 million Americans, or approximately one in eight people over the age of 65, are living with AD, which necessitates long-term care services in excess of $148 billion annually. In clinical practice today, a diagnosis of AD is derived from patient history, neuropsychological and routine laboratory tests, and imaging studies to exclude other causes of dementia and treatable forms of disease. The accuracy of diagnosis among experienced clinicians is approximately 85%, and even lower at the primary care level. Objective diagnostic tests could therefore aid in the clinical workup of patients. Existing laboratory tests currently measure proteins present in cerebral spinal fluid (CSF). However, because CSF collection requires an invasive lumbar puncture (spinal tap), these tests are

Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000253

The Wayback Machine - https://web.archive.org/web/20100529185326/http://www.quanterix.com:80/applications/ad.h…



## Applications: Alzheimer's Disease (AD)

High-Sensitivity Immunodiagnostics (Digital ELISA)

Prostate Cancer Recurrence Monitoring

Alzheimer's Disease (AD)

It is estimated that 5.3 million Americans, or approximately one in eight people over the age of 65, are living with AD, which necessitates long-term care services in excess of $148 billion annually. In clinical practice today, a diagnosis of AD is derived from patient history, neuropsychological and routine laboratory tests, and imaging studies to exclude other causes of dementia and treatable forms of disease. The accuracy of diagnosis among experienced clinicians is approximately 85%, and even lower at the primary care level. Objective diagnostic tests could therefore aid in the clinical workup of patients. Existing laboratory tests currently measure proteins present in cerebral spinal fluid (CSF). However, because CSF collection requires an invasive lumbar puncture (spinal tap), these tests are not widely utilized in primary care settings or geriatric practices. For the first time, using Quanterix's SiMoA technology, it is now possible to detect these same proteins with a simple blood test, even though they are present in the blood at exceedingly low concentrations, well below the limit of detection achieved by standard testing methods.

Quanterix is developing an Alzheimer's Disease test panel test that will enable "rule in" diagnosis of AD from a simple blood test, eliminating the need for invasive medical procedures, shortening time to diagnosis, and reducing the use of expensive imaging modalities. Quanterix will enter into clinical collaborations to validate that the changing levels of these biomarkers track with disease progression.

Selected biomarkers from this test panel may also have clinical utility in diagnosing other neurological disorders including Parkinson's disease, bipolar disorder, stroke and traumatic brain injury (TBI).

*The primary care doctors, internists, geriatricians; these are the people who are on the front-line diagnosing and caring for people with cognitive impairment and dementia. And I believe that this is also the group who would appreciate and benefit the most from having a simple blood-based panel available.*
***John Growdon, MD Massachusetts General Hospital***



One Kendall Square, Suite B14201, Cambridge, MA 02139
Tel: 617-301-9400 Fax: 617-301-9401



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000254

© 2010 Quanterix Corporation design by Digizyme



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000255

**EX-1034A** Webpage for *Assay* from Quanterix, archived by Internet Archive on May 29, 2013, available at https://web.archive.org/web/20130529112628/http://www.quanterix.com:80/products/assay-kits.

https://web.archive.org/web/20130529112628/http://www.quanterix.com:80/products/assa 133%
http://www.quanterix.com/products/assay-kits Go
APR MAY OCT
36 captures 29
15 Nov 2012 - 10 Aug 2019 2012 2013 2014
About this capture



Quanterix

high definition diagnostics℠






# Assay Kits

Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000257

The Wayback Machine - https://web.archive.org/web/20130529112628/http://www.quanterix.com:80/products/assay-kits



# Assay Kits




Quanterix is developing a rapidly growing menu of validated assays in a number of research fields. Visit this page often as new assays will be added as they become available.

- Cardiovascular
- Inflammation
- Metabolic
- Multiplex Panels
- Neurology
- Oncology and Vascular

Let us know if there is a particular biomarker for which you'd be interested in obtaining greater sensitivity with Simoa!

Contact sales@quanterix.com for more information.

© 2013 | privacy policy | site map

FOLLOW US:

113 Hartwell Avenue | Lexington, MA 02421 USA | +1 (617) 301-9400 | info@quanterix.com

Quanterix, Simoa, and High Definition Diagnostics are trademarks of Quanterix Corporation.



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000258

**EX-1035A** Copy of *Nalefski* obtained from the Linda Hall Library.

sequences representing all known high-risk HPV E6 were tested, and PDZ 88 interacted with all of them with greatest binding strength. Therefore, PDZ 88 was selected as the capture reagent. The recognition of PDZ 88 to only high-risk HPV E6 (e.g., HPV types 16, 18, 33, 35, 52, 58, and 66) but not low-risk HPV E6 (e.g., HPV types 77 and 57) provides a high degree of selectivity for the assay.

Antibodies to HPV E6 from high-risk HPV types were generated. The antibodies were screened for affinity and cross-reactivity with other HPV E6. The antibody with the strongest reactivity to HPV-16 E6 was selected as the detector.

The magnetic immunochromatographic strip was selected for evaluation as the assay platform on the basis of ease of use and acceptability in low-resource settings, inherent sensitivity of the technology, and the ability to quantify results. MagnaBioSciences has developed a magnetic immunochromatographic test platform including an assay cassette and reader that is suitable for developing quantitative assays for a variety of analytes. The assay described here was developed on this platform. Additional studies for the method have shown that strip-to-strip reproducibility yields a CV of <10%, and reader reproducibility yields a CV of 1.5% (data not shown).

The PDZ capture reagent was immobilized on a nitrocellulose membrane. Assays were assembled with a laminate backing, membrane with immobilized PDZ, hydrophilic sample pad, absorbent pad, and membrane cover tape. Test strips were cut to a width of 7.5 mm. The soluble-phase detection antibody was covalently conjugated to superparamagnetic particles.

Doubling dilutions of recombinant HPV-16 E6 from 332 to 5.2 μg/L were prepared in the proprietary assay running buffer containing Tris, surfactants, and blocking agents. The detection reagent was mixed with the sample, and 250 μL was applied to the strip. On migration of the sample, the strips were inserted into the magnetic strip reader. The strip reader generated data curves. Peak height was selected, and data were reported as relative magnetic units (RMUs).

The assay cutoff was conservatively set at 3 times the mean RMU of the negative controls. The RMU value for each sample was divided by the cutoff. Samples >1 were considered positive.

Lower amounts of the target protein led to lower RMU values (Fig. 1B). Strips titrated with recombinant HPV-16 E6 and read on the magnetic strip reader exhibited a linear response.

An initial prototype of the magnetic immunochromatographic strip assay is capable of detecting recombinant HPV-16 E6 down to 2.6 ng/assay (~2 600 000 cells). An early version of the assay in an ELISA format detected oncogenic E6 from cervical cancer cell lines down to 30 pg/assay (~30 000 cells). Future steps include further optimization to decrease detection limits and evaluation of cell cultures and cervical cell swabs from clients. Once utility with HPV16 is demonstrated, additional high-risk HPV types will be added to the assay.

Funding for this work was provided by the Bill and Melinda Gates Foundation and by National Institutes of Health SBIR award number 1 R43 CA103383-01.

**References**

1. Munger K, Phelps WC, Bubb V, Howley PM, Schlegel R. The E6 and E7 genes of the human papillomavirus type 16 together are necessary and sufficient for transformation of primary human keratinocytes. J Virol 1989;63:4417–21.
2. Munger K, Baldwin A, Edwards KM, Hayakawa H, Nguyen CL, Owens M, et al. Mechanisms of human papillomavirus-induced oncogenesis. J Virol 2004;78:11451–60.
3. Hawley-Nelson P, Vousden KH, Hubbert NL, Lowy DR, Schiller JT. HPV13 E6 and E7 proteins cooperate to immortalize human foreskin keratinocytes. EMBO J 1989;8:3905–10.
4. Francis DA, Schmid SI, Howley PM. Repression of the integrated papillomavirus E6/E7 promoter is required for growth suppression of cervical cancer cells. J Virol 2000;74:2679–86.
5. DeFilippis RA, Goodwin EC, Wu L, DiMaio D. Endogenous human papillomavirus E6 and E7 proteins differentially regulate proliferation, senescence, and apoptosis in HeLa cervical carcinoma cells. J Virol 2003;77:1551–63.
6. Kiyono T, Hiraiwa A, Fujita M, Hayashi Y, Akiyama T, Ishibashi M. Binding of high-risk human papillomavirus E6 oncoproteins to the human homologue of the *Drosophila* discs large tumor suppressor protein. Proc Natl Acad Sci U S A 1997;94:11612–6.
7. Lee C, Laimins LA. Role of the PDZ domain-binding motif of the oncoprotein E6 in the pathogenesis of human papillomavirus type 31. J Virol 2004;78:12366–77.
8. Nguyen ML, Nguyen MM, Lee D, Griep AE, Lambert PF. The PDZ ligand domain of the human papillomavirus type 16 E6 protein is required for E6's induction of epithelial hyperplasia in vivo. J Virol 2003;77:6957–64.
9. Ledwaba T, Dlamini Z, Naicker S, Bhoola K. Molecular genetics of human cervical cancer: role of papillomavirus and the apoptotic cascade [Review]. Biol Chem 385:671–82, 2004.

DOI: 10.1373/clinchem.2006.072884

**Single-Molecule Detection for Femtomolar Quantification of Proteins in Heterogeneous Immunoassays,** *Eric A. Nalefski, Christina M. D'Antoni, Evan P. Ferrell, Janice A. Lloyd, Haoqun Qiu, John L. Harris, and Duncan H. Whitney** (U.S. Genomics, Woburn, MA; * address correspondence to this author at: U.S. Genomics, 12 Gill St., Suite 4700, Woburn, MA 01801; fax 781-938-0060, e-mail dwhitney@usgenomics.com)

There is growing interest in the development of ultrasensitive immunoassays to facilitate validation of novel biomarkers, especially serum biomarkers, and the application of those assays in clinical settings *(1)*. Current assays focus predominantly on abundantly produced protein biomarkers, such as cardiovascular structural proteins that leak into the bloodstream, and less so on lower abundance cytokines and chemokines *(2)*. Even rarer markers, such as those released from cancerous cells into the bloodstream, remain more elusive *(3)*. Approaches that exploit recent technological advances in molecular imaging, especially at the single-molecule level *(4)*, are likely to improve the detection limits of the immunoassay, and therefore enable improved detection of these markers.

Microfluidic sample delivery and confocal microscopic detection of labeled biomolecules are useful for detecting targets of interest *(5, 6)*. Two-color correlation counting

Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000260

derived from focused laser-induced excitation allows for high signal-to-noise detection even in the presence of large excesses of free probes, enabling measurement of single molecular events (*6*). Flow velocity and data acquisition rates can be matched to provide highly accurate quantification, even for rapid analyses on the order of seconds per sample, and analysis time can easily be extended to provide increased detection efficiency of rare targets.

Development and application of new assays are straightforward processes based on well-understood fluorescence methods. We describe application of the Trilogy® 2020 Single Molecule Analyzer for analysis of heterogeneous immunoassays. The human gonadotropin follicle-stimulating hormone (FSH), which plays a central role in fertility (*7*), was chosen as a representative analyte because of its clinical importance and current clinical requirements for high-sensitivity detection (*8*).

The Trilogy 2020 instrument uses laser beams shaped into stripes for fluorescence illumination and focuses the beams through a microscope objective into the center of a sample-delivering microcapillary (see the Data Supplement that accompanies the online version of this article at http://www.clinchem.org/content/vol52/issue11). Fluorescence collected through the objective lens is separated into channels and focused onto a charge-coupled device (CCD) camera. Photon counts are integrated over 110 μs in each of 10 superpixels spanning the width of each laser stripe and stored in data bins. We developed a dynamic thresholding approach to identify and count fluorescence events arising from "in focus" probes (see the online Data Supplement).

We developed a direct immunometric (sandwich) assay for FSH based on a matched monoclonal antibody (mAb) pair specific for FSH (Medix Biochemica). An α-chain–specific capture mAb was biotinylated by reaction with EZ-Link™ NHS-$PEO_4$-Biotin (Pierce Biotechnology), leading to 2 biotins/antibody based on biotin quantification by the avidin-2–4′-hydroxyazobenzene benzoic acid method. We Cy5-labeled a β-chain–specific reporter mAb by reaction with a FluoroLink™ Cy5 reactive dye (GE Healthcare), leading to 5 dyes/antibody as measured with dye quantification by ultraviolet/visible spectrophotometry. The source of FSH was a purified preparation of FSH (Scripps Laboratories, cat. no. F0613) calibrated by the manufacturer. Capture antibody was coupled to Dynabeads® MyOne™ Streptavidin C1 magnetic beads (Dynal Biotech) at 20 μg per mg of beads in PBS/2% bovine serum albumin and washed extensively before use. Immunoreactions, performed in 96-well plates, consisted of a 100-μL sample, 2.5 μg prepared capture beads (50 ng capture antibody), and 2 nmol/L (30 ng) reporter antibody. After orbital shaking for 1 h at room temperature, we collected beads with a plate magnet and washed them 3 times with cold PBS/0.1% NP40. Reporter antibodies were eluted by addition of 30 μL of 2 mol/L glycine, 0.15 mol/L NaCl, and 0.01% NP40 for 5 min; longer times did not lead to release of more molecules. After the magnetic beads were removed, we neutralized the eluent with 3 μL of 2 mol/L Tris, pH 8.6, and 0.01% NP40, and then analyzed the eluent on the Trilogy instrument.

To characterize the platform sensitivity of the Trilogy 2020 instrument, we collected data on control dilutions of the Cy5-labeled reporter antibody. Representative digitized data traces from a buffer control or a solution containing the Cy5-labeled antibody collected in the Red channel over a 10 ms period are shown in Fig 1A. To illustrate the increase in detected fluorescent events from reporter antibody, signals recorded on the CCD camera in each of the 10 pixels were gray-scaled on the basis of increasing intensity (from white to black). Histogram analysis of bin intensities collected in individual pixels (Fig. 1B) illustrates the increase in mean intensity with increasing antibody concentrations over a wide concentration range. A dynamic thresholding approach to analyze a dilution series of the Cy5-labeled antibody (Fig. 1C) reveals that the Trilogy 2020 device exhibits a lower limit of detection (LLOD) of 15 fmol/L, defined as the smallest antibody concentration that generates a mean (−2 SD) signal that is greater than the mean (+2 SD) signal of a buffer control. At this concentration of antibody, ~100 fluorescent events, which corresponds to less than a zeptomole, above background levels were counted in 12 s. The signal response in detecting dye-labeled antibodies was linear up to at least 125 pmol/L, above which there was a slight deviation downward from the prediction line, revealing a linear response of ~4 orders of magnitude. The signal response, however, continued to increase with even 1 nmol/L antibodies, indicating a dynamic response of $>6 \times 10^4$.

After releasing the captured reporter antibodies into solution, we analyzed eluents from heterogeneous FSH immunoreactions on the Trilogy instrument. Short segments of representative trace files are provided in Fig. 1, D–E. Without added FSH, we detected only a few reporter antibodies over the dynamic threshold (Fig. 1D). In contrast, considerably more reporter antibodies were detected when FSH was included in the immunoreaction (Fig. 1E). A dose–response curve was generated in which FSH concentrations were increased over several logs, and we used the dynamic thresholding approach to determine the resulting antibody signal (Fig. 1F). Detailed analysis of the curve revealed that the LLOD for the immunoassay conducted under these conditions was 20 mIU/L FSH (~34 fmol/L), in this case defined as the smallest concentration of FSH that generates a mean signal that is 2 SDs above that of a buffer control. For this concentration of FSH, hundreds of fluorescent events, corresponding to zeptomoles of antibodies, were counted above background in 12 s. The signal response continued to increase to ≥200 IU/L FSH, yielding a total dynamic range >4000. In contrast, commonly used enzymatic signal amplification assays are reported to be at least 1 order of magnitude less sensitive (*8*).

In conclusion, with the Trilogy platform, based on confocal microscopic detection in microcapillaries, photon bursts corresponding to fluorescently labeled antibodies

Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000261

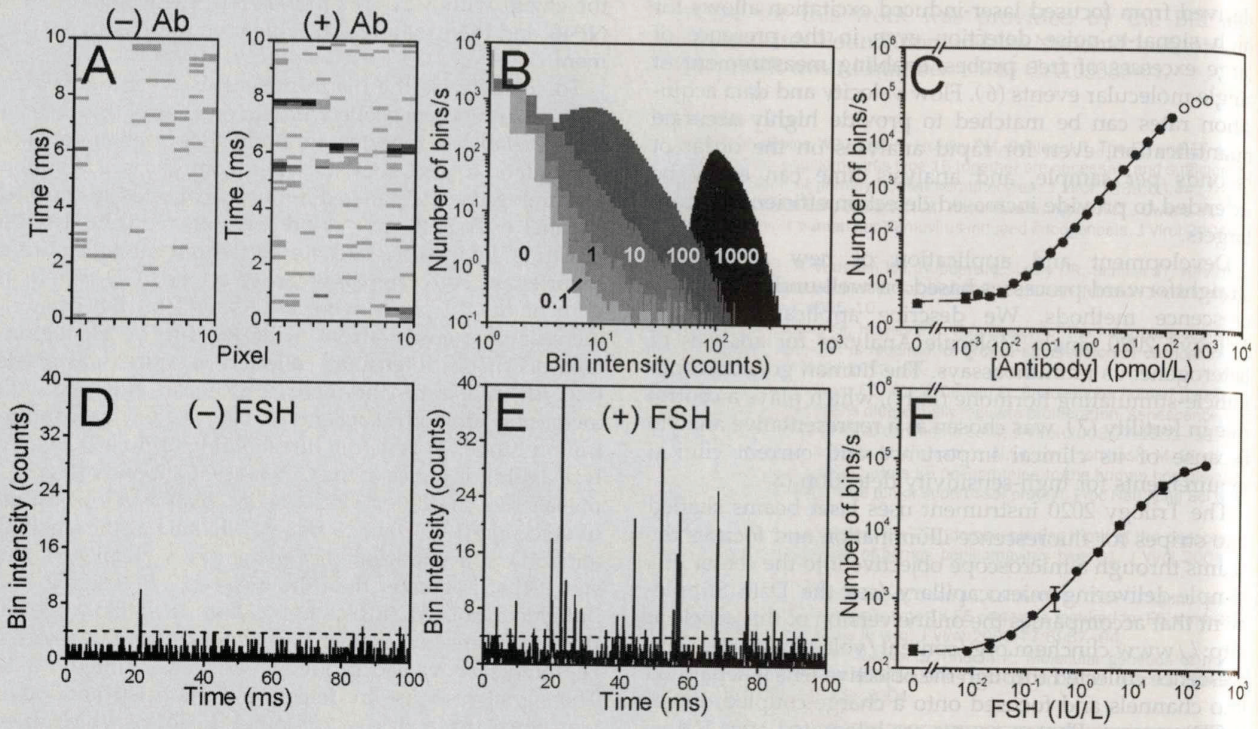



Fig. 1. Single molecule detection.

*(A)*, digitized data recorded in 10 adjacent pixels, represented on the *x*-axis, of the Red channel over 10 ms, represented on the *y*-axis, from control buffer *(left)* or a 4 pmol/L solution of Cy5-labeled antibody *(right)*. Bin intensities recorded on the CCD were scaled downward 20-fold and then gray-scaled equivalently in both panels from low intensity *(white)*, to intermediate *(grays)*, and to high intensity *(black)* for this representation. *(B)*, histograms of bin intensities for data collected in single pixels of the Red channel over 12 s from increasing concentrations of Cy5-labeled antibody (0–1000 pmol/L), illustrating the increase in mean bin intensity. The number of bins was normalized to time. *(C)*, dose dependence of the number of bins observed to exceed the dynamic fluorescence threshold, normalized to time, on the concentration of Cy5-labeled antibody. Symbols represent the mean of multiple replicates for no antibody (n = 20) or the indicated concentrations of antibody (n = 3). Standard deviations of replicates are indicated by *bars*, which are in most cases smaller than *symbols*. The *solid line* represents linear fitting of the data over 100 ms in single pixels on eluents from immunoreactions containing no FSH *(D)* or 1 IU/L FSH *(E)*. The dynamic threshold value of 4 counts used to detect antibody molecules is indicated by the dashed horizontal line. *(F)*, FSH immunoassay dose–response curve, illustrating the dependence of observed numbers of bins that exceed dynamically applied thresholds, normalized to time, on the amount of FSH in the reaction. *Symbols* represent mean values for multiple replicates of no FSH (n = 11) or 12 different FSH dilutions (n = 3). Standard deviations of replicates are indicated by *bars*, which are smaller than *symbols* in most cases. The *solid line* represents fitting of data with a 4-parameter logistic equation. LLOD is calculated here at 20 mIU/L.

are readily distinguishable from background. Counting molecular events, in turn, provides a very sensitive and precise way to quantify biomolecules of interest. Analysis times of only a few seconds are required to detect as little as zeptomoles of protein analytes, leading to low femtomolar LODs.

In addition to several advantages offered by heterogeneous formats *(9)*, analyte enrichment during the capture step provides a unique opportunity to capitalize on the exquisite sensitivity provided by single-molecule analysis. Because the interrogation zone is on the order of femtoliters, the inner diameter of the sample delivery microcapillary is on the order of tens of micrometers, suitable counting statistics are achieved in seconds, and only small volumes of captured and released reporter antibodies are required for analysis. For instance, at 10 μm/ms, the typical linear flow velocity, only a few microliters are consumed in 12 s, a small fraction of the tens of microliters of reporter antibodies eluted from immune reactions conducted on 100 μL of sample, as reported here. Liquid handling procedures designed to deal with smaller volumes would further decrease the required sample size. This feature would be very useful in pediatric tests, for which only small sample volumes are dedicated per test. An added advantage of the single molecule approach is the requirement for only small quantities of probe reagents: for the FSH assay described here, only 30–50 ng of capture and reporter antibodies are consumed per sample per well, and even less would be needed with further miniaturization.

We used FSH as an example to demonstrate the principles and features of single-molecule, heterogeneous-immunoassays. The platform should be equally suitable for the analysis of other fluorescently labeled reporter antibodies and antigens. Although interference, antibody cross-reactivity, and matrix effects that potentially limit other immunoassays must be considered, they pose no particular challenge for the single-molecule approach. The present study used a capture approach involving biotinylated antibodies immobilized to streptavidin-con-

Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000262

jugated beads, but the method is not limited to this approach; we have successfully quantified antigens with capture strategies involving antibodies covalently attached or nonspecifically adsorbed to beads and membranes (data not shown). Furthermore, with inclusion of additional sets of capture reagents and reporter antibodies matching the other fluorescent channels offered by the Trilogy instrument, the platform can simultaneously detect multiple analytes (data not shown). Finally, the platform can be used for precise and sensitive detection of fluorescently labeled probe molecules used in other assays, including those specific for particular nucleic acids *(5)*.

**References**


1. Parsons G. An introduction to clinical laboratory immunodiagnostics. In: Lewandrowski K, ed. Clinical Chemistry: Management, Analysis and Clinical Correlation. Philadelphia, PA: Lippincott, Williams and Wilkins, 2002:413–28.
2. O'Sullivan MJ, Capper S, Horton JK, Whateley J, Baxendale P. Immunoassay applications in life-science research. In: Wild D, ed. The Immunoassay Handbook, 2nd ed. London: Nature Publishing Group, 2001:817–45.
3. Anderson NL, Anderson NG. The human plasma proteome: history, character, and diagnostic prospects. Mol Cell Proteomics 2002;1:845–67.
4. Li H, Ying L, Ren X, Balasubramanian S, Klenerman D. Fluorescence studies of single biomolecules. Biochem Soc Trans 2004;32:753–6.
5. Neely LA, Patel S, Garver J, Gallo M, Hackett M, McLaughlin S, et al. A single-molecule method for the quantitation of microRNA gene expression. Nature Methods 2006;3:41–6.
6. D'Antoni CM, Fuchs M, Harris JL, Ko H-P, Meyer RE, Nadel ME, et al. Rapid quantitative analysis using a single molecule counting method. Anal Biochem 2006;352:97–109.
7. Rose MP, Gaines Das RE, Balen AH. Definition and measurement of follicle stimulating hormone. Endocr Rev 2000;21:5–22.
8. Taylor AE, Khoury RH, Crowley WF Jr. A comparison of 13 different immunometric assay kits for gonadotropins: implications for clinical investigation. J Clin Endocrinol Metab 1994;79:240–7.
9. Wild D. Separation systems. In: Wild D, ed. The Immunoassay Handbook, 2nd ed. London: Nature Publishing Group, 2001:149–58.


DOI: 10.1373/clinchem.2006.072850

Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000263

# Clinical Chemistry

11
06

CLCHAU 52 (11) 1985–2175 (2006)

International Journal of Molecular Diagnostics and Laboratory Medicine


## in this issue


- Rapid Detection and Identification of Bacteria
  See Pages 1985 and 1997
- Adiponectin Gene Variations and Cardiovascular Risk
  See Page 2021
- Health Outcomes Associated with Current and Previous Definitions of Acute Myocardial Infarction
  See Page 2028
- Lipoprotein Subclasses and Coronary Artery Disease
  See Page 2049
- Urinary Metanephrines to Screen for Pheochromocytoma
  See Page 2060

Oak Ridge Conference
See Pages 2129–2175


www.clinchem.org


Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000264

# Clinical Chemistry

11
06

CLCHAU 52 (11) 1985–2175 (2006)

International Journal of Molecular Diagnostics and Laboratory Medicine



LINDA HALL LIBRARY
NOV - 7 2006



**Editor**
**David E. Bruns**
University of Virginia
Charlottesville, VA

**Associate Editors**

**Thomas M. Annesley**
University of Michigan
Ann Arbor, MI

**Fred S. Apple**
Hennepin Co. Medical Center
University of Minnesota
Minneapolis, MN

**James C. Boyd**
University of Virginia
Charlottesville, VA

**Glen L. Hortin**
National Institutes of Health
Bethesda, MD

**Larry J. Kricka**
University of Pennsylvania
Philadelphia, PA

**Nader Rifai**
Children's Hospital Boston
Harvard Medical School
Boston, MA

**David B. Sacks**
Brigham and Women's Hospital
Harvard Medical School
Boston, MA

**Mitchell G. Scott**
Washington University
School of Medicine
St. Louis, MO

**Carl T. Wittwer**
University of Utah
Salt Lake City, UT

**Publisher**
**Mac Fancher**
AACC
Washington, DC

**Board of Editors**

**Douglas G. Altman**
Centre for Statistics in Medicine
Oxford, United Kingdom

**Michael J. Bennett**
University of Pennsylvania
Philadelphia, PA

**Patrick M.M. Bossuyt**
Academic Medical Center
University of Amsterdam
Amsterdam, The Netherlands

**Carlo Brugnara**
Harvard Medical School
Boston, MA

**Robert H. Christenson**
University of Maryland Medical Center
Baltimore, MD

**Kevin R. Coombes**
UT MD Anderson Cancer Center
Houston, TX

**W. Edward Highsmith, Jr.**
Mayo Clinic
Rochester, MN

**Marilyn Huestis**
NIDA, NIH
Baltimore, MD

**David R. Jacobs, Jr.**
University of Minnesota
Minneapolis, MN

**Allan S. Jaffe**
Mayo Clinic
Rochester, MN

**Ishwarlal Jialal**
University of California
Davis, CA

**Klaus Jung**
University Hospital Charité
Berlin, Germany

**Kristian Linnet**
University of Copenhagen
Copenhagen, Denmark

**Y.M. Dennis Lo**
The Chinese University of Hong Kong
Hong Kong, China

**Mark E. Meyerhoff**
University of Michigan
Ann Arbor, MI

**W. Greg Miller**
Virginia Commonwealth University
Richmond, VA

**Chad A. Mirkin**
Northwestern University
Evanston, IL

**David A. Morrow**
Brigham and Women's Hospital
Harvard Medical School
Boston, MA

**Michael Oellerich**
Georg-August-University
Göttingen, Germany

**Thomas W. Prior**
Ohio State University
Columbus, OH

**Robert Rej,** Book Reviews Editor
Wadsworth Center for Laboratories and Research
Albany, NY

**Alan Remaley**
National Institutes of Health
Bethesda, MD

**William Roberts**
University of Utah
Salt Lake City, UT

**Ulf-Håkan Stenman**
Helsinki University Central Hospital
Helsinki, Finland

**Linda M. Thienpont**
University of Gent
Gent, Belgium

**Per Magne Ueland**
Haukeland Hospital
Bergen, Norway

**Ian Young**
Royal Group of Hospitals
Belfast, Northern Ireland

Manuscript Editor
**Linda Sherman**
Charlottesville, VA

Senior Editorial Assistant
**Sandy Weaver**
Charlottesville, VA

Editorial Assistant
**Donna L. Brandl**
Charlottesville, VA

Editorial Systems Coordinator
**Valarie Massie Watersun**
Charlottesville, VA



http://www.clinchem.org


©2006 American Association for Clinical Chemistry



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000265

# Contents

Volume 52, Number 11

## Editorial

**Melting of the Ribosomal RNA Gene Reveals Bacterial Species Identity: A Step toward a New Rapid Test in Clinical Microbiology.** U. Reischl 1985

## Articles

### Molecular Diagnostics and Genetics

**Targeted Gene-Expression Analysis by Genome-Controlled Reverse Transcription-PCR.**
J. Stenman, A. Paju, O. Rissanen, T. Tenkanen, C. Haglund, J. Räsänen, J. Salo, U.-H. Stenman, and A. Orpana 1988

**Rapid Detection and Identification of Clinically Important Bacteria by High-Resolution Melting Analysis after Broad-Range Ribosomal RNA Real-Time PCR.** J.-C. Cheng, C.-L. Huang, C.-C. Lin, C.-C. Chen, Y.-C. Chang, S.-S. Chang, and C.-P. Tseng 1997

**Detection of Exon Deletions within an Entire Gene (*CFTR*) by Relative Quantification on the LightCycler.**
M. Schneider, F. Joncourt, J. Sanz, T. von Känel, and S. Gallati 2005

**Use of Routinely Collected Amniotic Fluid for Whole-Genome Expression Analysis of Polygenic Disorders.**
G.R. Nagy, B. Gyõrffy, O. Galamb, B. Molnár, B. Nagy, and Z. Papp 2013

**Association of Adiponectin Gene Variations with Risk of Incident Myocardial Infarction and Ischemic Stroke: A Nested Case-Control Study.** H.H. Hegener, I-M. Lee, N.R. Cook, P.M. Ridker, and R.Y.L. Zee 2021

### Evidence-Based Laboratory Medicine and Test Utilization

**Health Outcomes Categorized by Current and Previous Definitions of Acute Myocardial Infarction in an Unselected Cohort of Troponin-Naïve Emergency Department Patients.**
P.A. Kavsak, A.R. MacRae, G.E. Palomaki, A.M. Newman, D.T. Ko, V. Lustig, J.V. Tu, and A.S. Jaffe 2028

### Lipids, Lipoproteins, and Cardiovascular Risk Factors

**Inhibitory Effects of Micronized Fenofibrate on Carotid Atherosclerosis in Patients with Essential Hypertension.** S. Zhu, G. Su, and Q.H. Meng 2036

**Lipoprotein(a) in the Cerebrospinal Fluid of Neurological Patients with Blood–Cerebrospinal Fluid Barrier Dysfunction.** G. Pepe, G. Chimienti, G.M. Liuzzi, B.L. Lamanuzzi, M. Nardulli, F. Lolli, E. Anglés-Cano, and S. Matà 2043

**Component Analysis of HPLC Profiles of Unique Lipoprotein Subclass Cholesterols for Detection of Coronary Artery Disease.** M. Okazaki, S. Usui, A. Fukui, I. Kubota, and H. Tomoike 2049

**Factors Affecting *S*-Homocysteinylation of LDL Apoprotein B.**
A. Zinellu, E. Zinellu, S. Sotgia, M. Formato, G.M. Cherchi, L. Deiana, and C. Carru 2054

Clinical Chemistry (ISSN 0009-9147) is published monthly by the American Association for Clinical Chemistry, 1850 K Street, Suite 625, Washington, DC 20006. New subscriptions, renewals, changes of address, back issues, and all customer service questions should be addressed to: AACC, Subscription Department, 1850 K Street, Suite 625, Washington, DC 20006. Telephone (202) 857-0717 or 1 (800) 892-1400; fax (202) 887-5093; e-mail custserv@aacc.org. Subscription rates: Institutional subscription USA $866, elsewhere $999. Individual subscription USA $261, elsewhere $406. Airmail outside USA is an additional $250. Individual subscriptions are for personal use and not to be used in a library. Periodicals postage paid at Washington, DC and at additional mailing offices. Postmaster: Send address changes to Clinical Chemistry, 1850 K Street, Suite 625, Washington, DC 20006. Copyright © 2006 The American Association for Clinical Chemistry.



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000266

Clinical Chemistry
November 2006

## Endocrinology and Metabolism

**Measurement of Urinary Metanephrines to Screen for Pheochromocytoma in an Unselected Hospital Referral Population.** K.L. Brain, J. Kay, and B. Shine 2060

## Automation and Analytical Techniques

**Rapid, Simple, and Sensitive Immunoagglutination Assay with $SiO_2$ Particles and Quartz Crystal Microbalance for Quantifying *Schistosoma japonicum* Antibodies.**
H. Wang, Y. Zhang, B. Yan, L. Liu, S. Wang, G. Shen, and R. Yu 2065

## Laboratory Management

**Improvement of Technical and Analytical Performance in DNA Sequencing by External Quality Assessment-Based Molecular Training.** A. Dorn-Beineke, P. Ahmad-Nejad, U. Pfeiffer, S. Ramsden, M. Pazzagli, and M. Neumaier 2072

## General Clinical Chemistry

**Circulating Proteasomes Are Functional and Have a Subtype Pattern Distinct from 20S Proteasomes in Major Blood Cells.** A. Zoeger, M. Blau, K. Egerer, E. Feist, and B. Dahlmann 2079

**Reproducibility of Risk Figures in 2nd-Trimester Maternal Serum Screening for Down Syndrome: Comparison of 2 Laboratories.** P.A. Benn, G.S. Makowski, J.F.X. Egan, and D. Wright 2087

## Pediatric Clinical Chemistry

**Adiponectin and Leptin in Maternal Serum, Cord Blood, and Breast Milk.**
M. Weyermann, C. Beermann, H. Brenner, and D. Rothenbacher 2095

## Technical Briefs

**Direct-Tissue SELDI-TOF Mass Spectrometry Analysis: A New Application for Clinical Proteomics.**
A. Bouamrani, J. Ternier, D. Ratel, A.-L. Benabid, J.-P. Issartel, E. Brambilla, and F. Berger 2103

## Case Report

**Markedly Increased Vitamin $B_{12}$ Concentrations Attributable to IgG–IgM–Vitamin $B_{12}$ Immune Complexes.**
R.A.R. Bowen, S.K. Drake, R. Vanjani, E.D. Huey, J. Grafman, and M.K. Horne III 2107

## Letters to the Editor

**Surface-Enhanced Laser Desorption Ionization/Time-of-Flight Mass Spectrometry Reveals Significant Artifacts in Serum Obtained from Clot Activator–Containing Collection Devices.**
R. Pilny, P. Bouchal, S. Borilova, P. Ceskova, J. Zaloudik, R. Vyzula, B. Vojtesek and, D. Valik 2115

**Equimolar Ammonia Interference in Potassium Measurement on the Osmetech OPTI CCA: A Reply.**
C. Lin and J.K. Tusa 2116

**Preparation of Uric Acid Standard Stock Solution.** D. Xinhua 2117

**Plasma Aldosterone: Comparison of a New Automated Assay with a Standard Extraction Method.**
D. Hartman, T.W. Doulton, C.A. Chesters, G.A. Sagnella, and G.A. MacGregor 2118

**More on Reporting Medical Errors.** J.S. Krouwer 2120

**Evaluation of the Efficacy of Chloroform Extraction of Amniotic Fluid Bilirubin.**
J.A. Bornhorst, R. Cousin, A.T. Pili, J.A. Erickson, and E.R. Ashwood 2120



(Continued)

Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000267

# Contents

Volume 52, Number 11

**Cell-Free DNA Is More Sensitive than Cell-Free mRNA as a Marker for Evaluation of Fetal-Maternal Hemorrhage.** K. Miura, K. Yoshiura, S. Miura, K. Yamasaki, D. Nakayama, T. Ishimaru, J. Wagstaff, N. Niikawa, and H. Masuzaki 2121

**Choline Concentration in Normal Blood Donor and Cardiac Troponin–Positive Plasma Samples.** M. Adamczyk, R.J. Brashear, and P.G. Mattingly 2123

**Laboratory Reporting of 25-Hydroxyvitamin D Results: Potential for Clinical Misinterpretation.** N. Binkley, M.K. Drezner, and B.W. Hollis 2124

**Falsely Low LDL Cholesterol Results and Cholestasis.** C. Garcia-Hejl, P. Vest, C. Renard, A. Merens-Gonthier, A. Boukhira, and H. Thefenne-Astier 2125

**Reliability of Thrombin Generation Assay on Frozen-Thawed Platelet-Rich Plasma: A Reply.** N. Hézard, M.-G. Remy, B. Florent, and P. Nguyen 2127

## Oak Ridge Conference

**Electron Spin Resonance Spectroscopy of Serum Albumin: A Novel New Test for Cancer Diagnosis and Monitoring.** S.C. Kazmierczak, A. Gurachevsky, G. Matthes, and V. Muravsky 2129

**High-Speed Interferometric Detection of Label-Free Immunoassays on the Biological Compact Disc.** M. Zhao, D. Nolte, W. Cho, F. Regnier, M. Varma, G. Lawrence, and J. Pasqua 2135

**Chip Electrophoresis as a Method for Quantifying Total Microalbuminuria.** O.T.M. Chan and D.A. Herold 2141

## Abstracts of Oak Ridge Posters

**DNA-Programmed Chemistry in Rapid Homogeneous Assays for DNA and Protein Targets.** L.A. Haff, C.G.M. Wilson, Y. Huang, B.K. Benton, J.F. Bond, A.M. Stern, R.F. Begley, and J.M. Coull 2147

**Real-Time Label-Free Acoustic Technology for Rapid Detection of *Escherichia coli* O157:H7.** L. Huang and M.A. Cooper 2148

**An Innovative, Flow-Assisted, Noncompetitive Chemiluminescent Immunoassay for the Detection of Pathogenic Bacteria.** M. Magliulo, B. Roda, A. Zattoni, E. Michelini, M. Luciani, R. Lelli, P. Reschiglian, and A. Roda 2151

**Application of Liquid Chromatography–Mass Spectrometry Technology for Early Detection of Microalbuminuria in Patients with Kidney Disease.** N. Babic, T.S. Larson, S.K. Grebe, S.T. Turner, R. Kumar, and R.J. Singh 2155

**Development and Preliminary Clinical Validation of a High Sensitivity Assay for Cardiac Troponin Using a Capillary Flow (Single Molecule) Fluorescence Detector.** A.H.B. Wu, N. Fukushima, R. Puskas, J. Todd, and P. Goix 2157

**A Systematic Method for Selection of Promising Serum Protein Biomarkers to Improve Prostate Cancer (PCa$^{I}$) Detection.** J.A. Finlay, E.W. Klee, C. McDonald, J.R. Attewell, D. Hebrink, R. Dyer, B. Love, G. Vasmatzis, T.M. Li, J.M. Beecham, and G.G. Klee 2159

**Bioinformatics Methods for Prioritizing Serum Biomarker Candidates.** E.W. Klee, J.A. Finlay, C. McDonald, J.R. Attewell, D. Hebrink, R. Dyer, B. Love, G. Vasmatzis, T.M. Li, J.M. Beecham, and G.G. Klee 2162

**Representational Fragment Amplification: Exponential Amplification of Fragmented cDNA Enables Multimillion-Fold Expression Testing.** G.D. Sgarlato and H.H. Sussman 2164

**Diffractive Optics Technology: A Novel Detection Technology for Immunoassays.** V. Borisenko, W. Hu, P. Tam, I. Chen, J.-F. Houle, and W. Ausserer 2168

(Continued)



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000268

Clinical Chemistry
November 2006

**A Magnetic Immunochromatographic Strip Test for Detection of Human Papillomavirus 16 E6.**
R.B. Peck, J. Schweizer, B.H. Weigl, C. Somoza, J. Silver, J.W. Sellors, and P.S. Lu 217(

**Single-Molecule Detection for Femtomolar Quantification of Proteins in Heterogeneous Immunoassays.**
E.A. Nalefski, C.M. D'Antoni, E.P. Ferrell, J.A. Lloyd, H. Qiu, J.L. Harris, and D.H. Whitney 2172

## ACCENT®—Continuing Education Credit for Readers of *Clinical Chemistry*

**For more information go to www.aacc.org/ccj/accent/**



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000269

## Information for Authors

*Clinical Chemistry* is published by the American Association for Clinical Chemistry (AACC). The journal welcomes contributions of original information, experimental or theoretical, that advance the science of clinical chemistry. Submissions should adhere to the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (N Engl J Med 1991;324:424–8).

**Manuscript Review.** Manuscripts are evaluated by anonymous peer reviewers. Authors are usually notified of the disposition of a manuscript within three to four weeks of its receipt. Equal consideration is given to manuscripts in English from any country, whether or not the author is a member of the AACC.

**Author's Assurances.** Manuscripts are considered with the understanding that each author has participated in the work and assumes responsibility for the content; that the authors have disclosed any potential conflicts of interest; that the same information has not been and will not be submitted for concurrent review, nor published elsewhere (other than as an abstract, preliminary report, or poster cited in the manuscript); that unique materials necessary to reproduce the results are available to readers; and that if the manuscript is accepted, copyright will be transferred to the publisher. To convey these assurances, all authors must sign the Author's Assurances and Assignment of Copyright form (available on the AACC web site at http://www.aacc.org/ccj/authors.stm). Signatures may be submitted by fax, by e-mail or uploaded as scanned documents, or (as originals) by post or courier (see contact information below).

**Unpublished Work.** When citing unpublished work or opinions of others, provide a permission letter from them.

**Manuscript Preparation.** Most common wordprocessing software formats are accepted; Microsoft Word is preferred. PDF is also acceptable for initial submission, but source files will be required with revisions. Use wide margins and double spacing throughout. Do not use headers or footers, but page numbering is acceptable. For guidance on manuscript preparation and style, consult *Scientific Style and Format: The CBE Manual for Authors, Editors, and Publishers,* Sixth Edition; and our Information for Authors, available at www.clinchem.org and at http://www.aacc.org/ccj/infoauth.stm.

The acceptable image file format for print publication is TIFF (tagged image file format) at 600 dpi resolution, and the figures must be submitted as independent files, not embedded within a wordprocessing document. Microsoft PowerPoint (PPT) files are also acceptable, but each file must have embedded fonts and only one image per slide, one slide per file. GIF, JPEG, PDF, and embedded figures may be used for initial submission and review; however, authors are advised to create and keep print-quality files on hand, as they will be required on first revision of the manuscript. Verify that symbols and lettering will be legible when reduced to publication size. Figures should be redesigned or recreated if they do not appear sharp and clear on paper. Authors are advised to test print figures before submitting them for publication.

Color illustrations will be considered for publication. The author will be required to bear the full cost of their preparation and publication, invited contributions excepted. The charge for the first color figure is $1500. Subsequent color figures or parts of figures are $500 each.

For tables, most common wordprocessing formats are acceptable. Spreadsheet-generated tables should be placed in a wordprocessing document.

**Submission and Tracking of Manuscripts.** Submit and track status of manuscripts at http://submit.clinchem.org.

The complete Information for Authors is available at www.clinchem.org and at http://www.aacc.org/ccj/infoauth.stm.

© 2006 The American Association for Clinical Chemistry

*Clinical Chemistry* (ISSN 0009-9147) is published monthly by the American Association for Clinical Chemistry, 1850 K Street, Suite 625, Washington, DC 20006.

**Editorial Office Address.** For additional information about new manuscripts and reviewing, contact the editorial office. Telephone (434) 979-7709; fax (434) 979-7599; e-mail clinchemed@clinchem.aacc.org. Address for regular mail or courier: Clinical Chemistry, 1224 Jefferson Park Avenue, Suite 609, Charlottesville, VA 22903.

**Subscriptions:** Contact the AACC Subscriptions Department at 1850 K Street, Suite 625, Washington, DC 20006. Telephone (800) 892-1400 or (202) 857-0717; fax (202) 887-5093; or Web sites http://www.clinchem.org or http://www.aacc.org. Annual 2006 rates: Print and online institutional subscription USA $866, elsewhere $999. Individual subscription USA $261, elsewhere $406. Airmail delivery outside USA is an additional $250. Online only (no print) institutional subscription $625; individual subscription $189. Individual subscriptions are for personal use and not to be used in a library.

**Reprints:** Reprint order forms are mailed to authors with their page proof. Reprints can also be ordered at any time by contacting the Cadmus Reprint Department. Telephone (800) 407-9190 or (410) 819-3967; fax (410) 820-9765. Minimum reprint order is 100 copies.

**Back Issues:** Selected complete back volumes and single copies of current and back issues are available from AACC. Contact the Subscription Department for pricing. Complete volumes of the journal are available in microform from ProQuest, 300 North Zeeb Road, P.O. Box 1346, Ann Arbor, MI 48106-1346. Telephone (800) 521-0600 or (734) 761-4700. Contact ProQuest directly for prices.

**Missing Copies:** Claims will not be allowed (*a*) unless we are notified within 3 months after the issue date for domestic and Canadian subscribers, or 6 months after the issue date for foreign subscribers; (*b*) if notice of a recent change of address has not been received; or (*c*) if the reason for claim is 'missing from files'. For claims to be processed, the subscriber's number and exact name and address as they appear on the mailing label must be included in correspondence.

**Abstracting and Indexing Services:** *Clinical Chemistry* is covered by Abstracts Express, Analytical Abstracts, Biological Abstracts, BIOSIS, Chemical Abstracts Service, Current Awareness in Biological Sciences, Current Clinical Cancer, Current Contents/Life Sciences, Excerpta Medica/EMBASE, Index Medicus, MEDLINE, Reference Update, Research Alert, Science Citation Index, Sociedad Iberoamericana de Información Científica (SIIC) Data Bases, and SciSearch.

**Disclaimers:** Manuscripts published in *Clinical Chemistry* reflect the individual views of their authors and, in the absence of a statement to the contrary, not the views of the institutions with which the authors are affiliated. The contents of advertisements or articles are not to be construed as official statements, evaluations, or endorsements by the Editor or the American Association for Clinical Chemistry.

**Advertising Inquiries:** Contact Scherago International, Inc., 525 Washington Blvd., Suite 3310, Jersey City, NJ 07310. Telephone (201) 653-4777; fax (201) 653-5205; e-mail aacc@scherago.com; Internet http://www.scherago.com.

Copyright © 2006 The American Association for Clinical Chemistry. All rights reserved. Printed in the United States of America. Photocopying beyond that permitted by Sections 107 or 108 of the US Copyright Law is authorized by the American Association for Clinical Chemistry, for internal or personal use, provided that (*a*) the fee is paid directly to the Copyright Clearance Center, Inc., 222 Rosewood Drive, Danvers, MA 01923; or (*b*) a photocopy license has been granted by the CCC. Fees are subject to change. This consent does not extend to other kinds of copying, such as for general or external distribution, resale, advertising, promotional purposes, or for creating new collective works; for these purposes, contact the Publisher, AACC, 1850 K Street, Suite 625, Washington, DC 20006. Telephone (202) 857-0717; fax (202) 833-4568, e-mail clinchem@aacc.org.

Periodicals postage paid at Washington, DC and at additional mailing offices. POSTMASTER: send address changes to Clinical Chemistry, 1850 K Street, Suite 625, Washington, DC 20006.

**www.clinchem.org**

AACC
Advancing Clinical Laboratory Science Worldwide

**AACC Officers**
John E. Sherwin, *President*
Gary L. Myers, *President Elect*
Mitchell G. Scott, *Past-President*
Robert L. Murray, *Secretary*
Larry A. Broussard, *Treasurer*

**AACC Board of Directors**
Thomas M. Annesley
J. Rex Astles
Michael J. Bennett
Susan Fisher Gross
Anthony O. Okorodudu
Steven H. Wong

**The National Academy of Clinical Biochemistry is the Academy of AACC.**

NACB
Advancing Scholarship in Laboratory Medicine



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000270

**EX-1035B** Bibliographic and MARC records for *Clinical Chemistry* that contains *Nalefski*, available at https://catalog.lindahall.org/permalink/01LINDAHALL_INST/19lda7s/alma992798393405961 from the online catalog of the Linda Hall Library.

JOURNAL

# Clinical chem

For optimum display, please use Chrome or Firefox. Safari users may not be able to see all the relev

American Association of Clinical Chemists; American Association for Clinical Chemistry

c1955-

Available at Linda Hall Library Closed Stacks - Serials (Clinical chemistry.)

Top
Send to
Get It
Details
Virtual Browse
Links

## Send to

Email | QR | Permalink | Citation | EasyBib | Export RIS | Export to Excel

https://catalog.lindahall.org/permalink/01LINDAHALL_INST/19lda7s/alma992798393405961

Copy permalink to clipboard

## Get It

Back to Locations

LOCATION ITEMS

Linda Hall Library

Available , Closed Stacks - Serials ; Clinical chemistry.

Holdings: v.1(1955)-
v.58:no.3(2012:Mar.),v.58:no.5(2012:May)-
v.58:no.12(2012:Dec.)

Supplementary Material: v.50:no.6(2004:June)-v.55:no. S6(2009:June)

Note: Index in last issue of volume. Library's subscription cancelled with completion of 2012.

Item in place (0 requests)
Loanable

Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000272

| | | |
|---|---|---|
| Item in place (0 requests)<br>Loanable | v. 57, no. 12<br>(2011 Dec.) | |
| Item in place (0 requests)<br>Loanable | v. 58, no. 12<br>(2012 Dec.) | |

For optimum display, please use Chrome or Firefox. Safari users may not be able to see all the relev

| | | |
|---|---|---|
| Item in place (0 requests)<br>Loanable | v. 58, no. 10<br>(2012 Oct.) | |
| Item in place (0 requests)<br>Loanable | v. 58, no. 6 (2012<br>June) | |
| Item in place (0 requests)<br>Loanable | v. 58, no. 2 (2012<br>Feb.) | |

Show more items

## Details

| | |
|---|---|
| **Title** | Clinical chemistry |
| **Other title** | Clin. chem. (Baltim. Md.)<br>Clinical chemistry (Baltimore, Md.) |
| **Creator/Contributor** | American Association of Clinical Chemists ›<br>American Association for Clinical Chemistry › |
| **Subjects** | Clinical chemistry ›<br>Pharmaceutical chemistry ›<br>Biochemistry › |
| **Identifier** | ISSN : 0009-9147<br>OCLC : (OCoLC)1554929 |
| **Related title** | Other editions : Clinical chemistry (Reference edition) ›<br>Earlier title : Clinical chemist › |
| **Publisher** | Baltimore, Md. : P.B. Hoeber<br>Vol. 1, no. 1 (Feb. 1955)- |
| **Creation date** | c1955- |
| **Format** | v. : ill. ; 25 cm. |
| **Frequency** | Monthly, <1983-> |
| **General notes** | Imprint varies.<br>Title from cover.<br>Issued also in a Reference ed., available only to institutions, 1983- . |
| **Citations/References** | Index medicus,<br>Biological abstracts,<br>Chemical abstracts,<br>CIS abstracts,<br>Energy research abstracts,<br>Environment abstracts,<br>Excerpta medica, |

International aerospace abstracts,
Life sciences collection,
Reference sources,
RINGDOC,
International nursing index,

Virtual Brows

For optimum display, please use Chrome or Firefox. Safari users may not be able to see all the relev

## Links

Display Source Record

```
leader  02933cas a2200757 a 4500
001     992798393405961
005     20230906182634.0
008     750817c19559999mdumr1p       0   a0eng d
010     ##$a 58002529 //r936 $zsn 78006218
012     ##$b3 $en $i8606 $j2 $k1 $m1
022     0#$a0009-9147
030     ##$aCLCHAU $zCLCHA
032     ##$a118220 $bUSPS
035     ##$a(OCoLC)1554929
035     ##$a(Horizon)388090
035     ##$a(MoKL)279839-lhalldb
035     ##$a(lhalldb)279839-lhalldb
040     ##$aMUL $cMUL $dNSD $dOCL $dDLC $dNSD $dIUL $dHUL $dSER $dRCS $dAIP $dNSD $dAIP $dNSD $dAIP $dDLC $dHUL $dDLC $dNST $dEBZ $dNSD
042     ##$ansdp $alc
049     ##$aLHLA
050     00$aRB1 $b.A28
060     0#$aW1 $bCL685
069     0#$a9421549
069     1#$aC24980000
082     ##$a615.05
210     0#$aClin. chem. $b(Baltim. Md.)
222     #0$aClinical chemistry $b(Baltimore, Md.)
245     00$aClinical chemistry.
260     ##$aBaltimore, Md. : $bP.B. Hoeber, $c[c1955-
300     ##$av. : $bill. ; $c25 cm.
310     ##$aMonthly, $b<1983->
321     ##$aBimonthly, $b1955-
362     0#$aVol. 1, no. 1 (Feb. 1955)-
500     ##$aImprint varies.
500     ##$aTitle from cover.
510     1#$aIndex medicus, $x0019-3879 $b1965-
510     2#$aBiological abstracts, $x0006-3169
510     2#$aChemical abstracts, $x0009-2258
510     2#$aCIS abstracts, $x0302-7651
510     2#$aEnergy research abstracts, $x0160-3604
510     2#$aEnvironment abstracts, $x0093-3287
510     2#$aExcerpta medica,
510     2#$aInternational aerospace abstracts, $x0020-5842
510     2#$aLife sciences collection,
510     2#$aReference sources, $x0163-3546
510     2#$aRINGDOC,
510     0#$aInternational nursing index, $x0020-8124
525     ##$aInclude separate supplements.
525     ##$aStarting in 2010, the June annual meeting abstracts supplement will be available only as PDF download from AACC's website.
550     ##$aJournal of: American Association of Clinical Chemists, 1955-1975; of: American Association for Clinical Chemistry, 1976-
555     0#$aIndex: 1-18(1955-72) bd w/21 n9; auth., subj.: 19-26(1973-80) bd w/27.
580     ##$aIssued also in a Reference ed., available only to institutions, 1983- .
650     #0$aClinical chemistry $vPeriodicals
650     #0$aPharmaceutical chemistry $vPeriodicals
650     #0$aBiochemistry $vPeriodicals
710     2#$aAmerican Association of Clinical Chemists
710     2#$aAmerican Association for Clinical Chemistry
775     1#$sClinical chemistry (Reference edition) $w(OCoLC)9763559
780     00$tClinical chemist $x0097-4005 $w(DLC) 59037292 $w(OCoLC)1397491
850     ##$aDLC $aIaAS $aMnSU $aNcRS $aNcU-H $aNjP $aPU-Med
890     ##$aClinical chemistry. (American Association of Clinical Chemists) Baltimore. 1955-
936     ##$aUnknown $aAug. 1992 (surrogate)
948     ##$aLTI 09/01/2008
948     ##$aLTI 04/14/2009
948     ##$aLTI 07/14/2010
948     ##$aLTI 10/19/2010
```

**EX-1035C** Profile of the Linda Hall Library at https://librarytechnology.org/library/2294.

# libraries.org

## A directory of libraries throughout the world



found **2** items where the item contains **Linda Hall Library**. Showing item **1** of **2**.



## Linda Hall Library

**Linda Hall Library of Science, Engineering and Technology**

**Address:** 5109 Cherry Street
**Kansas City**, **Missouri**
64110-2498
United States

**County:** **Jackson**

**Phone:** 816-363-4600

**Connect to:** **Library Web Site**✔ **Online Catalog**

| Library Hours | | |
|---|---|---|
| **Day** | **Open** | **Close** |
| **Sunday** | Closed | |
| **Monday** | 9:00 am | 5:00 pm |
| **Tuesday** | 9:00 am | 5:00 pm |
| **Wednesday** | 9:00 am | 5:00 pm |
| **Thursday** | 9:00 am | 5:00 pm |
| **Friday** | 9:00 am | 5:00 pm |
| **Saturday** | Closed | |

**Library details:** **Linda Hall Library** is a **Independent Research** library. This library is affiliated with **Linda Hall Library** (**view map**) . The collection of the library contains **860,000** volumes. The library circulates **30,000** items per year.

**Other Info:** The Linda Hall Library is the world's foremost independent research library devoted to science, engineering, and technology. A not-for-profit, privately funded institution, the Library is open to the public free of charge and does circulate. This library shares an ILS with the Spencer Art Reference Library (of the Nelson-Atkins Museum of Art, also in Kansas City, MO). The combined catalog was formerly called LEONARDO (named for the artist/inventor Leonardo da Vinci). LHL is a member of the Independent Research Libraries Association.

**Permalink:** **https://librarytechnology.org/library/2294**
(Use this link to refer back to this listing.)

**Administration:** The director of the library is **Eric Dorfman** .

**Organizational structure:** The library is part of a **privately-funded** organization. It operates on a **Non-profit** financial model.

| | | | |
|---|---|---|---|
| **Collection size** | 860,000 | **volumes** |
| **Annual Circulation** | 30,000 | **transactions** |

| Technology Profile | | |
|---|---|---|
| | **Product Name** | **Year Contracted** |
| **Current Automation System** | **Alma** | **2018** |
| **Previous Automation System** | **Voyager** | 2010 |
| **Previous Automation System** | **Horizon** | 1994 |
| **Previous Automation System** | **None** | |
| **Discovery Service (w/index)** | **Ex Libris CDI** | 2010 |



Linda Hall Library




map location✔

### Related Libraries

- Libraries located in **Kansas City** (Missouri)
- Libraries located in **Jackson** county (Missouri)
- **View map of libraries in Jackson County**
- **all Independent Research libs in Missouri**

### About libraries.org

**libraries.org** is a free directory of libraries throughout the world.

This directory is a component of **Library Technology Guides**.

Please **contact Marshall Breeding** to report corrections about information listed for this library.



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000277

| | | |
|---|---|---|
| **Discovery Interface** | **Primo** | **2010** |
| **Digital Collection Management** | **CONTENTdm** | |
| **Web Content Management** | **WordPress** | |
| **Item ID Type** | Barcode | |

The library's automation system is hosted by the vendor through an **Software-as-a-Service** (**SaaS**) arrangement.

This library is responsible for the procurement of the library automation system.

| **Identifiers** | |
|---|---|
| **libraries.org ID** | 2294 |
| **OCLC Symbol** | LHL |
| **WorldCat Registry ID** | **99283** |

**Record History:** This listing was created on Aug 11, 1998 and was last modified on Apr 10, 2025.

**Updates:** Corrections or Updates? Registered members of Library Technology Guides can submit updates to library listings in libraries.org. **Registration** is free and easy. Already registered? **login**. Or, you can report corrections just by sending a message to **Marshall Breeding**.

libraries.org | Update this Entry | Library Technology Guides

Maintained by **Marshall Breeding**

terms of service
Copyright 1994-2025



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000278

**EX-1035D** PubMed metadata record for *Nalefski*, available at Pu at https://pubmed.ncbi.nlm.nih.gov/18061992/ and the record with field labels at https://pubmed.ncbi.nlm.nih.gov/18061992/?format=pubmed.

An official website of the United States government
Here's how you know

FULL TEXT LINKS
OXFORD ACADEMIC

Clin Chem. 2006 Nov;52(11):2172-5. doi: 10.1373/clinchem.2006.072850.

# Single-molecule detection for femtomolar quantification of proteins in heterogeneous immunoassays

Eric A Nalefski [1], Christina M D'Antoni, Evan P Ferrell, Janice A Lloyd, Haoqun Qiu, John L Harris, Duncan H Whitney

Affiliations

PMID: 18061992 DOI: 10.1373/clinchem.2006.072850

*No abstract available*

PubMed Disclaimer

## Related information

PubChem Compound (MeSH Keyword)

## LinkOut - more resources

**Full Text Sources**
Ovid Technologies, Inc.
Silverchair Information Systems

**Other Literature Sources**
The Lens - Patent Citations Database



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000280

PMID- 18061992
OWN - NLM
STAT- MEDLINE
DCOM- 20071219
LR - 20191110
IS - 0009-9147 (Print)
IS - 0009-9147 (Linking)
VI - 52
IP - 11
DP - 2006 Nov
TI - Single-molecule detection for femtomolar quantification of proteins i
heterogeneous immunoassays.
PG - 2172-5
FAU - Nalefski, Eric A
AU - Nalefski EA
AD - U.S. Genomics, 12 Gill St., Suite 4700, Woburn, MA 01801, USA.
FAU - D'Antoni, Christina M
AU - D'Antoni CM
FAU - Ferrell, Evan P
AU - Ferrell EP
FAU - Lloyd, Janice A
AU - Lloyd JA
FAU - Qiu, Haoqun
AU - Qiu H
FAU - Harris, John L
AU - Harris JL
FAU - Whitney, Duncan H
AU - Whitney DH
LA - eng
PT - Journal Article
PL - England
TA - Clin Chem
JT - Clinical chemistry
JID - 9421549
RN - 0 (Antibodies, Monoclonal)
RN - 9002-68-0 (Follicle Stimulating Hormone)
SB - IM
MH - Antibodies, Monoclonal
MH - Follicle Stimulating Hormone/*analysis/immunology
MH - Humans
MH - Immunoassay/methods
MH - Sensitivity and Specificity
EDAT- 2007/12/07 09:00
MHDA- 2007/12/20 09:00
CRDT- 2007/12/07 09:00
PHST- 2007/12/07 09:00 [pubmed]
PHST- 2007/12/20 09:00 [medline]
PHST- 2007/12/07 09:00 [entrez]

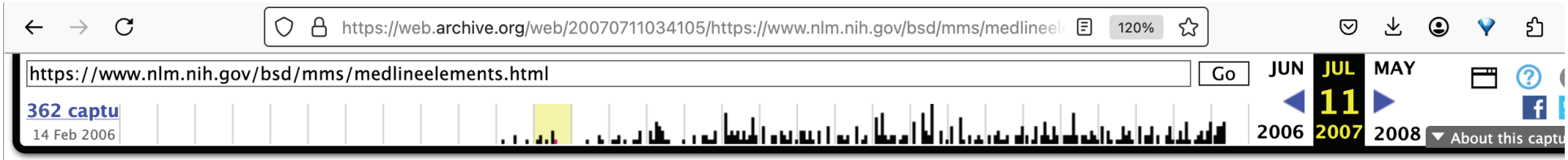

Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000281

AID - 10.1373/clinchem.2006.072850 [doi]
PST - ppublish
SO - Clin Chem. 2006 Nov;52(11):2172-5. doi: 10.1373/clinchem.2006.072850.



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000282

**EX-1035E** MEDLINE/PubMed Data Element (Field) Descriptions, archived by Internet Archive on July 11, 2007, available at https://web.archive.org/web/20070711034105/https://www.nlm.nih.gov/bsd/mms/medlineelements.html.




United States
National Library of Medicine
National Institutes of Health

Search NLM Web Site
Go
NLM Home | Contact NLM | Site Map | FA

Home > MEDLINE/PubMed Resources

# MEDLINE®/PubMed® Data Element (Field) Descriptions

Printer-friendly Version

This document describes the major elements (or fields) found on the MEDLINE display format for PubMed MEDLINE records. Some elements (e.g., Comment In) are not mandatory and will not appear in every record. Other elements (e.g., Author, MeSH term, Registry Number) may appear multiple times in one record. ***Some*** of the elements on this list are searchable fields in PubMed. For searching instructions, see the Search Field Tags section of PubMed Help. This document is supplementary information, to be used in conjuction with PubMed Help. MEDLINE/PubMed XML data element descriptions are also available.

PubMed MEDLINE display elements are presented in this section in alphabetical order, except in the case of certain elements that are closely related to one another.

| | | | | | |
|---|---|---|---|---|---|
| Abstract | (AB) | Investigator Name and Full Investigator Name | (IR) (FIR) | Full Personal Name as Subject | (FPS) |
| Copyright Information | (CI) | ISSN | (IS) | Place of Publication | (PL) |
| Affiliation | (AD) | Issue | (IP) | Publication History Status | (PHST) |
| Investigator Affiliation | (IRAD) | Journal Title Abbreviation | (TA) | Publication Status | (PST) |
| Article Identifier | (AID) | Journal Title | (JT) | Publication Type | (PT) |
| Author | (AU) | Language | (LA) | Publishing Model | (PUBM) |
| Full Author | (FAU) | MeSH Date | (MHDA) | PubMed Unique Identifier | (PMID) |
| Corporate Author | (CN) | MeSH Terms | (MH) | Registry Number/EC Number | (RN) |
| Comments/Corrections | | | | Substance Name | (NM) |

Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000284

The Wayback Machine - https://web.archive.org/web/20070711034105/http://www.nlm.nih.gov/bsd/mms/medlineelement...



# MEDLINE®/PubMed® Data Element (Field) Descriptions

Printer-friendly Version

This document describes the major elements (or fields) found on the MEDLINE display format for PubMed MEDLINE records. Some elements (e.g., Comment In) are not mandatory and will not appear in every record. Other elements (e.g., Author, MeSH term, Registry Number) may appear multiple times in one record. ***Some*** of the elements on this list are searchable fields in PubMed. For searching instructions, see the Search Field Tags section of PubMed Help. This document is supplementary information, to be used in conjuction with PubMed Help. MEDLINE/PubMed XML data element descriptions are also available.

PubMed MEDLINE display elements are presented in this section in alphabetical order, except in the case of certain elements that are closely related to one another.

| | | | | | |
|---|---|---|---|---|---|
| Abstract | (AB) | Investigator Name and Full Investigator Name | (IR) (FIR) | Full Personal Name as Subject | (FPS) |
| Copyright Information | (CI) | ISSN | (IS) | Place of Publication | (PL) |
| Affiliation | (AD) | Issue | (IP) | Publication History Status | (PHST) |
| Investigator Affiliation | (IRAD) | Journal Title Abbreviation | (TA) | Publication Status | (PST) |
| Article Identifier | (AID) | Journal Title | (JT) | Publication Type | (PT) |
| Author | (AU) | Language | (LA) | Publishing Model | (PUBM) |
| Full Author | (FAU) | MeSH Date | (MHDA) | PubMed Unique Identifier | (PMID) |
| Corporate Author | (CN) | MeSH Terms | (MH) | Registry Number/EC Number | (RN) |
| Comments/Corrections | | NLM Unique ID | (JID) | Substance Name | (NM) |
| Date Completed | (DCOM) | Number of References | (RF) | Secondary Source ID | (SI) |
| Date Created | (DA) | Other Abstract | (OAB) | Source | (SO) |
| Date Last Revised | (LR) | Other Copyright Information | (OCI) | Space Flight Mission | (SFM) |
| Date of Electronic Publication | (DEP) | Other ID | (OID) | Status | (STAT) |
| Date of Publication | (DP) | Other Term | (OT) | Subset | (SB) |
| Entrez Date | (EDAT) | Other Term Owner | (OTO) | Title | (TI) |
| Gene Symbol | (GS) | Owner | (OWN) | Transliterated Title | (TT) |
| General Note | (GN) | Pagination | (PG) | Volume | (VI) |
| Grant Number | (GR) | Personal Name as Subject | (PS) | | |

## Abstract (AB)

English-language abstracts are taken directly from the published article. If the article does not have a published abstract, the National Library of Medicine does not create one, thus the record lacks the Abstract element. If a collaborating data producer has created an abstract, it will appear in the Other Abstract (OAB) field. This field may be used in addition to or instead of Abstract.

Publishers have given the National Library of Medicine permission to use abstracts for which they claim copyright. NLM does not hold copyright on the abstracts in MEDLINE. Users should obtain an opinion from their legal counsel for any use they plan for the abstracts in the database.

Generally, there are no abstracts for records created before 1975. However, starting in April 2007 NLM began to add abstracts from articles in PubMed Central (PMC) to the equivalent MEDLINE/PubMed citation record if that record does not already contain an abstract. The abstracts are derived from the PMC scanning project which is digitizing the back issues of participating PMC journals. As a result, additional records published prior to 1975 will contain abstracts.

All abstracts are in English. Because data entry policies at NLM have changed over the years, abstracts in some records may be truncated, in which case one of the following phrases may appear at the end of the text enclosed in parentheses:



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000285

ABSTRACT TRUNCATED AT 250 WORDS
ABSTRACT TRUNCATED AT 400 WORDS
ABSTRACT TRUNCATED (This message occurred infrequently once the maximum length was raised to 4,096 characters in 1996.)

**Example:**

AB - Many disorders may result in delay of language. . . . . The reason for suggesting this diagnostic category is to stress that these children do initially behave in a similar way to those who are peripherally deaf. (ABSTRACT TRUNCATED AT 250 WORDS)

The maximum length of abstracts for records created after 2000 is 10,000 characters. Original policy on inclusion of abstracts set a limit of 250 words for acceptance. Effective with the January 1984 data (i.e., NLM's ELHILL legacy system 8401 Entry Month) two changes were made in this policy: 1) the word limit was expanded to 400 words for abstracts from articles ten pages or more in length or from articles in the core journals identified by the National Cancer Institute and 2) abstracts exceeding the 250- or 400-word limit are to be included in truncated form at the end of the sentence closest to the word limit. The percentage of records with abstracts has increased over the years as more publishers gave permission for NLM to include these data. A chart showing the number of MEDLINE records containing abstracts in various segments of MEDLINE is available at: http://www.nlm.nih.gov/bsd/medline_lang_distr.html.

Structured abstracts, describing key aspects of the purposes, methods, and results in a consistent way, are published in some journals. The key aspects of structured abstracts are capitalized to stand out, e.g., BACKGROUND, OBJECTIVES, METHOD, etc. The text is not broken into paragraphs. Structured abstracts were not truncated in the past, even if they surpassed the previous 250 or 400 word limit.

**Example:**

AB - BACKGROUND: Superantigens produced by Staphylococcus aureus and Streptococcus pyogenes are among the most lethal of toxins. Toxins in this family trigger an excessive cellular immune response leading to toxic shock. OBJECTIVES: To design an antagonist that is effective in vivo against a broad spectrum of superantigen toxins. METHODS: Short peptide antagonists were selected for their ability to inhibit superantigen-induced expression of human genes for cytokines that mediate shock. The ability of these peptides to protect mice against lethal toxin challenge was examined. RESULTS: Antagonist peptide protected mice against lethal challenge with staphylococcal enterotoxin B and toxic shock syndrome toxin-1, superantigens that share only 6% overall amino acid homology. Moreover, . . .

Table of Contents

## Copyright Information (CI)

Copyright Information (CI) associated with Abstract was introduced in 1999, and appears on a limited but increasing number of records. This singly-occurring element contains a copyright statement provided by the publisher of the journal and appears only on records supplied electronically to NLM by the publisher. This information is displayed at the end of the abstract.

**Example:**

AB - ... Copyright 1999 Academic Press.

See also the related Other Copyright Information (OCI) field.

Table of Contents

## Affiliation (AD)



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000286

The affiliation of the first author resides in this field. Starting in 1988, NLM began to include the address of the first author's affiliation on the record. Originally, the address was intended to help differentiate between two authors of the same name, not to provide detailed mailing information. It evolved that the institution, city, and state including zip code for U.S. addresses, and country for countries outside of the United States, were included if provided in the journal; sometimes the street address was also included if provided in the journal. In 1995, NLM began to add the designation USA at the end of this information where the first author's affiliation is in the fifty United States or the District of Columbia. Effective January 1, 1996, NLM includes the primary author's electronic mail (e-mail) address at the end of the Affiliation field, if present in the journal. Starting in 2003 the complete first author address is entered as it appears in the article with no words omitted.

**Examples:**

AD - Department of Anesthesiology, University of Virginia Health Sciences Center Charlottesville 22908, USA. med2p@virginia.edu

AD - Departamento de Farmacologia, Facultad de Medicina, Universidad Complutense de Madrid (UCM), 28040 Madrid, Spain.

AD - Center for Children With Special Needs, Children's Hospital, and the Department of Pediatrics, University of Washington School of Medicine, 4800 Sand Point Way NE, CM:09, Seattle, WA 98105-0371, USA. jneff@chmc.org

Table of Contents

### Investigator Affiliation (IRAD)

The Investigator Affiliation (IRAD) identifies the organization that the researcher was affiliated with at the time the article was written and as published in the journal. Unlike the Affiliation field, this affiliation generally does not include detailed address information. This field is associated with the Investigator (IR) field.

**Examples:**

IRAD - Marquette U, Milwaukee, WI
IRAD - VA Med Ctr, Richmond, VA

Table of Contents

### Article Identifier (AID)

This field is populated by the publisher. It may contain an identifier that links with records in the publisher's system. The article identifier values may include the controlled publisher identifier (pii) or the digital object identifier (doi). It is most often used for LinkOut.

**Examples:**

AID - S0272-7358(05)00023-1 [pii]
AID - 10.1016/j.cpr.2005.02.002 [doi]

Table of Contents

### Author (AU)

NLM's author indexing policy is as follows:

| | |
|---|---|
| 1966 - 1983: | For records created during this time period, MEDLINE did not limit the number of authors. |
| 1984 - 1995: | For records created during this time period, NLM limited the number of authors to 10, with "et al." to indicate the existence of additional authors. |



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000287

| | |
|---|---|
| 1996 - 1999: | For journal issues published during this time period, NLM increased the number of authors from 10 to 25. If there were more than 25 authors, the first 24 were listed, the last author was used as the 25th, and the 26th and beyond became "et al." |
| 2000 - Present: | Beginning with journal issues published in 2000, MEDLINE does not limit the number of listed authors. |

Beginning in mid-2005, the various policy restrictions on number of author names entered in past years were lifted so that on an individual basis, a record may be edited to include all author names present in the published article, regardless of the limitation in effect at the time the record was first created.

Note: Until 1990, NLM transliterated up to five authors' Cyrillic or Japanese names to the Roman alphabet. Since 1990, the first ten Cyrillic or Japanese names are transliterated. Chinese ideograms are not transliterated by NLM, but if transliterations of the authors names are available in the journal article or table of contents, they are included in the citation, even if that includes only one author in a multi-author article.

Format: last name followed by a space and up to the first two initials followed by a space and a suffix abbreviation, if applicable, all without periods or a comma after the last name.

**Examples:**

McCrary SV
Smith AB 3rd

See Full Author (FAU) for more information on initials.

Table of Contents

## Full Author (FAU)

Beginning with articles with a publication year of 2002, PubMed records may include full names. BIOETHICSLINE citations converted to MEDLINE citations in late 2001 have full names on citations prior to publication year 2002; those data are found in the General Note (GN) field. Citations from the Kennedy Institute of Ethics (KIE) may have full names in the Full Author field for publication dates of prior to 2002.

Full author names are entered when they appear in the author position of an article, usually on the title page of an article. If only the last name and initials appear in the author position, then only the last name and initials will be entered, even if a form of the fuller name appears elsewhere in the article or in the Table of Contents for the journal.

Author Initials:
Initials data are generated from the Data Creation and Maintenance System (DCMS) ForeName data element using an algorithm. Here are the highlights of that algorithm:

- Only two initials are included. Initials are at the beginning of a name string or following a break (a space or hyphen). Only capital letters in the ForeName elements are candidates for initials, except for the letter following a hyphen. The letter following a hyphen is a candidate for an initial, unless the string following the hyphen is "ichi."
- When the ForeName data element consists of only initials, there are spaces between initials.
- An initial includes the following particles: da, de, del, do, dos, du, el, el-, and le. All particles except "el-" are followed by a space and are preceded by a space or are at the beginning of the name string. If found, all particles are converted to lower case when generated as part of the Initials data element.
- If the language of the article is Bulgarian, Russian, Serbo-Croatian (Roman), or Ukranian, then one initial may be a 2- or 4-character transliterated mixed-case initial. Current, mixed-case transliteration values are: Dj, Lj, Nj, Ch, Sh, Iu, Ia, Ie, Zh, Kh, Ts, Dz, Shch.

**Examples:**

| Last Name | Fore Name | Suffix | Initials |
|---|---|---|---|
| Melosh | H J | 3rd | HJ |
| Abrams | Judith | | J |



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000288

| Last Name | Fore Name | Suffix | Initials |
|---|---|---|---|
| Buncke | Gregory M | | GM |
| Gonzales-loza | Maria del R | | Mdel R |
| Dubuisson | Jean-Bernard | | JB |
| Amara | Mohamed el-Walid | | Mel-W |
| Shan | Yu-fei | | YF |
| Krylov | Ia K | | IaK |
| De Avila | Luiz Francisco Rodriguez | | LF |

Note that the end result of generating the Initials data is that the two initials are closed up with no space between, even though there may be spaces elsewhere in the Initials string if one or both of the initials has embedded spaces.

There are some author names that have no initials. These are mostly Malaysian names, for which the entire name is entered in the LastName DCMS data element.

The full name will display on the PubMed MEDLINE display format above the respective name field as in the following example:

**Example:**

FAU - Foa, Edna B
AU - Foa EB

Note: When an author's name has been corrected from a published erratum, the corrected name is placed in the Author field and the incorrect name that was originally published is retained in the last occurrence of the Author field. In this case, there will be an associated commentary linkage.

NLM expended much effort to parse the data converted from the legacy ELHILL format at the end of the 2000 production year accurately. Many citations from the 1966-1974 timeframe were changed to follow data entry conventions established later. For example, particles such as "van der" were moved from the suffix position to the beginning of the last name, and the abbreviations "2d" and "3d" were changed to "2nd" and "3rd". It is possible to have particles associated with initials, such as "Mdel R" for "María del R". It is also possible to have only a last name. Some occurrences of author data in this category are in error and will be corrected manually as time permits.

For OLDMEDLINE records, every published author name is included in the list of authors for citations from the 1951 - 1959 *Current List of Medical Literature* (CLML) and for citations from the 1960 - 1965 *Cumulated Index Medicus* (CIM). For citations from the 1950 CLML, a maximum of three author names were entered. OLDMEDLINE first and last name author elements are in all upper case letters, except in some cases the particle is in lower case letters. A suffix is in upper and lower case letters. OLDMEDLINE records do not contain collective or corporate names. A small percentage of OLDMEDLINE records contain the last name only, because that is the only Author data present in the abstracting and indexing tool used to create the record.

Table of Contents

## Corporate Author (CN)

This field identifies the corporate authorship of an article. Corporate Author (CN) was introduced in 2001. Prior to 2001, corporate author information was contained at the end of the Title field, where it remains for those retrospective records. As they are encountered, these retrospective records may be individually maintained to move the Corporate Author information from the Title field to the Corporate Author field.

These names enter MEDLINE exactly as they appear in the journal (except to delete initial articles such as The, A or An). NLM will not edit the names to standardize them or translate them into English. NLM enters the Roman alphabet words (e.g., German, French) into the Corporate Author field. Transliterated Russian or other cyrillic names are also entered into the Corporate Author field, but for Japanese, Chinese, Hebrew, and Arabic, NLM puts the English translation of the name into this field.



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000289

**Example:**

CN - Centers for Disease Control and Prevention

Table of Contents

### Comments/Corrections (See fields and field tags listed below.)

The data in these fields, listed below, are citations to associated journal publications, e.g., comments, errata, or retractions. These data enable links between the record at hand and its associated citations.

MEDLINE records may contain one or more of the following:

| | | |
|---|---|---|
| **Comment on** | **(CON)** | cites the reference upon which the article comments; began use with journal issues published in 1989. |
| **Comment in** | **(CIN)** | cites the reference containing a commentary about the article (appears on citation for original article); began use with journal issues published in 1989. |
| **Erratum in** | **(EIN)** | cites a published erratum to the article (appears on citation for original article); began use in 1987. |
| **Erratum for** | **(EFR)** | cites the original article for which there is a published erratum. |
| **Corrected and Republished in** | **(CRI)** | cites the final, correct version of a corrected and republished article (appears on citation for original article). Began use in 1987 as Republished in (RPI); renamed in 2006. |
| **Corrected and Republished from** | **(CRF)** | cites the original article subsequently corrected and republished. Began use in 1987 as Republished from (RPF); renamed in 2006. |
| **Partial retraction in** | **(PRIN)** | cites the reference containing a partial retraction of the article (appears on citation for original article); began use in 2007. |
| **Partial retraction of** | **(PROF)** | cites the article being partially retracted; began use in 2007. |
| **Republished in** | **(RPI)** | cites the subsequent (and possibly abridged) version of a republished article (appears on citation for original article); began use in 2006. |
| **Republished from** | **(RPF)** | cites the first, originally published article; began use in 2006. |
| **Retraction in** | **(RIN)** | cites the retraction of the article (appears on citation for original article); began use in August 1984. |
| **Retraction of** | **(ROF)** | cites the article(s) being retracted; began use in August 1984. |
| **Update in** | **(UIN)** | cites an updated version of the article (appears on citation for original article); began limited use in 2001. |
| **Update of** | **(UOF)** | cites the article being updated; limited use; began limited use in 2001. |
| **Summary for patients in** | **(SPIN)** | cites a patient summary article; began use in November 2001 (these records contain Publication Type, Patient Education Handout). See the article 'Patient Education Handouts in MEDLINE®/PubMed®' in the *NLM Technical Bulletin* at http://www.nlm.nih.gov/pubs/techbull/ma02/ma02_new_pt.html for more information. |
| **Original report in** | **(ORI)** | cites a scientific article associated with the patient summary. |

The PubMed Identifier (PMID) of the associated record in PubMed is provided (if available) to create a link between an article and its commentary.

**Examples:**

CIN - N Engl J Med. 2003 Jul 17;349(3):211-2. PMID: 12867604
CON - Dev Cell. 2002 Jul;3(1):85-97. PMID: 12110170
CRI - Orthop Nurs. 2003 May-Jun;22(3):232-9. PMID: 12872752



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000290

CRF - Biochemistry. 1994 May 10;33(18):5614-22. PMID: 8180186
EIN - Acta Obstet Gynecol Scand. 2003 Jan;82(1):102
EFR - J Arthroplasty. 2002 Jun;17(4):524-6. PMID: 12066289
RIN - J Biochem Mol Biol. 2002 Nov 30;35(6):642. PMID: 12476908
ROF - Ware FE, Lehrman MA. J Biol Chem. 1996 Jun 14;271(24):13935-8. PMID: 8663248
SPIN- Ann Intern Med. 2003 Jun 3;138(11):I60. PMID: 12779314
ORI - Ann Intern Med. 2003 Jun 3;138(11):907-16. PMID: 12779301
UIN - Cochrane Database Syst Rev. 2002;(3):CD003688. PMID: 12137706
UOF - Cochrane Database Syst Rev. 2002;(2):CD003680. PMID: 12076500

Occasionally, a note is added to the Comment or Correction. The note clarifies the data in the Comments or Correction element. It is most often used with **Erratum In** for corrected author names. The following are some possible notes:

- [added] is used when an author name is added to the citation as the result of a published erratum
- [removed] when an author name is removed
- [dosage error in abstract] when there is a dosage error in a citation abstract (used with Erratum In)
- [dosage error in text] when the dosage error is in the text portion of the article
- [abstract no. xxx only] for an erratum of a numbered abstract which is part of an overall citation
- [abstract by author names on page xxx only] when an erratum refers to an unnumbered abstract which is authored and part of an overall citation. The author names and page numbers of the abstract are included.
- [abstract abstract title on page xxx only] when an erratum refers to an unnumbered abstract which is not authored. In this case, the abstract title and page number are included.

In records from OLDMEDLINE, Comments In (CIN) is the only Comment or Correction found. Other comment or correction elements may be used in the future.

See the NLM Fact Sheet "Errata, Retraction, Duplicate Publication and Comment Policy for MEDLINE®" at http://www.nlm.nih.gov/pubs/factsheets/errata.html for additional information.

Table of Contents

### Date Completed (DCOM)

Date Completed is the date processing of the record ends; i.e., MeSH® Headings have been added, quality assurance validations are completed, and the completed record subsequently is distributed to PubMed and licensees. This is contrasted with Date Created, which is the date processing begins.

Format: YYYYMMDD

**Example:**

DCOM - 20020207

In Process records lack the Date Completed field. For OLDMEDLINE records, the Date Completed is the approximate date the record entered PubMed, rather than the date processing ends. OLDMEDLINE records are created and processed differently than MEDLINE records.

Table of Contents

### Date Created (DA)

Date Created is the date that processing of the record begins.

Format: YYYYMMDD

**Example:**

DA - 20020516



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000291

This is contrasted with Date Completed, which is the date processing ends. Date Created is not the same as NLM's PubMed Entrez Date (EDAT), which is the date the record entered PubMed.

For citations up to about the year 2000, the Date Created (DA) and Date Completed (DCOM) data elements are identical. These dates were derived from NLM's legacy ELHILL system.

For OLDMEDLINE citations converted from the 1964 and 1965 *Index Medicus* (IM), Date Created represents the year and month the citations were printed in the monthly *Index Medicus*, and the day will always be "01". All other OLDMEDLINE records have a year based on the year of the printed index, the month is always "12" for December, and the day is always "01".

Table of Contents

### Date Last Revised (LR)

The Date Last Revised identifies the date a change is made to a record either as a result of individual or global maintenance. There is no indication of what the change is on the record. Only the latest revision date is displayed.

Format: YYYYMMDD

**Example:**

LR - 20020320

When the 10 million+ MEDLINE records through the 2000 production year were converted to XML from NLM's legacy ELHILL system, all records were assigned a Last Revision Date of 20001218 (December 18, 2000). Subsequently, many of these records have been or will be maintained and given a later (LR) date.

Table of Contents

### Date of Electronic Publication (DEP)

The Electronic Publication Date is the date the publisher made an electronic version of the article available. In January 2003, global maintenance was performed to add this element retrospectively.

Format: YYYYMMDD

**Example:**

DEP - 20050513

Table of Contents

### Date of Publication (DP)

Date of Publication contains the full date on which the issue of the journal was published. The standardized format consists of elements for a 4-digit year, a 3-character abbreviated month, and a 1 or 2-digit day. Every record does not contain all of these elements; the data are taken as they are published in the journal issue, with minor alterations by NLM such as abbreviations.

**Examples:**

DP - 2001 Apr 15
DP - 2001 Apr
DP - 2000 Spring
DP - 2000 Nov-Dec
DP - 2001



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000292

Table of Contents

### Entrez Date (EDAT)

This field contains the date the citation was added to PubMed.

Format: YYYY/MM/DD HH:MM

**Example:**

EDAT- 2003/01/02 04:00

Table of Contents

### Gene Symbol (GS): not currently input

This field contains the "symbol" or abbreviated form of gene names as reported in the literature. This element resides in records processed at NLM from 1991 through 1995. Up to 25 occurrences per record may appear. NLM entered the symbols used by authors; there was no authority list or effort to standardize the data.

**Examples:**

GS - dyrA
GS - PYRE-F
GS - cpa2

Greek characters, superscripts, and subscripts may appear as part of the gene symbol. The code designations for the Greek characters may be found at http://www.nlm.nih.gov/bsd/licensee/greek_characters.html.

Table of Contents

### General Note (GN)

This field contains supplemental or descriptive information related to the document. The data in this field may be preceded by the acronym for the collaborator who provided this information.

The acronyms and names are:

| | |
|---|---|
| HMD | History of Medicine Division, National Library of Medicine |
| HSR | National Information Center on Health Services Research and Health Care Technology, National Library of Medicine |
| KIE | Kennedy Institute of Ethics, Georgetown University |
| NASA | National Aeronautics and Space Administration |
| PIP | Population Information Program; Johns Hopkins School of Health |

**Examples:**

GN - KIE: Article and commentaries
GN - KIE: KIE BoB Subject Heading: health care/economics

Note: BoB Subject Headings are controlled subject vocabulary terms found in the Kennedy Institute of Ethics' Bioethics Thesaurus under which citations print in their publication, Bibliography of Bioethics. The current format of these data in MEDLINE is reflected in the second example beginning with "KIE Bob" or "KIE Bib".

Table of Contents

### Grant Number (GR)



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000293

This field was introduced in 1981 and is comprised of three parts:

1. **Number** contains the research grant or contract number (or both) that designates financial support by any agency of the United States Public Health Service or any institute of the National Institutes of Health. The data are generally recorded exactly as they appear in the published article*; there is no attempt to standardize the numbers.
2. **Acronym** contains the 2-letter grant acronym.
3. **Agency** contains the institute acronym or mnemonic.

Effective for prospective citations indexed with MeSH as of June 2, 2005, the value Wellcome Trust is added if an author acknowledges that the research was supported financially by this organization. Effective March 24, 2006, Wellcome Trust grant numbers may also be added from data entered via PubMed Central, or from the published article. The grant number may appear in either six-digit (e.g., 069355) or expanded (e.g., 067427/Z/02/Z) format.

**Examples:**

GR - LM0577/LM/NLM
GR - M0 1 RR01271/RR/NIDDK
GR - Wellcome Trust
GR - 058423/Wellcome Trust
GR - 067427/Z/02/Z/Wellcome Trust

A list of the possible values for the grant Acronym and Agency is available from: http://www.nlm.nih.gov/bsd/grant_acronym.html. Please be advised that while NLM enters the grant number, acronym and agency values are derived by using a machine algorithm against the grant number string. This may result in some inaccurate derivations, but the overall benefit of supplying the separate acronym and agency was considered to be worth the risk of some inaccuracies.

Through 1999, NLM entered up to three grant numbers for each record. Beginning in 2000, NLM began to transition to an unlimited number of grant numbers or contract numbers. Some MEDLINE citations from 2000 and 2001 may still be limited to three grant numbers or contract numbers, but beginning in 2002, NLM does not limit the number of grant numbers or contract numbers. Some collaborating partners record grant numbers for agencies outside the U.S. Public Health Service in the General Notes field.

*In July 2006, NLM corrected a large number of NIH grant number prefixes which were entered with the letter O (e.g., RO1) rather than the number 0 (e.g., R01). This practice deviates with NLM's general policy that the data in the online citation match what is in the published article.

Table of Contents

## Investigator Name (IR) and Full Investigator Name (FIR)

These fields reside on MEDLINE citations created or maintained by one of our collaborating data producers, the National Aeronautics and Space Administration (NASA). They identify the NASA-funded principal investigator(s) who conducted the research discussed in the article cited (but are not necessarily the authors). These fields are associated with the Investigator Affiliation field. See Author field for details on format.

**Examples:**

IR - Arrhenius G
FIR - Arrhenius, G

IR - Brody BA
FIR - Brody BA

Table of Contents

## ISSN (IS)

ISSN (International Standard Serial Number) is an eight-character value that uniquely identifies the cited journal. It is nine characters long in the hyphenated form: XXXX-XXXX. The ISSN field has a qualifier that follows the ISSN data which will state whether it is for the print or the electronic version ISSN of the journal. For journals with multiple ISSNs (e.g., those with separate ISSNs for the print and electronic versions), the ISSN in the MEDLINE citation


Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000294

reflects the version used for MeSH indexing.

**Examples:**

IS - 0021-5252 (Print)
IS - 1471-2202 (Electronic)

Some records do not contain an ISSN value.

The complete title of the journal can be found in the Journal Title (JT) field. For more information about journals cited in MEDLINE, see:

a. The NLM Catalog, located at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=nlmcatalog or via LocatorPlus at http://locatorplus.gov
b. The Entrez Journals database, located at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=journals
c. *The List of Serials Indexed for Online Users*, available at http://www.nlm.nih.gov/tsd/serials/lsiou.html, and
d. *The List of Journals Indexed for MEDLINE*, available at http://www.nlm.nih.gov/tsd/serials/lji.html.

See also NLM Unique ID (JID).

Table of Contents

## Issue (IP)

Issue identifies the issue, part or supplement of the journal in which the article was published.

**Examples:**

IP - 11
IP - 7 Pt 1
IP - First Half
IP - 3 Suppl 1

For records from OLDMEDLINE, some records contain Issue but lack Volume; some records contain Volume but lack Issue; and some records contain Volume and Issue data in the Volume element.

Table of Contents

## Title (TI)

The title field contains the entire title of the journal article. The title is always in English; those titles originally published in a non-English language and translated for the title field are enclosed in square brackets. All titles end with a period unless another punctuation mark such as a question mark or bracket is present. Explanatory information about the title itself is enclosed in parentheses, e.g.: (author's trans). Corporate/collective authors may appear at the end of the title field for citations up to about the year 2000. See also Corporate Author (CN) for more information about corporate or collective authors.

Records with (In Process Citation) in the title field are non-English language citations in In-Process status that do not yet have the article title translated into English.

**Examples:**

TI - The Kleine-Levin syndrome as a neuropsychiatric disorder: a case report.
TI - Why is xenon not more widely used for anaesthesia?
TI - [Biological rhythms and human disease]
TI - [In Process Citation]
TI - Prevalence of Helicobacter pylori resistance to antibiotics in Northeast Italy: a multicentre study. GISU. Interdisciplinary Group for the Study of Ulcer.

Table of Contents



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000295

### Journal Title Abbreviation (TA)

This field contains the standard abbreviation for the title of the journal in which an article appeared. See the NLM Fact Sheet "Construction of National Library of Medicine Title Abbreviations" at http://www.nlm.nih.gov/pubs/factsheets/constructitle.html, which discusses the rules currently used by the National Library of Medicine (NLM) to construct title abbreviations for journals cited in MEDLINE.

**Examples:**

TA - JAMA
TA - J Pediatr
TA - J Comp Physiol B
TA - Ann Biol Clin (Paris)

The complete title of the journal can be found in the Journal Title (JT) field. For more information about journals cited in MEDLINE, see:

a. The NLM Catalog, located at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=nlmcatalog or via LocatorPlus at http://locatorplus.gov
b. The PubMed Journals database, located at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=journals
c. *The List of Serials Indexed for Online Users*, available at http://www.nlm.nih.gov/tsd/serials/lsiou.html, and
d. *The List of Journals Indexed for MEDLINE*, available at http://www.nlm.nih.gov/tsd/serials/lji.html.

All MEDLINE/PubMed records must be linked to a parent serial record in NLM's online catalog. In OLDMEDLINE records, the journal title abbreviation may differ from that found on the original citation in the printed index.

Table of Contents

### Journal Title (JT)

This field contains the full journal title, taken from NLM's cataloging data following NLM rules for how to compile a serial name. The NLM journal title abbreviation is in the (TA) element.

Examples are:

**Examples:**

JT - Molecular microbiology
JT - American journal of physiology. Cell physiology

Some characters that are not part of NLM's MEDLINE/PubMed Character Set reside in a relatively small number of full journal titles. These characters will display as the string 'inverted question mark.'

Table of Contents

### Language (LA)

The language in which an article was published is recorded in the Language field. All entries are three letter abbreviations stored in lower case, such as eng, fre, ger, jpn, etc. A record may contain more than one language value. Some records provided by collaborating data producers may contain the value "und" to identify articles whose language is undetermined.

**Examples:**

LA - eng
LA - rus

A table listing all languages found in MEDLINE is available at: http://www.nlm.nih.gov/bsd/language_table.html. A chart showing the number of English language MEDLINE articles in various segments of MEDLINE is available at:


Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000296

http://www.nlm.nih.gov/bsd/medline_lang_distr.html.

Table of Contents

### MeSH Date (MHDA)

The date MeSH terms were added to the citation is recorded in the MeSH Date field. The MeSH date is the same as the Entrez date until MeSH are added.

Format: YYYYMMDD HH:MM

**Example:**

MHDA- 2005/08/03 09:00

Table of Contents

### MeSH Terms (MH)

NLM's controlled vocabulary, Medical Subject Headings (MeSH®), is used to characterize the content of the articles represented by MEDLINE citations.

Of the various MeSH headings assigned to a record, those representing the most significant points are identified with an asterisk (*) in the MeSH display. The remaining descriptors are used to identify concepts that have also been discussed in the item, but that are not the primary topics. In Process and publisher-supplied records lack MeSH terms. See the MeSH Fact Sheet (http://www.nlm.nih.gov/pubs/factsheets/mesh.html) or the MeSH home page (http://www.nlm.nih.gov/mesh/meshhome.html) for additional information about MeSH.

Subheadings (also known as Qualifiers) are often used with MeSH terms to help describe more completely a particular aspect of a subject. Subheadings are displayed after the MH and a slash (/). A major topic asterisk before a subheading indicates when the combination of that subheading with its associated MeSH term is a central concept of the article.

The presentation of MeSH terms is alphabetical. The Subheadings associated with a MeSH term are also in alphabetical order, without regard to the presence of the major topic asterisk (*).

**Example 1:**

MH - Adult
MH - Cardiovascular Diseases/etiology/*mortality
MH - Child Development/*physiology
MH - Embryo and Fetal Development/*physiology
MH - English Abstract
MH - Fetal Growth Retardation/complications/*physiopathology
MH - Human
MH - Infant, Newborn
MH - Nutrition
MH - Risk Factors
MH - Survival Rate

In the above example, the mortality aspect of cardiovascular diseases, the physiology of child development, as well as embryo and fetal development, and the physiopathology aspect of fetal growth retardation are the central concepts of the article. Note that the MeSH term English Abstract (also present in above example) means that a substantive English language abstract is present in the journal or was written by one of NLM's collaborating data producers. The abstract may or may not be present in the MEDLINE citation as the input policy changed over the years. There are many older non-English language citations without abstracts in MEDLINE but with the MeSH term English Abstract; this indicates that an English abstract is present in the journal, even if not a part of the online record.

**Example 2:**

MH - Animal



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000297

MH - Dogs
MH - *Myocardial Contraction
MH - Myocardium/*metabolism
MH - *Oxygen Consumption
MH - Surface Tension

In the above example, myocardial contraction, the metabolism aspect of myocardium, and oxygen consumption are the central concepts of the article.

The original subject headings assigned to OLDMEDLINE records were updated to current MeSH in December, 2005 (with the exception of approximately 8% of OLDMEDLINE records, which will be updated as resources permit). All of the terms assigned to OLDMEDLINE citations are identified as the major topic of the article. The original subject headings have been placed in the Other Term (OT) field.

Table of Contents

## NLM Unique ID (JID)

This field is the alpha-numeric identifier for the cited journal. The element's value is the accession number for the journal's record assigned in the NLM Catalog, available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=NlmCatalog or via LocatorPlus at http://locatorplus.gov/. An NLM Unique ID may appear as seven, eight or nine characters.

Examples:

Citations from the *New England Journal of Medicine* will have the following JID field value:
JID - 0255562

Citations from the *Japanese Journal of Infectious Diseases* will have the following JID field value:
JID - 100893704

Table of Contents

## Number of References (RF)

This element appears on records indexed with Review as a Publication Type. This field contains the number of bibliographic references listed in the review article.

**Example:**

RF - 21

When collaborating data partners recorded the number of references for non-review articles, these data are found in the General Notes field.

Table of Contents

## Other Abstract (OAB)

NLM creates MEDLINE records without an Abstract field when the source journal article does not contain an abstract. In cases where a collaborating data partner provides an abstract, this abstract appears in the Other Abstract field for that record. This field is associated with the Other Copyright Information (OCI) field, which displays beneath (OAB) if present. The abstract included in this field is not written by the authors of the article. The internal tracking number of the source document used by the collaborating partner resides in the Other ID field.

Acronyms used in the OAB field are:
**AAMC** - American Association of Medical Colleges; not currently used
**AIDS** - Special HIV/AIDS publications with abstracts written by someone other than the author
**KIE** - Kennedy Institute of Ethics, Georgetown University
**PIP** - Population Information Program, Johns Hopkins School of Public Health
**NASA** - National Aeronautics and Space Administration

**Example:**



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000298

OAB - NASA: The purpose of this review is to delineate the ubiquitous and pivotal role of Ca2+ in diverse physiological processes. Emphasis will be given to the role of Ca2+ in stimulus-response coupling. In addition to reviewing the present status of research, our intention is to critically evaluate the existing data and describe the newly developing areas of Ca2+ research in plants.

Table of Contents

### Other Copyright Information (OCI)

This field identifies the copyright owner. It appears on some records created by a collaborating data producer if that producer has written the abstract. The information for this field displays beneath the Other Abstract field.

**Example:**

OCI - NASA Edited

Table of Contents

### Other ID (OID)

This field may reside on a record owned by a collaborating partner or on an NLM-owned record to which a collaborating partner added additional information. The data identify: a) the organization responsible for the information on the citation or the document where the information originated, and b) a unique number for that citation or document.

The acronyms used in this field are listed below. Some of the values on this list currently are not in use at this time and some may never be used.

| | |
|---|---|
| **NASA** | National Aeronautics and Space Administration |
| **KIE** | Kennedy Institute of Ethics, Georgetown University |
| **PIP** | Population Information Program, Johns Hopkins School of Public Health; not currently used |
| **POP** | former NLM POPLINE database; not currently used |
| **ARPL** | Annual Review of Population Law; not currently used |
| **CPC** | Carolina Population Center; not currently used |
| **IND** | Population Index; not currently used |
| **CPFH** | Center for Population and Family Health Library/Information Program; not currently used |
| **NRCBL** | National Reference Center for Biomedical Literature (for the KIE Reference Library shelving location) |
| **CLML** | Current List of Medical Literature; reserved for future use |
| **IM** | Index Medicus; reserved for future use (intended for pre-1966 publications) |
| **SGC** | Surgeon General's Catalog; reserved for future use |

For OLDMEDLINE records, this field occurs on records from 1950-1959 and is for internal use at NLM. CLML is currently the value for all OLDMEDLINE citations containing this field. The value IM may be used on a limited basis. Other values that may be defined for future use with OLDMEDLINE records are QCICL and QCIM.

**Examples:**

OID - KIE: 30206
OID - NRCBL: 18.2
OID - CLML: 5834:20412:395

Table of Contents



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000299

### Other Term (OT)

This field contains largely non-MeSH subject terms (also referred to as Keywords) that describe the content of the article. These are assigned by a collaborating data producer who is identified in the Other Term Owner field. This information is present on a small percentage of citations in the database. The Other Term data may be marked with an asterisk (*) to indicate a major concept. Asterisks are for display only.

**Examples:**

OT - Legal Approach
OT - Health Care and Public Health

Other Terms appear in addition to MeSH terms, with the exception of some OLDMEDLINE records which do not yet contain MeSH headings. OLDMEDLINE subject terms were mapped to current MeSH in preparation for NLM's 2006 production year. Both MeSH Headings and Other Terms are on all but approximately 8% of OLDMEDLINE records as of December, 2005. Additional mappings will occur as resources permit.

Table of Contents

### Other Term Owner (OTO)

This field contains an acronym that precedes the Other Term field. It identifies the organization that provided the Other Term data. The Other Term Owner acronyms and their respective organizations are:

| | |
|---|---|
| **KIE** | Kennedy Institute of Ethics, Georgetown University |
| **NASA** | National Aeronautics and Space Administration |
| **PIP** | Population Information Program, Johns Hopkins School of Public Health |
| **NLM** | National Library of Medicine (used for the OLDMEDLINE records) |

Table of Contents

### Owner (OWN)

The acronym for the organization that supplied the citation data is recorded in this field. Each citation has only one Owner and there are eight possible values in this field:

| | |
|---|---|
| **NLM** | National Library of Medicine, Index Section |
| **NASA** | National Aeronautics and Space Administration |
| **PIP** | Population Information Program, Johns Hopkins School of Public health (not a current value; only on older citations) |
| **KIE** | Kennedy Institute of Ethics, Georgetown University |
| **HSR** | National Information Center on Health Services Research and Health Care Technology, National Library of Medicine |
| **HMD** | History of Medicine Division, National Library of Medicine |
| **SIS** | Specialized Information Services Division, National Library of Medicine (not yet used; reserved for possible future use) |
| **NOTNLM** | For licensees' use. Not used by NLM. |

Table of Contents

### Pagination (PG)

Pagination indicates the inclusive pages for the article cited. The pagination can be entirely non-digit data. Redundant digits are omitted. Document numbers for electronic articles are also found here.

**Examples:**

PG - 12-9
PG - 304-10



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000300

PG - 335-6
PG - 1199-201
PG - 24-32, 64
PG - suppl 111-2
PG - 564
PG - E101-6
PG - 44; discussion 44-8
PG - 925; author reply 925-6
PG - e66
PG - XC-CIII

Beginning in December 2002, new rules are followed for pagination for letters to the editor that include text consisting of an author reply. If the reply is written by one or more of the authors of the original article, the words "author reply" are used in the pagination field rather than the word "discussion". "Discussion" continues to be used within pagination for other types of articles, such as an article presented at a meeting that is followed by the text of a separate discussion or verbal exchange by a panel or others attending the meeting. This new rule for pagination that includes "author reply" applies only to citations with Publication Type of Letter.

Table of Contents

### Personal Name as Subject (PS)

Individuals' names appear in this field for citations that contain a biographical note or obituary, or are entirely about the life or work of an individual or individuals. Data is entered in the same format as author names in the Author field. See Author (AU) field for details of format. See also the associated Full Personal Name as Subject (FPS) field description.

**Examples:**

PS - Koop CE
PS - Zerhouni EA

Table of Contents

### Full Personal Name as Subject (FPS)

This field contains the full name of the subject of the article for citations with a date of publication beginning with 2002. It is associated with the Personal Name as Subject (PS) field. See details on format in the Full Author (FAU) field description.

**Examples:**

FPS - Koop, C Everett
FPS - Zerhouni, Elias Adam

Table of Contents

### Place of Publication (PL)

This field indicates the cited journal's country of publication. Valid values are those country names found in the Z category of the Medical Subject Headings (MeSH) that may be displayed from the MeSH Browser at http://www.nlm.nih.gov/cgi/mesh/2007/MB_cgi?term=Geographic+Locations&field=entry#TreeZ01. Values may appear in all upper case or in mixed case. On older records, in cases where the place of publication is unknown, the (PL) value is Unknown.


Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000301

**Examples:**

PL - United States
PL - FRANCE
PL - Nigeria

Place of Publication data are not maintained when names may change over time. These data indicate where the journal is published, not where the research was conducted.

Table of Contents

## Publication History Status (PHST)

This field contains information from the publisher regarding important events in the publishing process. It contains a date, and one of the following values for each date in the publication history:

| | |
|---|---|
| **[received]** | date manuscript received for review |
| **[accepted]** | accepted for publication |
| **[revised]** | article revised by publisher or author |
| **[aheadofprint]** | published electronically, to be followed by the print |

**Examples:**

PHST- 2004/06/01 [received]
PHST- 2004/09/01 [revised]
PHST- 2005/02/15 [accepted]

Table of Contents

## Publication Status (PST)

This field contains the current status of the publication, as submitted by the publisher. Possible values are:

**ppublish** - published in print (default value)
**epublish** - electronically published only, never published in print
**aheadofprint** - electronically published, but followed by print

**Examples:**

PST - aheadofprint
PST - ppublish

The date on which the current status took effect is submitted in the Date of Publication field.

Table of Contents

## Publication Type (PT)

This field describes the type of material that the article represents; it characterizes the nature of the information or the manner in which it is conveyed (e.g., Review, Letter, Retracted Publication, Clinical Trial). Records may contain more than one Publication Type, which are listed in alphabetical order.



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000302

**Examples:**

PT - Review
PT - Multicenter Study

A list of the Publication Types is available from PubMed Help at: http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=helppubmed.table.pubmedhelp.T42. A list with definitions is available at http://www.nlm.nih.gov/mesh/pubtypes2007.html. Publication Types are also available in the MeSH Database at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=mesh.

Table of Contents

## Publishing Model (PUBM)

This field describes the medium/media in which the cited article is published. This information is derived from data submitted by the publishers.

**Examples:**

PUBM - Print
PUBM - Print-Electronic

Table of Contents

## PubMed Unique Identifier (PMID)

This field is a 1- to 8-digit accession number with no leading zeros. It is present on all records and is the accession number for managing and disseminating records. PMIDs are not reused after records are deleted.

**Examples:**

PMID - 10097079
PMID - 6012557

Prior to the 2004 version of PubMed (available December 3, 2003), many records contained a MEDLINE Unique Identifier in addition to the PMID. NLM no longer displays the MEDLINE Unique Identifier. The PMID has become the unique identifier for the MEDLINE record.

Table of Contents

## Registry Number/EC Number (RN)

This field contains the unique 5- to 9-digit number in hyphenated format assigned by the Chemical Abstracts Service (CAS) to specific chemical substances. For enzymes, the EC number derived from Enzyme Nomenclature is placed in this element. A zero (0) is a valid value when an actual number cannot be located or is not yet available.

Following the RN/EC field display is the Substance Name (NM) field value, enclosed in parentheses. Please see Substance Name (NM) field section for an explanation of that field.

**Examples:**

RN - 69-93-2 (Uric Acid)
RN - EC 3.1.1.34 (Lipoprotein Lipase)

Table of Contents

## Substance Name (NM)



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000303

This field contains the name of the substance that the registry number or the EC number identifies. The MeSH Database (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=mesh) or MeSH Browser (http://www.nlm.nih.gov/mesh/MBrowser.html) contain the Substance Names. These records are of two types: 1) Supplementary Concept Records, which can be found in the MeSH Browser with a record type of C, or 2) MeSH Category D descriptors, identified in the MeSH Browser with a tree number that begins with D. The Substance Name follows the RN/EC field display, enclosed within parentheses.

**Examples:**

RN - 69-93-2 (Uric Acid)
RN - 6964-20-1 (tiadenol)

Table of Contents

## Secondary Source ID (SI)

The SI field identifies secondary source databanks and accession numbers of molecular sequences discussed in MEDLINE articles. The field is composed of the source followed by a slash followed by an accession number.

**Examples:**

SI - GENBANK/AF306859
SI - SWISSPROT/P13209
SI - ClinicalTrials.gov/NCT00000419
SI - GEO/GDS275

NLM cooperates with international efforts to collect molecular sequence data. There are, at present, six databanks that register molecular sequences deposited with them by researchers. In the journal literature, a reference to the databank and the accession number assigned to the sequence may accompany, or substitute for, a lengthy graphic representation of the sequence itself. NLM enters this data in the SI field if this information appears in the printed journal article. If the article lists a databank but no accession number, only the abbreviation for the databank will be entered. There is no attempt to edit or verify the databank accession numbers that appear in the journal. Since sequences may be deposited with more than one databank, there may be multiple occurrences of this field in a single citation. This information may appear on the article title page, in a footnote or in a statement such as:

> Sequence data from this article have been deposited with the EMBL, GenBank and DDBJ Data Libraries under Accession No. M16978.

The six databanks registering molecular sequence data at the present time are:

| MEDLINE Abbreviation | Databank |
|---|---|
| **GDB** | Johns Hopkins University Genome Data Bank |
| **GENBANK** | GenBank Nucleic Acid Sequence Database |
| **OMIM** | Mendelian Inheritance in Man (McKusick) |
| **PDB** | Protein Data Bank |
| **PIR** | Protein Identification Resource |
| **RefSeq** | Reference Sequence |
| **SWISSPROT** | Protein Sequence Database |

NLM first began to include this information with the 1988 indexing year. Prior to 2000, NLM's policy was to enter up to 30 databank accession numbers for each record. Some global maintenance was done over the years to add databank names/accession numbers whether or not the article itself contained those references. From 2000 forward, NLM enters all databank accession numbers published in the journal. Data in this field are sorted first by databank name and then by the accession number.

The SI field and the Entrez sequence database links are not related. The PubMed links to these databases are created from the reference field of the GenBank or GenPept flatfile. These references include citations that discuss the specific sequence presented in these flatfiles.



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000304

Beginning in the Summer of 2005, NLM includes the ClinicalTrials.gov identifier number in the SI field when that information appears in the original publication as recommended by the International Committee of Medical Journal Editors (ICMJE). The ICMJE Web site (http://www.icmje.org/) contains an editorial and updates on the topic of registering clinical trials before publication of the results. NLM will include all ClinicalTrials.gov identifier numbers in the SI field if present in the published article.

Beginning mid-2006, MEDLINE citations also carry the International Standard Randomised Controlled Trial Number (ISRCTN) when that information appears in the original publication. The ISRCTN Register (http://isrctn.org/) is a clinical trials deposit site based in the UK that meets the criteria set forth by the ICMJE (International Committee of Medical Journal Editors) for responsible disclosure of information to the public. The letters ISRCTN are a part of the trial number.

Beginning in February 2006, accession numbers for data deposited in NLM's Gene Expression Omnibus (GEO) database are included in SI field. GEO is a gene expression/molecular abundance repository supporting data submissions, and a curated, online resource for gene expression data browsing, query and retrieval.

The databank abbreviation is GEO and the accession number is any one of four prefixes followed by a numeric string:

GDSxxxx (GEO Data Set)
GSExxxx (GEO SEries)
GPLxxxx (GEO PLatform)
GSMxxxx (GEO SaMple)

Beginning in September 2006, accession numbers for sequences in NLM's Reference Sequence (RefSeq) database are included in the SI field. RefSeq is a curated, non-redundant set of sequences, including genomic DNA, transcript RNA and protein products.

Table of Contents

## Source (SO)

NLM concatenates the following elements to create the journal source:

Journal Title Abbreviation (TA)
Publication Date (DP)
Volume (VI)
Issue (IP)
Pagination (PG)

Elements of other date fields may be added to indicate an additional Epub or Print publication date.

**Examples:**

SO - Am J Med. 2005 May;118(5):567.
SO - Hepatology. 2004 Apr;39(4):915-23.
SO - Health Care Finance Rev. 2003 Winter;25(2):77-90.
SO - Eur Spine J. 2005 Nov;14(9):887-94. Epub 2005 Sep 8.

Table of Contents

## Space Flight Mission (SFM)

This field resides on citations created by one of our collaborating data producers, the National Aeronautics and Space Administration (NASA). It is the space flight/mission name and/or number when results of research conducted in space are covered in the cited publication. View a complete list of Space Flight Missions and their associated values (manned/unmanned; short/long duration) at http://www.nlm.nih.gov/bsd/space_flight.html.

**Examples:**

SFM - Flight Experiment
SFM - Mir Project
SFM - long duration
SFM - manned



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000305

Table of Contents

### Status (STAT)

The status field indicates the status of the record. There are seven possible values for this field:

- **In-Data-Review:** Records in this status have been submitted to NLM electronically by the publisher, and the journal title, date of publication and volume/issue (source data) have been checked. The source data have either been:
    1. matched to the print copy in NLM's collection and are correct;
    2. matched to the online version of the journal (when NLM assigns MeSH headings from the online version) and are correct; or
    3. compared to previously checked-in issues and appear to match the pattern or have been changed to match the established pattern. In these cases, the physical item has not yet been received for NLM's collection and the data have not been positively verified and may still change during NLM's processing cycle.

  While all three reviews are at the issue level, most citations fit into the last condition above. It is possible that the source information may be changed at a later point in the NLM quality assurance cycle once the hard copy issue is available for exact comparison.

  In-Data-Review records lack a Date Completed field. They are not yet MEDLINE records because they have not undergone complete quality review and MeSH indexing. The issue level review for In-Data-Review status is the first step in quality control. The records will typically either be reissued as In-process status records or go to PubMed-not-MEDLINE final record status.

- **In-Process:** Records in this status have undergone a citation level review; i.e., the author names, article title, and pagination are checked.

  In-process records do not have a Date Completed field, however, they do contain the Subset field. In-process records are not yet MEDLINE records because they have not undergone complete quality review and MeSH indexing.

  Most in-process records are eventually indexed with MeSH terms and are elevated to completed MEDLINE status. However, some are determined to be out of scope (e.g., articles on plate tectonics or astrophysics from certain MEDLINE journals, primarily general science and chemistry journals, for which the life sciences articles are indexed for MEDLINE) and are not elevated to MEDLINE status; instead they become PubMed-not-Medline final status records. In rare cases the records are deleted and do not become PubMed-not-MEDLINE records.

- **MEDLINE:** In-process records undergo rigorous quality assurance routines before they are elevated to MEDLINE status or to PubMed-not-MEDLINE status.

  Records in MEDLINE status are the only 'true' MEDLINE records in PubMed. They contain Date Completed and Subset fields and, in most cases, contain MeSH terms. MEDLINE records that are Retractions of Publications (see Publication Type element) are exceptions and do not contain MeSH terms.

- **OLDMEDLINE:** Citations from the OLDMEDLINE subset begin in OLDMEDLINE status. Once *all* of the original subject terms from the printed index have been mapped to current MeSH, the citation status is changed to MEDLINE. See more information about OLDMEDLINE.

- **PubMed-not-MEDLINE:** Records in this status are from journals included in MEDLINE and have undergone quality review but are not assigned MeSH headings because the cited item is not in scope for MEDLINE either by topic or by date of publication, or is from a non-MEDLINE journal. The categories of non-MEDLINE records in this status are:
    1. citations to articles that precede the date a journal was selected for MEDLINE indexing and are submitted for inclusion in PubMed after July 2003;
    2. out of scope citations to articles in journals covered by MEDLINE;
    3. analytical summaries of articles published elsewhere (see the article, "Linking MEDLINE Citations to Evidence-Based Medicine Assessments and Summaries", in the May-Jun 2002 *NLM Technical Bulletin*, page e2); and
    4. (starting in the Summer of 2005) prospective citations to articles from non-MEDLINE journals that submit full text to PubMed Central®, and are thus cited in PubMed.

  PubMed-not-MEDLINE records contain a Date Completed field and lack Subset and MeSH term fields.

- **Publisher:** The non-MEDLINE records in Publisher Status in PubMed contain the notation [PubMed - as supplied by publisher] in the PubMed display. At this time the records in Publisher Status are:



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000306

1. the retrospective records (prior to July 2005) for the relatively few non-MEDLINE journals in PubMed;
2. the retrospective records for MEDLINE journals prior to date of selection for MEDLINE and that were submitted electronically by the publishers before late July 2003;
3. the prospective records for currently indexed journals when the publisher has submitted an issue's citation data electronically and NLM still awaits its print copy or access to the electronic copy to use for issue level review (i.e., the journal title, date of publication and volume/issue elements) AND the publisher-supplied record contains a validation error of some kind that prevents it from being exported from NLM's Data Creation and Maintenance System (DCMS) along with the records not containing errors from the same issue. If there were no errors, the record would move to In-Data-Review status right away and be exported. In these cases, however, NLM staff must take corrective action before the record can be elevated to In-Data-Review status for export; and
4. citations electronically submitted for articles that appear on the Web in advance of the journal issue's release (i.e., ahead of print citations). Following publication of the completed issue, the item will be queued for issue level review and released in In-Data-Review status.

Table of Contents

## Subset (SB)

This field identifies the subset for MEDLINE records from certain journal lists or records on specialized topics. Some of these values are found on extremely small numbers of records. Citations may contain more than one occurrence of this field. The value is true at the time the record was created. If the status of a journal changes, the value on the record does not change.

Subset field values and their definitions are as follows. Note that several are closed subsets no longer being assigned.

| | |
|---|---|
| **AIM** | citations from *Abridged Index Medicus* journals, a list of about 120 core clinical, English language journals. |
| **B** | citations from non-*Index Medicus* journals in the field of biotechnology (not currently used). |
| **C** | citations from non-*Index Medicus* journals in the field of communication disorders (not currently used). |
| **D** | citations from dental journals. See the current List of Journals Indexed for MEDLINE (LJI) under *Dentistry* and *Orthodontics*. |
| **E** | citations in the field of bioethics. (includes records from the former BIOETHICSLINE database) |
| **F** | older citations from one journal prior to its selection for *Index Medicus*. Used to augment the database for NLM's International MEDLARS Centers (not currently used). |
| **H** | citations from non-*Index Medicus* journals in the field of health administration. (includes records from the former HealthSTAR database) |
| **IM** | citations from *Index Medicus* journals. |
| **J** | citations in the field of population information. (not currently used; on records from the former POPLINE® database) |
| **K** | citations from non-*Index Medicus* journals relating to consumer health. |
| **N** | citations from nursing journals. See the current List of Journals Indexed for MEDLINE (LJI) under *Nursing*. |
| **OM** | citations from the OLDMEDLINE project that originated from the *Cumulated Index Medicus* and the *Current List of Medical Literature* (in 2007 this includes citations from the 1950-1965 print indexes). The ways they differ from other MEDLINE records are documented under the applicable element descriptions. The original MeSH Headings assigned at the time the citation was created in print reside in the Other Term field. Records in the OLDMEDLINE subset have a status of OLDMEDLINE until *all* of their original subject terms are mapped to current MeSH; then their status changes to MEDLINE. NLM makes available both new and revised OLDMEDLINE records on an irregular and infrequent basis. |
| **Q** | citations in the field of the history of medicine. (includes records from the former HISTLINE® database) |



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000307

| | |
|---|---|
| **QIS** | citations from non-*Index Medicus* journals in the field of the history of medicine. (For NLM use effective in late 2006 because they require special handling at NLM; not a subset of Q; some journals previously designated as Q are now QIS.) |
| **QO** | is subset of Q - indicates older history of medicine journal citations that were created before the former HISTLINE file was converted to a MEDLINE-like format. (For NLM use because they require special handling at NLM). |
| **R** | citations from non-*Index Medicus* journals in the field of population and reproduction (not currently used). |
| **S** | citations in the field of space life sciences. (includes records from the former SPACELINE™ database) |
| **T** | citations from non-*Index Medicus* journals in the field of health technology assessment. (includes records from the former HealthSTAR database) |
| **X** | citations in the field of AIDS/HIV. (includes records from the former AIDSLINE® database) |

**Examples:**

SB - AIM
SB - IM
SB - X

Do not confuse these journal/citation subsets with the Topics subsets available on PubMed's Limits screen, which are search strategies.

Table of Contents

### Transliterated Title (TT)

This field contains the title of each item originally published in a non-English language, in that language. Transliterations of article titles in some Cyrillic languages (Greek, Bulgarian, Russian, Serbian and Ukrainian) were added to this field through 2004.

**Examples:**

TT - Temoignages et lettres.
TT - Wplyw przebiegu rozwoju plodu i noworodka na ujawnienie sie niektórych chorób okresu doroslego.

For OLDMEDLINE records, the TT field for citations from the 1964 and 1965 *Cumulated Index Medicus* (CIM) is in all uppercase letters. Some OLDMEDLINE citations to articles originally published in a non-English language lack the TT field.

Table of Contents

### Volume (VI)

The volume number of the journal in which the article was published is recorded here.

**Examples:**

VI - 7
VI - 5 Spec No
VI - 49 Suppl 20

Some records (especially records from OLDMEDLINE) contain the Issue field but lack the Volume field; some contain



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000308

the Volume field but lack the Issue field; and some records contain Volume and Issue data in the Volume element.

Table of Contents

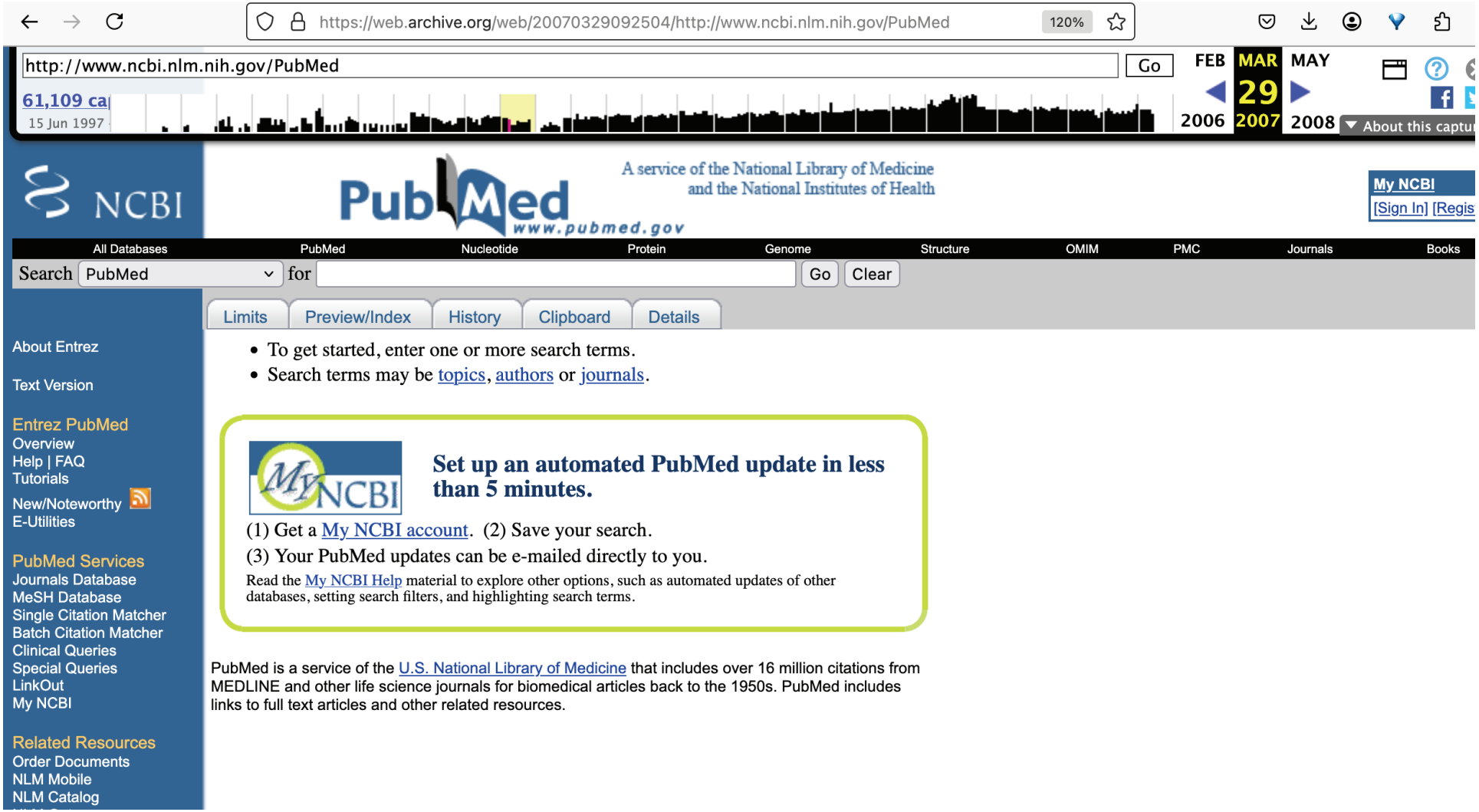
**Last reviewed:** 12 December 2006
**Last updated:** 19 April 2007
**First published:** 17 May 2005
**Metadata**| **Permanence level:** Permanent: Dynamic Content

Copyright, Privacy, Accessibility
U.S. National Library of Medicine, 8600 Rockville Pike, Bethesda, MD 20894
National Institutes of Health, Health & Human Services



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000309

**EX-1035F** PubMed website archived by Internet Archive on March 29, 2007, available at https://web.archive.org/web/20070329092504/http://www.ncbi.nlm.nih.gov/PubMed.




Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000311

**EX-1035G** *Clinical Chemistry* vol. 52, no. 11 Table of Contents, archived by Internet Archive on January 28, 2007, available at https://web.archive.org/web/20070128193542/http://www.clinchem.org/content/vol52/issue11/;

PDF download page for *Nalefski*, archived by Internet Archive on April 26, 2007, available at https://web.archive.org/web/20070426113525/http://www.clinchem.org/cgi/reprint/52/11/2172;

Full text of *Nalefski* in HTML, archived by Internet Archive on May 11, 2008, available at https://web.archive.org/web/20080511153458/http://www.clinchem.org/cgi/content/full/52/11/2172; and

Full text of *Nalefski* in PDF, archived by Internet Archive on May 11, 2008, available at https://web.archive.org/web/20080511152327/http://www.clinchem.org/cgi/reprint/52/11/2172 and select "Begin manual download" to view the PDF version at

https://web.archive.org/web/20080513140918/http://www.clinchem.org/cgi/reprint/52/11/2172.pdf.

web.archive.org/web/20070128193542/http://www.clinchem.org/content/vol52/issue11/

http://www.clinchem.org/content/vol52/issue11/ Go

27 captures
28 Jan 2007 - 21 Jul 2022

DEC JAN MAR
2006 28 2007 2008
About this capture

# Clinical Chemistry

Link to Randox Laboratories W



**Receive this page by email each issue:** [Sign up for eTOCs]




**Other Issues:**

## Contents: November 1 2006, Volume 52, Issue 11 [Index by Author]

- Editorials
- Molecular Diagnostics and Genetics
- Evidence-Based Laboratory Medicine and Test Utilization
- Lipids, Lipoproteins, and Cardiovascular Risk Factors
- Endocrinology and Metabolism
- Automation and Analytical Techniques
- Laboratory Management
- General Clinical Chemistry
- Pediatric Clinical Chemistry
- Technical Briefs
- Case Reports
- Letters to the Editor
- Oak Ridge Conference
- Abstracts of Oak Ridge Posters

**Find articles in this issue containing these words:**
Enter [Search ALL Issues]

Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000313

The Wayback Machine - https://web.archive.org/web/20070128193542/http://www.clinchem.org:80/content/v…



**Receive this page by email each issue:** [Sign up for eTOCs]




**Other Issues:**

# Contents: November 1 2006, Volume 52, Issue 11 [Index by Author]

- Editorials
- Molecular Diagnostics and Genetics
- Evidence-Based Laboratory Medicine and Test Utilization
- Lipids, Lipoproteins, and Cardiovascular Risk Factors
- Endocrinology and Metabolism
- Automation and Analytical Techniques
- Laboratory Management
- General Clinical Chemistry
- Pediatric Clinical Chemistry
- Technical Briefs
- Case Reports
- Letters to the Editor
- Oak Ridge Conference
- Abstracts of Oak Ridge Posters

**Find articles in this issue containing these words:**
Enter [Search ALL Issues]

Table of Contents (PDF) |
**To see an article**, click its [Full Text] link. **To review many abstracts**, check the boxes to the left of the titles you want, and click the 'Get All Checked Abstract(s)' button. **To see one abstract at a time**, click its [Abstract] link.

Clear Get All Checked Abstract(s)

## Editorials:

Udo Reischl

**Melting of the Ribosomal RNA Gene Reveals Bacterial Species Identity: A Step toward a New Rapid Test in Clinical Microbiology**
Clin Chem 2006 52: 1985-1987. [Extract] [Full Text] [PDF]

## Molecular Diagnostics and Genetics:

☐ Jakob Stenman, Annukka Paju, Oso Rissanen, Tuomas Tenkanen, Caj Haglund, Jari Räsänen, Jarmo Salo, Ulf-Håkan Stenman, and Arto Orpana

**Targeted Gene-Expression Analysis by Genome-Controlled Reverse Transcription-PCR**
Clin Chem 2006 52: 1988-1996. Published online September 21, 2006; 10.1373/clinchem.2006.073064
[Abstract] [Full Text] [PDF] 073064.Supplemental Data Table 1

☐ Ju-Chien Cheng, Chien-Ling Huang, Chung-Ching Lin, Chi-Ching Chen, Yi-Chih Chang, Shy-Shin Chang, and Ching-Ping Tseng



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000314

**Rapid Detection and Identification of Clinically Important Bacteria by High-Resolution Melting Analysis after Broad-Range Ribosomal RNA Real-Time PCR**
Clin Chem 2006 52: 1997-2004. Published online September 21, 2006; 10.1373/clinchem.2006.069286
[Abstract] [Full Text] [PDF] 069286.Supplemental Data

☐ Mircea Schneider, Franziska Joncourt, Javier Sanz, Thomas von Känel, and Sabina Gallati
**Detection of Exon Deletions within an Entire Gene (*CFTR*) by Relative Quantification on the LightCycler**
Clin Chem 2006 52: 2005-2012. Published online September 21, 2006; 10.1373/clinchem.2005.065136
[Abstract] [Full Text] [PDF] 065136.Supplemental Data

☐ Gyula Richárd Nagy, Balázs Gyõrffy, Orsolya Galamb, Béla Molnár, Bálint Nagy, and Zoltán Papp
**Use of Routinely Collected Amniotic Fluid for Whole-Genome Expression Analysis of Polygenic Disorders**
Clin Chem 2006 52: 2013-2020. Published online September 28, 2006; 10.1373/clinchem.2006.074971
[Abstract] [Full Text] [PDF] 074971.Supplemental Data

☐ Hillary H. Hegener, I-Min Lee, Nancy R. Cook, Paul M. Ridker, and Robert Y.L. Zee
**Association of Adiponectin Gene Variations with Risk of Incident Myocardial Infarction and Ischemic Stroke: A Nested Case-Control Study**
Clin Chem 2006 52: 2021-2027. Published online September 21, 2006; 10.1373/clinchem.2006.074476
[Abstract] [Full Text] [PDF] 074476.Supplemental Data

## Evidence-Based Laboratory Medicine and Test Utilization:

☐ Peter A. Kavsak, Andrew R. MacRae, Glenn E. Palomaki, Alice M. Newman, Dennis T. Ko, Viliam Lustig, Jack V. Tu, and Allan S. Jaffe
**Health Outcomes Categorized by Current and Previous Definitions of Acute Myocardial Infarction in an Unselected Cohort of Troponin-Naïve Emergency Department Patients**
Clin Chem 2006 52: 2028-2035. Published online September 21, 2006; 10.1373/clinchem.2006.073403
[Abstract] [Full Text] [PDF]

## Lipids, Lipoproteins, and Cardiovascular Risk Factors:

☐ Shiming Zhu, Guohai Su, and Qing H. Meng
**Inhibitory Effects of Micronized Fenofibrate on Carotid Atherosclerosis in Patients with Essential Hypertension**
Clin Chem 2006 52: 2036-2042. Published online September 21, 2006; 10.1373/clinchem.2006.074724
[Abstract] [Full Text] [PDF]

☐ Gabriella Pepe, Guglielmina Chimienti, Grazia Maria Liuzzi, Biagia Leila Lamanuzzi, Marina Nardulli, Francesco Lolli, Eduardo Anglés-Cano, and Sabrina Matà
**Lipoprotein(a) in the Cerebrospinal Fluid of Neurological Patients with Blood–Cerebrospinal Fluid Barrier Dysfunction**
Clin Chem 2006 52: 2043-2048. Published online September 21, 2006; 10.1373/clinchem.2006.073544
[Abstract] [Full Text] [PDF]

☐ Mitsuyo Okazaki, Shinichi Usui, Akio Fukui, Isao Kubota, and Hitonobu Tomoike
**Component Analysis of HPLC Profiles of Unique Lipoprotein Subclass Cholesterols for Detection of Coronary Artery Disease**
Clin Chem 2006 52: 2049-2053. Published online September 21, 2006; 10.1373/clinchem.2006.070094
[Abstract] [Full Text] [PDF] 070094.Supplemental Data



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000315

☐ Angelo Zinellu, Elisabetta Zinellu, Salvatore Sotgia, Marilena Formato, Gian Mario Cherchi, Luca Deiana, and Ciriaco Carru
**Factors Affecting *S*-Homocysteinylation of LDL Apoprotein B**
Clin Chem 2006 52: 2054-2059. Published online September 21, 2006; 10.1373/clinchem.2006.071142
[Abstract] [Full Text] [PDF]

## Endocrinology and Metabolism:

☐ Keith L. Brain, Jonathan Kay, and Brian Shine
**Measurement of Urinary Metanephrines to Screen for Pheochromocytoma in an Unselected Hospital Referral Population**
Clin Chem 2006 52: 2060-2064. Published online September 21, 2006; 10.1373/clinchem.2006.070805
[Abstract] [Full Text] [PDF]

## Automation and Analytical Techniques:

☐ Hua Wang, Yun Zhang, Bani Yan, Li Liu, Shiping Wang, Guoli Shen, and Ruqin Yu
**Rapid, Simple, and Sensitive Immunoagglutination Assay with $SiO_2$ Particles and Quartz Crystal Microbalance for Quantifying *Schistosoma japonicum* Antibodies**
Clin Chem 2006 52: 2065-2071. Published online September 21, 2006; 10.1373/clinchem.2006.071555
[Abstract] [Full Text] [PDF] 071555.Supplemental Data

## Laboratory Management:

☐ Alexandra Dorn-Beineke, Parviz Ahmad-Nejad, Ulrike Pfeiffer, Simon Ramsden, Mario Pazzagli, and Michael Neumaier
**Improvement of Technical and Analytical Performance in DNA Sequencing by External Quality Assessment-Based Molecular Training**
Clin Chem 2006 52: 2072-2078. Published online September 21, 2006; 10.1373/clinchem.2006.072405
[Abstract] [Full Text] [PDF]

## General Clinical Chemistry:

☐ Annette Zoeger, Michael Blau, Karl Egerer, Eugen Feist, and Burkhardt Dahlmann
**Circulating Proteasomes Are Functional and Have a Subtype Pattern Distinct from 20S Proteasomes in Major Blood Cells**
Clin Chem 2006 52: 2079-2086. Published online September 21, 2006; 10.1373/clinchem.2006.072496
[Abstract] [Full Text] [PDF]

☐ Peter A. Benn, Gregory S. Makowski, James F.X. Egan, and Dave Wright
**Reproducibility of Risk Figures in 2nd-Trimester Maternal Serum Screening for Down Syndrome: Comparison of 2 Laboratories**
Clin Chem 2006 52: 2087-2094. Published online September 21, 2006; 10.1373/clinchem.2006.068783
[Abstract] [Full Text] [PDF]

## Pediatric Clinical Chemistry:

☐ Maria Weyermann, Christopher Beermann, Hermann Brenner, and Dietrich Rothenbacher



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000316

**Adiponectin and Leptin in Maternal Serum, Cord Blood, and Breast Milk**
Clin Chem 2006 52: 2095-2102. Published online September 21, 2006; 10.1373/clinchem.2006.071019
[Abstract] [Full Text] [PDF]

## Technical Briefs:

☐ Ali Bouamrani, Jessica Ternier, David Ratel, Alim-Louis Benabid, Jean-Paul Issartel, Elisabeth Brambilla, and François Berger

**Direct-Tissue SELDI-TOF Mass Spectrometry Analysis: A New Application for Clinical Proteomics**
Clin Chem 2006 52: 2103-2106. Published online September 21, 2006; 10.1373/clinchem.2006.070979
[Abstract] [Full Text] [PDF] 070979.Supplemental Data

## Case Reports:

☐ Raffick A.R. Bowen, Steven K. Drake, Rachna Vanjani, Edward D. Huey, Jordan Grafman, and McDonald K. Horne, III

**Markedly Increased Vitamin $B_{12}$ Concentrations Attributable to IgG–IgM–Vitamin $B_{12}$ Immune Complexes**
Clin Chem 2006 52: 2107-2114. [Abstract] [Full Text] [PDF]

## Letters to the Editor:

Radomir Pilny, Pavel Bouchal, Sarka Borilova, Pavla Ceskova, Jan Zaloudik, Rostislav Vyzula, Borivoj Vojtesek, and Dalibor Valik

**Surface-Enhanced Laser Desorption Ionization/Time-of-Flight Mass Spectrometry Reveals Significant Artifacts in Serum Obtained from Clot Activator–Containing Collection Devices**
Clin Chem 2006 52: 2115-2116. [Extract] [Full Text] [PDF]

Chao Lin and James K. Tusa

**Equimolar Ammonia Interference in Potassium Measurement on the Osmetech OPTI CCA: A Reply**
Clin Chem 2006 52: 2116-2117. [Extract] [Full Text] [PDF]

Dai Xinhua

**Preparation of Uric Acid Standard Stock Solution**
Clin Chem 2006 52: 2117-2118. [Extract] [Full Text] [PDF]

Deirdré Hartman, Timothy W. Doulton, Christine A. Chesters, Giuseppe A. Sagnella, and Graham A. MacGregor

**Plasma Aldosterone: Comparison of a New Automated Assay with a Standard Extraction Method**
Clin Chem 2006 52: 2118-2119. [Extract] [Full Text] [PDF]

Joshua A. Bornhorst, Roxann Cousin, Auono T. Pili, J. Alan Erickson, and Edward R. Ashwood

**Evaluation of the Efficacy of Chloroform Extraction of Amniotic Fluid Bilirubin**
Clin Chem 2006 52: 2120-2121. [Extract] [Full Text] [PDF]

Jan S. Krouwer

**More on Reporting Medical Errors**
Clin Chem 2006 52: 2120. [Extract] [Full Text] [PDF]

Kiyonori Miura, Koh-ichiro Yoshiura, Shoko Miura, Kentaro Yamasaki, Daisuke Nakayama, Tadayuki Ishimaru, Joseph Wagstaff, Norio Niikawa, and Hideaki Masuzaki

**Cell-Free DNA Is More Sensitive than Cell-Free mRNA as a Marker for Evaluation of Fetal-Maternal Hemorrhage**



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000317

Clin Chem 2006 52: 2121-2123. [Extract] [Full Text] [PDF]

Maciej Adamczyk, R. Jeffrey Brashear, and Phillip G. Mattingly
**Choline Concentration in Normal Blood Donor and Cardiac Troponin–Positive Plasma Samples**
Clin Chem 2006 52: 2123-2124. [Extract] [Full Text] [PDF]

Neil Binkley, Marc K. Drezner, and Bruce W. Hollis
**Laboratory Reporting of 25-Hydroxyvitamin D Results: Potential for Clinical Misinterpretation**
Clin Chem 2006 52: 2124-2125. [Extract] [Full Text] [PDF]

Carine Garcia-Hejl, Philippe Vest, Christophe Renard, Audrey Merens-Gonthier, Abderrahaman Boukhira, and Helene Thefenne-Astier
**Falsely Low LDL Cholesterol Results and Cholestasis**
Clin Chem 2006 52: 2125-2127. [Extract] [Full Text] [PDF]

Nathalie Hézard, Marie-Geneviève Remy, Bernadette Florent, and Philippe Nguyen
**Reliability of Thrombin Generation Assay on Frozen-Thawed Platelet-Rich Plasma: A Reply**
Clin Chem 2006 52: 2127-2128. [Extract] [Full Text] [PDF]

## Oak Ridge Conference:

Steven C. Kazmierczak, Andrey Gurachevsky, Gert Matthes, and Vladimir Muravsky
**Electron Spin Resonance Spectroscopy of Serum Albumin: A Novel New Test for Cancer Diagnosis and Monitoring**
Clin Chem 2006 52: 2129-2134. Published online September 21, 2006; 10.1373/clinchem.2006.073148
[Abstract] [Full Text] [PDF]

Ming Zhao, David Nolte, Wonryeon Cho, Fred Regnier, Manoj Varma, Greg Lawrence, and John Pasqua
**High-Speed Interferometric Detection of Label-Free Immunoassays on the Biological Compact Disc**
Clin Chem 2006 52: 2135-2140. Published online September 21, 2006; 10.1373/clinchem.2006.072793
[Abstract] [Full Text] [PDF]

Owen T.M. Chan and David A. Herold
**Chip Electrophoresis as a Method for Quantifying Total Microalbuminuria**
Clin Chem 2006 52: 2141-2146. Published online September 21, 2006; 10.1373/clinchem.2006.072801
[Abstract] [Full Text] [PDF]

## Abstracts of Oak Ridge Posters:

Lawrence A. Haff, Christopher G.M. Wilson, Yumei Huang, Benjamin K. Benton, Julian F Bond, Andrew M. Stern, Richard F. Begley, and James M. Coull
**DNA-Programmed Chemistry in Rapid Homogeneous Assays for DNA and Protein Targets**
Clin Chem 2006 52: 2147-2148. [Extract] [Full Text] [PDF]

Ling Huang and Matthew A. Cooper
**Real-Time Label-Free Acoustic Technology for Rapid Detection of *Escherichia coli* O157:H7**
Clin Chem 2006 52: 2148-2151. [Extract] [Full Text] [PDF]

Maria Magliulo, Barbara Roda, Andrea Zattoni, Elisa Michelini, Mirella Luciani, Rossella Lelli, Pierluigi Reschiglian, and Aldo Roda
**An Innovative, Flow-Assisted, Noncompetitive Chemiluminescent Immunoassay for the Detection of Pathogenic Bacteria,**
Clin Chem 2006 52: 2151-2155. [Extract] [Full Text] [PDF]



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000318

N. Babic, T.S. Larson, S.K. Grebe, S.T. Turner, R. Kumar, and R.J. Singh
**Application of Liquid Chromatography–Mass Spectrometry Technology for Early Detection of Microalbuminuria in Patients with Kidney Disease**
Clin Chem 2006 52: 2155-2157. [Extract] [Full Text] [PDF]

Alan H.B. Wu, Noelle Fukushima, Robert Puskas, John Todd, and Philippe Goix
**Development and Preliminary Clinical Validation of a High Sensitivity Assay for Cardiac Troponin Using a Capillary Flow (Single Molecule) Fluorescence Detector**
Clin Chem 2006 52: 2157-2159. [Extract] [Full Text] [PDF]

Judith A. Finlay, Eric W. Klee, Cari McDonald, John R. Attewell, Deanne Hebrink, Roy Dyer, Brad Love, George Vasmatzis, Thomas M. Li, Joseph M. Beechem, and George G. Klee
**A Systematic Method for Selection of Promising Serum Protein Biomarkers to Improve Prostate Cancer (PCa[1]) Detection**
Clin Chem 2006 52: 2159-2162. [Extract] [Full Text] [PDF]

Eric W. Klee, Judith A. Finlay, Cari McDonald, John R. Attewell, Deanne Hebrink, Roy Dyer, Brad Love, George Vasmatzis, Thomas M. Li, Joseph M. Beechem, and George G. Klee
**Bioinformatics Methods for Prioritizing Serum Biomarker Candidates**
Clin Chem 2006 52: 2162-2164. [Extract] [Full Text] [PDF]

Gregory D. Sgarlato and Howard H. Sussman
**Representational Fragment Amplification: Exponential Amplification of Fragmented cDNA Enables Multimillion-Fold Expression Testing**
Clin Chem 2006 52: 2164-2168. [Extract] [Full Text] [PDF]

Vitali Borisenko, Wei Hu, Pui Tam, Irene Chen, Jean-François Houle, and Walter Ausserer
**Diffractive Optics Technology: A Novel Detection Technology for Immunoassays**
Clin Chem 2006 52: 2168-2170. [Extract] [Full Text] [PDF]

Roger B. Peck, Johannes Schweizer, Bernhard H. Weigl, Chamorro Somoza, Jon Silver, John W. Sellors, and Peter S. Lu
**A Magnetic Immunochromatographic Strip Test for Detection of Human Papillomavirus 16 E6**
Clin Chem 2006 52: 2170-2172. [Extract] [Full Text] [PDF]

Eric A. Nalefski, Christina M. D'Antoni, Evan P. Ferrell, Janice A. Lloyd, Haoqun Qiu, John L. Harris, and Duncan H. Whitney
**Single-Molecule Detection for Femtomolar Quantification of Proteins in Heterogeneous Immunoassays**
Clin Chem 2006 52: 2172-2175. [Extract] [Full Text] [PDF]

Clear Get All Checked Abstract(s)

**To see an article**, click its [Full Text] link. **To review many abstracts**, check the boxes to the left of the titles you want, and click the 'Get All Checked Abstract(s)' button. **To see one abstract at a time**, click its [Abstract] link.


Copyright © 2006 by the American Association for Clinical Chemistry.


Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000319

web.archive.org/web/20070426113525/http://www.clinchem.org/cgi/reprint/52/11/2172

http://www.clinchem.org/cgi/reprint/52/11/2172 Go

5 captures
26 Apr 2007 - 26 Nov 2009

MAR APR MAY
2006 26 2007 2008
About this capture



**This item requires a subscription to Clinical Chemistry Online.**



PDF

Single-Molecule Detection for Femtomolar Quantification of Proteins in Heterogeneous...

Nalefski et al. *Clin Chem.*2006; 52: 2172-2175

To view this item, select one of the options below:

Sign In

User Name
Password
Sign In
Remember my user name & password.
Forgot your user name or password?

- Sign in without cookies.
- Can't get past this page?
- Help with Cookies.
- Need to Activate?

**This Article**

- Extract FREE
- Full Text (HTML)
- 072850.Supplemental Data
- Submit an electronic Letter to the Editor about this paper
- Alert me when this article is cited
- Alert me when eLetters are posted
- Alert me if a correction is posted

**Services**

- Email this article to a friend
- Similar articles in this journal
- Similar articles in ISI Web of Science
- Alert me to new issues of the journal
- Download to citation manager

Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000320

The Wayback Machine - https://web.archive.org/web/20070426113525/http://www.clinchem.org:80/cgi/reprint/52/11/2172



**This item requires a subscription to Clinical Chemistry Online.**



PDF

Single-Molecule Detection for Femtomolar Quantification of Proteins in Heterogeneous...

Nalefski et al. *Clin Chem.*2006; 52: 2172-2175

To view this item, select one of the options below:

## Sign In

User Name
Password
Sign In
Remember my user name & password.
Forgot your user name or password?

- Sign in without cookies.
- Can't get past this page?
- Help with Cookies.
- Need to Activate?

## Purchase Short-Term Access

- Pay per Article - You may access **this article** (from the computer you are currently using) for 1 day for US$15.00.
- Pay per Issue - You may access **this issue** (from the computer you are currently using) for 1 day for US$25.00.
- Pay for Admission - You may access **all content in Clinical Chemistry Online** (from the computer you are currently using) for 24 hours for US$35.00.
- Regain Access - You can regain access to a recent Pay per Article, Pay per Issue **or** Pay for Admission purchase if your access period has not yet expired.

## Sign Up

- Subscribe to the Journal - Subscribe to the print and/or online journal.

*This Article*

- Extract FREE
- Full Text (HTML)
- 072850.Supplemental Data
- Submit an electronic Letter to the Editor about this paper
- Alert me when this article is cited
- Alert me when eLetters are posted
- Alert me if a correction is posted

*Services*

- Email this article to a friend
- Similar articles in this journal
- Similar articles in ISI Web of Science
- Alert me to new issues of the journal
- Download to citation manager

*Google Scholar*

- Articles by Nalefski, E. A.
- Articles by Whitney, D. H.

*PubMed*

- Articles by Nalefski, E. A.
- Articles by Whitney, D. H.

*Related Collections*

- Automation and Analytical Techniques
- Oak Ridge Conference

HOME HELP FEEDBACK SUBSCRIPTIONS ARCHIVE SEARCH

Copyright © 2006 by the American Association for Clinical Chemistry.



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000321

web.archive.org/web/20080511153458/http://www.clinchem.org/cgi/content/full/52/11/2172

http://www.clinchem.org/cgi/content/full/52/11/2172 Go

3 captures
11 May 2008 – 3 Feb 2009

APR MAY OCT
2007 11 2008 2009
About this capture



*Clinical Chemistry* 52: 2172-2175, 2006; 10.1373/clinchem.2006.072850
(*Clinical Chemistry*. 2006;52:2172-2175.)
© 2006 American Association for Clinical Chemistry, Inc.

## Abstracts of Oak Ridge Posters

# Single-Molecule Detection for Femtomolar Quantification of Proteins in Heterogeneous Immunoassays

**Eric A. Nalefski, Christina M. D'Antoni, Evan P. Ferrell, Janice A. Lloyd, Haoqun Qiu, John L. Harris and Duncan H. Whitney[a]**

(U.S. Genomics, Woburn, MA;

[a]address correspondence to this author at: U.S. Genomics, 12 Gill St., Suite 4700, Woburn, MA 01801; fax 781-938-0060, e-mail dwhitney@usgenomics.com)

There is growing interest in the development of ultrasensitive immunoassays to facilitate validation of novel biomarkers, especially serum biomarkers, and the application of those assays in clinical settings (1). Current assays focus predominantly on abundantly produced protein biomarkers, such as cardiovascular structural

**This Article**
- Extract FREE
- Full Text (PDF)
- 072850.Supplemental Data
- Submit an electronic Letter to the Editor about this paper
- Alert me when this article is cited
- Alert me when eLetters are posted
- Alert me if a correction is posted

**Services**
- Email this article to a friend
- Similar articles in this journal
- Similar articles in ISI Web of Science
- Alert me to new issues of the journal
- Download to citation manager
- Get Permissions

**Citing Articles**
- Citing Articles via HighWire
- Citing Articles via ISI Web of Science (1)
- Citing Articles via Google Scholar

Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000322

The Wayback Machine - https://web.archive.org/web/20080511153458/http://www.clinchem.org:80/cgi/content/full/52/11/2172

Clinical Chemistry

AACC Online Job Center

QUICK SEARCH: [advanced]
Author: Keyword(s):
Go
Year: Vol: Page:

HOME HELP FEEDBACK SUBSCRIPTIONS ARCHIVE SEARCH TABLE OF CONTENTS

*Clinical Chemistry* 52: 2172-2175, 2006; 10.1373/clinchem.2006.072850
(*Clinical Chemistry*. 2006;52:2172-2175.)
© 2006 American Association for Clinical Chemistry, Inc.

This Article
- Extract FREE
- Full Text (PDF)
- 072850.Supplemental Data
- Submit an electronic Letter to the Editor about this paper
- Alert me when this article is cited
- Alert me when eLetters are posted
- Alert me if a correction is posted

Services
- Email this article to a friend
- Similar articles in this journal
- Similar articles in ISI Web of Science
- Alert me to new issues of the journal
- Download to citation manager
- © Get Permissions

Citing Articles
- Citing Articles via HighWire
- Citing Articles via ISI Web of Science (1)
- Citing Articles via Google Scholar

Google Scholar
- Articles by Nalefski, E. A.
- Articles by Whitney, D. H.
- Search for Related Content

PubMed
- Articles by Nalefski, E. A.
- Articles by Whitney, D. H.

Related Collections
- Automation and Analytical Techniques
- Oak Ridge Conference

## Abstracts of Oak Ridge Posters

# Single-Molecule Detection for Femtomolar Quantification of Proteins in Heterogeneous Immunoassays

**Eric A. Nalefski, Christina M. D'Antoni, Evan P. Ferrell, Janice A. Lloyd, Haoqun Qiu, John L. Harris and Duncan H. Whitney[a]**

(U.S. Genomics, Woburn, MA;

[a]address correspondence to this author at: U.S. Genomics, 12 Gill St., Suite 4700, Woburn, MA 01801; fax 781-938-0060, e-mail dwhitney@usgenomics.com)

There is growing interest in the development of ultrasensitive immunoassays to facilitate validation of novel biomarkers, especially serum biomarkers, and the application of those assays in clinical settings (1). Current assays focus predominantly on abundantly produced protein biomarkers, such as cardiovascular structural proteins that leak into the bloodstream, and less so on lower abundance cytokines and chemokines (2). Even rarer markers, such as those released from cancerous cells into the bloodstream, remain more elusive (3). Approaches that exploit recent technological advances in molecular imaging, especially at the single-molecule level (4), are likely to improve the detection limits of the immunoassay, and therefore enable improved detection of these markers.

Microfluidic sample delivery and confocal microscopic detection of labeled biomolecules are useful for detecting targets of interest (5)(6). Two-color correlation counting derived from focused laser-induced excitation allows for high signal-to-noise detection even in the presence of large excesses of free probes, enabling measurement of single molecular events (6). Flow velocity and data acquisition rates can be matched to provide highly accurate quantification, even for rapid analyses on the order of seconds per sample, and analysis time can easily be extended to provide increased detection efficiency of rare targets.

Development and application of new assays are straightforward processes based on well-understood fluorescence methods. We describe application of the Trilogy® 2020 Single Molecule Analyzer for analysis of heterogeneous immunoassays. The human gonadotropin follicle-stimulating hormone (FSH), which plays a central role in fertility (7), was chosen as a representative analyte because of its clinical importance and current clinical requirements for high-sensitivity detection (8).

The Trilogy 2020 instrument uses laser beams shaped into stripes for fluorescence illumination and focuses the beams through a microscope objective into the center of a sample-delivering microcapillary (see the Data Supplement that accompanies the online version of this article at http://www.clinchem.org/content/vol52/issue11). Fluorescence collected through the objective lens is separated into channels and focused onto a charge-coupled device (CCD) camera. Photon counts are integrated over 110 $\mu$s in each of 10 superpixels spanning the width of each laser stripe and stored in data bins. We developed a dynamic thresholding approach to identify and count fluorescence events arising from "in focus" probes (see the online Data Supplement).

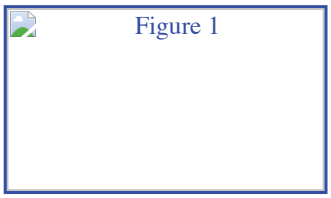
We developed a direct immunometric (sandwich) assay for FSH based on a matched monoclonal antibody (mAb) pair specific for FSH (Medix Biochemica). An $\alpha$-chain–specific capture mAb was biotinylated by reaction with EZ-Link™ NHS-$PEO_4$-Biotin (Pierce Biotechnology), leading to 2 biotins/antibody based on biotin quantification by the avidin-2–4'-hydroxyazobenzene benzoic acid



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000323

method. We Cy5-labeled a ß-chain–specific reporter mAb by reaction with a FluoroLink™ Cy5 reactive dye (GE Healthcare), leading to 5 dyes/antibody as measured with dye quantification by ultraviolet/visible spectrophotometry. The source of FSH was a purified preparation of FSH (Scripps Laboratories, cat. no. F0613) calibrated by the manufacturer. Capture antibody was coupled to Dynabeads® MyOne™ Streptavidin C1 magnetic beads (Dynal Biotech) at 20 μg per mg of beads in PBS/2% bovine serum albumin and washed extensively before use. Immunoreactions, performed in 96-well plates, consisted of a 100-μL sample, 2.5 μg prepared capture beads (50 ng capture antibody), and 2 nmol/L (30 ng) reporter antibody. After orbital shaking for 1 h at room temperature, we collected beads with a plate magnet and washed them 3 times with cold PBS/0.1% NP40. Reporter antibodies were eluted by addition of 30 μL of 2 mol/L glycine, 0.15 mol/L NaCl, and 0.01% NP40 for 5 min; longer times did not lead to release of more molecules. After the magnetic beads were removed, we neutralized the eluent with 3 μL of 2 mol/L Tris, pH 8.6, and 0.01% NP40, and then analyzed the eluent on the Trilogy instrument.

To characterize the platform sensitivity of the Trilogy 2020 instrument, we collected data on control dilutions of the Cy5-labeled reporter antibody. Representative digitized data traces from a buffer control or a solution containing the Cy5-labeled antibody collected in the Red channel over a 10 ms period are shown in Fig 1A. To illustrate the increase in detected fluorescent events from reporter antibody, signals recorded on the CCD camera in each of the 10 pixels were gray-scaled on the basis of increasing intensity (from white to black). Histogram analysis of bin intensities collected in individual pixels (Fig. 1B) illustrates the increase in mean intensity with increasing antibody concentrations over a wide concentration range. A dynamic thresholding approach to analyze a dilution series of the Cy5-labeled antibody (Fig. 1C) reveals that the Trilogy 2020 device exhibits a lower limit of detection (LLOD) of 15 fmol/L, defined as the smallest antibody concentration that generates a mean (–2 SD) signal that is greater than the mean (+2 SD) signal of a buffer control. At this concentration of antibody, ~100 fluorescent events, which corresponds to less than a zeptomole, above background levels were counted in 12 s. The signal response in detecting dye-labeled antibodies was linear up to at least 125 pmol/L, above which there was a slight deviation downward from the prediction line, revealing a linear response of ~4 orders of magnitude. The signal response, however, continued to increase with even 1 nmol/L antibodies, indicating a dynamic response of >6 x $10^4$.




**View larger version** (32K):
[in this window]
[in a new window]

**Figure 1.** Single molecule detection.

*(A)*, digitized data recorded in 10 adjacent pixels, represented on the *x*-axis, of the Red channel over 10 ms, represented on the *y*-axis, from control buffer *(left)* or a 4 pmol/L solution of Cy5-labeled antibody *(right)*. Bin intensities recorded on the CCD were scaled downward 20-fold and then gray-scaled equivalently in both panels from low intensity *(white)*, to intermediate *(grays)*, and to high intensity *(black)* for this representation. *(B)*, histograms of bin intensities for data collected in single pixels of the Red channel over 12 s from increasing concentrations of Cy5-labeled antibody (0–1000 pmol/L), illustrating the increase in mean bin intensity. The number of bins was normalized to time. *(C)*, dose dependence of the number of bins observed to exceed the dynamic fluorescence threshold, normalized to time, on the concentration of Cy5-labeled antibody. Symbols represent the mean of multiple replicates for no antibody (n = 20) or the indicated concentrations of antibody (n = 3). Standard deviations of replicates are indicated by *bars*, which are in most cases smaller than *symbols*. The *solid line* represents linear fitting of the data over 125 pmol/L; *open symbols* represent data deviating from linearity. LLOD is calculated here as 15 fmol/L. *(D–E)*. Raw trace files collected in the Red channel over 100 ms in single pixels on eluents from immunoreactions containing no FSH *(D)* or 1 IU/L FSH *(E)*. The dynamic threshold value of 4 counts used to detect antibody molecules is indicated by the dashed horizontal line. *(F)*, FSH immunoassay dose–response curve, illustrating the dependence of observed numbers of bins that exceed dynamically applied thresholds, normalized to time, on the amount of FSH in the reaction. *Symbols* represent mean values for multiple replicates of no FSH (n = 11) or 12 different FSH dilutions (n = 3). Standard deviations of replicates are indicated by *bars*, which are smaller than *symbols* in most cases. The *solid line* represents fitting of data with a 4-parameter logistic equation. LLOD is calculated here at 20 mIU/L.

After releasing the captured reporter antibodies into solution, we analyzed eluents from heterogeneous FSH immunoreactions on the Trilogy instrument. Short segments of representative trace files are provided in Fig. 1, D–E. Without added FSH, we detected only a few reporter antibodies over the dynamic threshold (Fig. 1D). In contrast, considerably more reporter antibodies were detected when FSH was included in the immunoreaction (Fig. 1E). A dose–response curve was generated in which FSH concentrations were increased over several logs, and we used the dynamic thresholding approach to determine the resulting antibody signal (Fig. 1F).



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000324

Detailed analysis of the curve revealed that the LLOD for the immunoassay conducted under these conditions was 20 mIU/L FSH (~34 fmol/L), in this case defined as the smallest concentration of FSH that generates a mean signal that is 2 SDs above that of a buffer control. For this concentration of FSH, hundreds of fluorescent events, corresponding to zeptomoles of antibodies, were counted above background in 12 s. The signal response continued to increase to ≥200 IU/L FSH, yielding a total dynamic range >4000. In contrast, commonly used enzymatic signal amplification assays are reported to be at least 1 order of magnitude less sensitive (8).

In conclusion, with the Trilogy platform, based on confocal microscopic detection in microcapillaries, photon bursts corresponding to fluorescently labeled antibodies are readily distinguishable from background. Counting molecular events, in turn, provides a very sensitive and precise way to quantify biomolecules of interest. Analysis times of only a few seconds are required to detect as little as zeptomoles of protein analytes, leading to low femtomolar LODs.

In addition to several advantages offered by heterogeneous formats (9), analyte enrichment during the capture step provides a unique opportunity to capitalize on the exquisite sensitivity provided by single-molecule analysis. Because the interrogation zone is on the order of femtoliters, the inner diameter of the sample delivery microcapillary is on the order of tens of micrometers, suitable counting statistics are achieved in seconds, and only small volumes of captured and released reporter antibodies are required for analysis. For instance, at 10 $\mu$m/ms, the typical linear flow velocity, only a few microliters are consumed in 12 s, a small fraction of the tens of microliters of reporter antibodies eluted from immune reactions conducted on 100 $\mu$L of sample, as reported here. Liquid handling procedures designed to deal with smaller volumes would further decrease the required sample size. This feature would be very useful in pediatric tests, for which only small sample volumes are dedicated per test. An added advantage of the single molecule approach is the requirement for only small quantities of probe reagents: for the FSH assay described here, only 30–50 ng of capture and reporter antibodies are consumed per sample per well, and even less would be needed with further miniaturization.

We used FSH as an example to demonstrate the principles and features of single-molecule, heterogeneous-immunoassays. The platform should be equally suitable for the analysis of other fluorescently labeled reporter antibodies and antigens. Although interference, antibody cross-reactivity, and matrix effects that potentially limit other immunoassays must be considered, they pose no particular challenge for the single-molecule approach. The present study used a capture approach involving biotinylated antibodies immobilized to streptavidin-conjugated beads, but the method is not limited to this approach; we have successfully quantified antigens with capture strategies involving antibodies covalently attached or nonspecifically adsorbed to beads and membranes (data not shown). Furthermore, with inclusion of additional sets of capture reagents and reporter antibodies matching the other fluorescent channels offered by the Trilogy instrument, the platform can simultaneously detect multiple analytes (data not shown). Finally, the platform can be used for precise and sensitive detection of fluorescently labeled probe molecules used in other assays, including those specific for particular nucleic acids (5).

## References

1. Parsons G. An introduction to clinical laboratory immunodiagnostics. Lewandrowski K eds. Clinical Chemistry: Management, Analysis and Clinical Correlation 2002:413-428 Lippincott, Williams and Wilkins Philadelphia, PA. .
2. O'Sullivan MJ, Capper S, Horton JK, Whateley J, Baxendale P. Immunoassay applications in life-science research. Wild D eds. The Immunoassay Handbook, 2nd ed 2001:817-845 Nature Publishing Group London. .
3. Anderson NL, Anderson NG. The human plasma proteome: history, character, and diagnostic prospects. Mol Cell Proteomics 2002;1:845-867.[Abstract/Free Full Text]
4. Li H, Ying L, Ren X, Balasubramanian S, Klenerman D. Fluorescence studies of single biomolecules. Biochem Soc Trans 2004;32:753-756.[CrossRef][ISI][Medline] [Order article via Infotrieve]
5. Neely LA, Patel S, Garver J, Gallo M, Hackett M, McLaughlin S, et al. A single-molecule method for the quantitation of microRNA gene expression. Nature Methods 2006;3:41-46.
6. D'Antoni CM, Fuchs M, Harris JL, Ko H-P, Meyer RE, Nadel ME, et al. Rapid quantitative analysis using a single molecule counting method. Anal Biochem 2006;352:97-109.[CrossRef][ISI][Medline] [Order article via Infotrieve]
7. Rose MP, Gaines Das RE, Balen AH. Definition and measurement of follicle stimulating hormone. Endocr Rev 2000;21:5-22. [Abstract/Free Full Text]
8. Taylor AE, Khoury RH, Crowley WF, Jr. A comparison of 13 different immunometric assay kits for gonadotropins: implications for clinical investigation. J Clin Endocrinol Metab 1994;79:240-247.[Abstract]
9. Wild D. Separation systems. Wild D eds. The Immunoassay Handbook, 2nd ed 2001:149-158 Nature Publishing Group London. .



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000325

# The following articles in journals at HighWire Press have cited this article:



Clinical Chemistry HOME

H. Qiu, E. P. Ferrell, N. Nolan, B. H. Phelps, R. Tabibiazar, D. H. Whitney, and E. A. Nalefski
**Fluorescence single-molecule counting assays for high-sensitivity detection of cytokines and chemokines.**
Clin. Chem., November 1, 2007; 53(11): 2010 - 2012.
[Full Text] [PDF]

*This Article*

- Extract FREE
- Full Text (PDF)
- 072850.Supplemental Data
- Submit an electronic Letter to the Editor about this paper
- Alert me when this article is cited
- Alert me when eLetters are posted
- Alert me if a correction is posted

*Services*

- Email this article to a friend
- Similar articles in this journal
- Similar articles in ISI Web of Science
- Alert me to new issues of the journal
- Download to citation manager
- © Get Permissions

*Citing Articles*

- Citing Articles via HighWire
- Citing Articles via ISI Web of Science (1)
- Citing Articles via Google Scholar

*Google Scholar*

- Articles by Nalefski, E. A.
- Articles by Whitney, D. H.
- Search for Related Content

*PubMed*

- Articles by Nalefski, E. A.
- Articles by Whitney, D. H.

*Related Collections*

- Automation and Analytical Techniques
- Oak Ridge Conference



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000326

web.archive.org/web/20080511152327/http://www.clinchem.org/cgi/reprint/52/11/2172

http://www.clinchem.org/cgi/reprint/52/11/2172 Go

APR MAY JUL

5 captures

26 Apr 2007 – 26 Nov 2009

2007 2008 2009 About this capture

2172.full.pdf 1 / 4 117%



sequences representing all known high-risk HPV E6 were tested, and PDZ 88 interacted with all of them with greatest binding strength. Therefore, PDZ 88 was selected as the capture reagent. The recognition of PDZ 88 to only high-risk HPV E6 (e.g., HPV types 16, 18, 33, 35, 52, 58, and 66) but not low-risk HPV E6 (e.g., HPV types 77 and 57) provides a high degree of selectivity for the assay.

Antibodies to HPV E6 from high-risk HPV types were generated. The antibodies were screened for affinity and cross-reactivity with other HPV E6. The antibody with the strongest reactivity to HPV-16 E6 was selected as the detector.

The magnetic immunochromatographic strip was selected for evaluation as the assay platform on the basis of ease of use and acceptability in low-resource settings, inherent sensitivity of the technology, and the ability to quantify results. MagnaBioSciences has developed a magnetic immunochromatographic test platform including an assay cassette and reader that is suitable for developing quantitative assays for a variety of analytes. The assay described here was developed on this platform. Additional studies for the method have shown that strip-to-strip reproducibility yields a CV of <10%, and reader reproducibility yields a CV of 1.5% (data not shown).

The PDZ capture reagent was immobilized on a nitro-

Funding for this work was provided by the Bill and Melinda Gates Foundation and by National Institutes of Health SBIR award number 1 R43 CA103383-01.

**References**

1. Munger K, Phelps WC, Bubb V, Howley PM, Schlegel R. The E6 and E7 genes of the human papillomavirus type 16 together are necessary and sufficient for transformation of primary human keratinocytes. J Virol 1989;63:4417–21.
2. Munger K, Baldwin A, Edwards KM, Hayakawa H, Nguyen CL, Owens M, et al. Mechanisms of human papillomavirus-induced oncogenesis. J Virol 2004;78:11451–60.
3. Hawley-Nelson P, Vousden KH, Hubbert NL, Lowy DR, Schiller JT. HPV16 E6 and E7 proteins cooperate to immortalize human foreskin keratinocytes. EMBO J 1989;8:3905–10.
4. Francis DA, Schmid SI, Howley PM. Repression of the integrated papillomavirus E6/E7 promoter is required for growth suppression of cervical cancer cells. J Virol 2000;74:2679–86.
5. DeFilippis RA, Goodwin EC, Wu L, DiMaio D. Endogenous human papillomavirus E6 and E7 proteins differentially regulate proliferation, senescence, and apoptosis in HeLa cervical carcinoma cells. J Virol 2003;77:1551–63.
6. Kiyono T, Hiraiwa A, Fujita M, Hayashi Y, Akiyama T, Ishibashi M. Binding of high-risk human papillomavirus E6 oncoproteins to the human homologue of the *Drosophila* discs large tumor suppressor protein. Proc Natl Acad Sci U S A 1997;94:11612–6.
7. Lee C, Laimins LA. Role of the PDZ domain-binding motif of the oncoprotein E6 in the pathogenesis of human papillomavirus type 31. J Virol 2004;78:12366–77.
8. Nguyen ML, Nguyen MM, Lee D, Griep AE, Lambert PF. The PDZ ligand domain of the human papillomavirus type 16 E6 protein is required for E6's induction of epithelial hyperplasia in vivo. J Virol 2003;77:6957–64.
9. Ledwaba T, Dlamini Z, Naicker S, Bhoola K. Molecular genetics of human cervical cancer: role of papillomavirus and the apoptotic cascade [Review]. Biol Chem 385:671–82, 2004.

INTERNET ARCHIVE WayBackMac DONATE

http://w

Hrm.

The Wayba

Click here t

Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000327

sequences representing all known high-risk HPV E6 were tested, and PDZ 88 interacted with all of them with greatest binding strength. Therefore, PDZ 88 was selected as the capture reagent. The recognition of PDZ 88 to only high-risk HPV E6 (e.g., HPV types 16, 18, 33, 35, 52, 58, and 66) but not low-risk HPV E6 (e.g., HPV types 77 and 57) provides a high degree of selectivity for the assay.

Antibodies to HPV E6 from high-risk HPV types were generated. The antibodies were screened for affinity and cross-reactivity with other HPV E6. The antibody with the strongest reactivity to HPV-16 E6 was selected as the detector.

The magnetic immunochromatographic strip was selected for evaluation as the assay platform on the basis of ease of use and acceptability in low-resource settings, inherent sensitivity of the technology, and the ability to quantify results. MagnaBioSciences has developed a magnetic immunochromatographic test platform including an assay cassette and reader that is suitable for developing quantitative assays for a variety of analytes. The assay described here was developed on this platform. Additional studies for the method have shown that strip-to-strip reproducibility yields a CV of <10%, and reader reproducibility yields a CV of 1.5% (data not shown).

The PDZ capture reagent was immobilized on a nitrocellulose membrane. Assays were assembled with a laminate backing, membrane with immobilized PDZ, hydrophilic sample pad, absorbent pad, and membrane cover tape. Test strips were cut to a width of 7.5 mm. The soluble-phase detection antibody was covalently conjugated to superparamagnetic particles.

Doubling dilutions of recombinant HPV-16 E6 from 332 to 5.2 $\mu$g/L were prepared in the proprietary assay running buffer containing Tris, surfactants, and blocking agents. The detection reagent was mixed with the sample, and 250 $\mu$L was applied to the strip. On migration of the sample, the strips were inserted into the magnetic strip reader. The strip reader generated data curves. Peak height was selected, and data were reported as relative magnetic units (RMUs).

The assay cutoff was conservatively set at 3 times the mean RMU of the negative controls. The RMU value for each sample was divided by the cutoff. Samples >1 were considered positive.

Lower amounts of the target protein led to lower RMU values (Fig. 1B). Strips titrated with recombinant HPV-16 E6 and read on the magnetic strip reader exhibited a linear response.

An initial prototype of the magnetic immunochromatographic strip assay is capable of detecting recombinant HPV-16 E6 down to 2.6 ng/assay (~2 600 000 cells). An early version of the assay in an ELISA format detected oncogenic E6 from cervical cancer cell lines down to 30 pg/assay (~30 000 cells). Future steps include further optimization to decrease detection limits and evaluation of cell cultures and cervical cell swabs from clients. Once utility with HPV16 is demonstrated, additional high-risk HPV types will be added to the assay.

Funding for this work was provided by the Bill and Melinda Gates Foundation and by National Institutes of Health SBIR award number 1 R43 CA103383-01.

**References**

1. Munger K, Phelps WC, Bubb V, Howley PM, Schlegel R. The E6 and E7 genes of the human papillomavirus type 16 together are necessary and sufficient for transformation of primary human keratinocytes. J Virol 1989;63:4417–21.
2. Munger K, Baldwin A, Edwards KM, Hayakawa H, Nguyen CL, Owens M, et al. Mechanisms of human papillomavirus-induced oncogenesis. J Virol 2004;78:11451–60.
3. Hawley-Nelson P, Vousden KH, Hubbert NL, Lowy DR, Schiller JT. HPV16 E6 and E7 proteins cooperate to immortalize human foreskin keratinocytes. EMBO J 1989;8:3905–10.
4. Francis DA, Schmid SI, Howley PM. Repression of the integrated papillomavirus E6/E7 promoter is required for growth suppression of cervical cancer cells. J Virol 2000;74:2679–86.
5. DeFilippis RA, Goodwin EC, Wu L, DiMaio D. Endogenous human papillomavirus E6 and E7 proteins differentially regulate proliferation, senescence, and apoptosis in HeLa cervical carcinoma cells. J Virol 2003;77:1551–63.
6. Kiyono T, Hiraiwa A, Fujita M, Hayashi Y, Akiyama T, Ishibashi M. Binding of high-risk human papillomavirus E6 oncoproteins to the human homologue of the *Drosophila* discs large tumor suppressor protein. Proc Natl Acad Sci U S A 1997;94:11612–6.
7. Lee C, Laimins LA. Role of the PDZ domain-binding motif of the oncoprotein E6 in the pathogenesis of human papillomavirus type 31. J Virol 2004;78:12366–77.
8. Nguyen ML, Nguyen MM, Lee D, Griep AE, Lambert PF. The PDZ ligand domain of the human papillomavirus type 16 E6 protein is required for E6's induction of epithelial hyperplasia in vivo. J Virol 2003;77:6957–64.
9. Ledwaba T, Dlamini Z, Naicker S, Bhoola K. Molecular genetics of human cervical cancer: role of papillomavirus and the apoptotic cascade [Review]. Biol Chem 385:671–82, 2004.

DOI: 10.1373/clinchem.2006.072884

**Single-Molecule Detection for Femtomolar Quantification of Proteins in Heterogeneous Immunoassays,** *Eric A. Nalefski, Christina M. D'Antoni, Evan P. Ferrell, Janice A. Lloyd, Haoqun Qiu, John L. Harris, and Duncan H. Whitney** (U.S. Genomics, Woburn, MA; * address correspondence to this author at: U.S. Genomics, 12 Gill St., Suite 4700, Woburn, MA 01801; fax 781-938-0060, e-mail dwhitney@usgenomics.com)

There is growing interest in the development of ultrasensitive immunoassays to facilitate validation of novel biomarkers, especially serum biomarkers, and the application of those assays in clinical settings *(1)*. Current assays focus predominantly on abundantly produced protein biomarkers, such as cardiovascular structural proteins that leak into the bloodstream, and less so on lower abundance cytokines and chemokines *(2)*. Even rarer markers, such as those released from cancerous cells into the bloodstream, remain more elusive *(3)*. Approaches that exploit recent technological advances in molecular imaging, especially at the single-molecule level *(4)*, are likely to improve the detection limits of the immunoassay, and therefore enable improved detection of these markers.

Microfluidic sample delivery and confocal microscopic detection of labeled biomolecules are useful for detecting targets of interest *(5, 6)*. Two-color correlation counting

Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000328

derived from focused laser-induced excitation allows for high signal-to-noise detection even in the presence of large excesses of free probes, enabling measurement of single molecular events *(6)*. Flow velocity and data acquisition rates can be matched to provide highly accurate quantification, even for rapid analyses on the order of seconds per sample, and analysis time can easily be extended to provide increased detection efficiency of rare targets.

Development and application of new assays are straightforward processes based on well-understood fluorescence methods. We describe application of the Trilogy® 2020 Single Molecule Analyzer for analysis of heterogeneous immunoassays. The human gonadotropin follicle-stimulating hormone (FSH), which plays a central role in fertility *(7)*, was chosen as a representative analyte because of its clinical importance and current clinical requirements for high-sensitivity detection *(8)*.

The Trilogy 2020 instrument uses laser beams shaped into stripes for fluorescence illumination and focuses the beams through a microscope objective into the center of a sample-delivering microcapillary (see the Data Supplement that accompanies the online version of this article at http://www.clinchem.org/content/vol52/issue11). Fluorescence collected through the objective lens is separated into channels and focused onto a charge-coupled device (CCD) camera. Photon counts are integrated over 110 μs in each of 10 superpixels spanning the width of each laser stripe and stored in data bins. We developed a dynamic thresholding approach to identify and count fluorescence events arising from "in focus" probes (see the online Data Supplement).

We developed a direct immunometric (sandwich) assay for FSH based on a matched monoclonal antibody (mAb) pair specific for FSH (Medix Biochemica). An α-chain–specific capture mAb was biotinylated by reaction with EZ-Link™ NHS-$PEO_4$-Biotin (Pierce Biotechnology), leading to 2 biotins/antibody based on biotin quantification by the avidin-2–4′-hydroxyazobenzene benzoic acid method. We Cy5-labeled a β-chain–specific reporter mAb by reaction with a FluoroLink™ Cy5 reactive dye (GE Healthcare), leading to 5 dyes/antibody as measured with dye quantification by ultraviolet/visible spectrophotometry. The source of FSH was a purified preparation of FSH (Scripps Laboratories, cat. no. F0613) calibrated by the manufacturer. Capture antibody was coupled to Dynabeads® MyOne™ Streptavidin C1 magnetic beads (Dynal Biotech) at 20 μg per mg of beads in PBS/2% bovine serum albumin and washed extensively before use. Immunoreactions, performed in 96-well plates, consisted of a 100-μL sample, 2.5 μg prepared capture beads (50 ng capture antibody), and 2 nmol/L (30 ng) reporter antibody. After orbital shaking for 1 h at room temperature, we collected beads with a plate magnet and washed them 3 times with cold PBS/0.1% NP40. Reporter antibodies were eluted by addition of 30 μL of 2 mol/L glycine, 0.15 mol/L NaCl, and 0.01% NP40 for 5 min; longer times did not lead to release of more molecules. After the magnetic beads were removed, we neutralized the eluent with 3 μL of 2 mol/L Tris, pH 8.6, and 0.01% NP40, and then analyzed the eluent on the Trilogy instrument.

To characterize the platform sensitivity of the Trilogy 2020 instrument, we collected data on control dilutions of the Cy5-labeled reporter antibody. Representative digitized data traces from a buffer control or a solution containing the Cy5-labeled antibody collected in the Red channel over a 10 ms period are shown in Fig 1A. To illustrate the increase in detected fluorescent events from reporter antibody, signals recorded on the CCD camera in each of the 10 pixels were gray-scaled on the basis of increasing intensity (from white to black). Histogram analysis of bin intensities collected in individual pixels (Fig. 1B) illustrates the increase in mean intensity with increasing antibody concentrations over a wide concentration range. A dynamic thresholding approach to analyze a dilution series of the Cy5-labeled antibody (Fig. 1C) reveals that the Trilogy 2020 device exhibits a lower limit of detection (LLOD) of 15 fmol/L, defined as the smallest antibody concentration that generates a mean (−2 SD) signal that is greater than the mean (+2 SD) signal of a buffer control. At this concentration of antibody, ~100 fluorescent events, which corresponds to less than a zeptomole, above background levels were counted in 12 s. The signal response in detecting dye-labeled antibodies was linear up to at least 125 pmol/L, above which there was a slight deviation downward from the prediction line, revealing a linear response of ~4 orders of magnitude. The signal response, however, continued to increase with even 1 nmol/L antibodies, indicating a dynamic response of $>6 \times 10^4$.

After releasing the captured reporter antibodies into solution, we analyzed eluents from heterogeneous FSH immunoreactions on the Trilogy instrument. Short segments of representative trace files are provided in Fig. 1, D–E. Without added FSH, we detected only a few reporter antibodies over the dynamic threshold (Fig. 1D). In contrast, considerably more reporter antibodies were detected when FSH was included in the immunoreaction (Fig. 1E). A dose–response curve was generated in which FSH concentrations were increased over several logs, and we used the dynamic thresholding approach to determine the resulting antibody signal (Fig. 1F). Detailed analysis of the curve revealed that the LLOD for the immunoassay conducted under these conditions was 20 mIU/L FSH (~34 fmol/L), in this case defined as the smallest concentration of FSH that generates a mean signal that is 2 SDs above that of a buffer control. For this concentration of FSH, hundreds of fluorescent events, corresponding to zeptomoles of antibodies, were counted above background in 12 s. The signal response continued to increase to ≥200 IU/L FSH, yielding a total dynamic range >4000. In contrast, commonly used enzymatic signal amplification assays are reported to be at least 1 order of magnitude less sensitive *(8)*.

In conclusion, with the Trilogy platform, based on confocal microscopic detection in microcapillaries, photon bursts corresponding to fluorescently labeled antibodies

Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000329

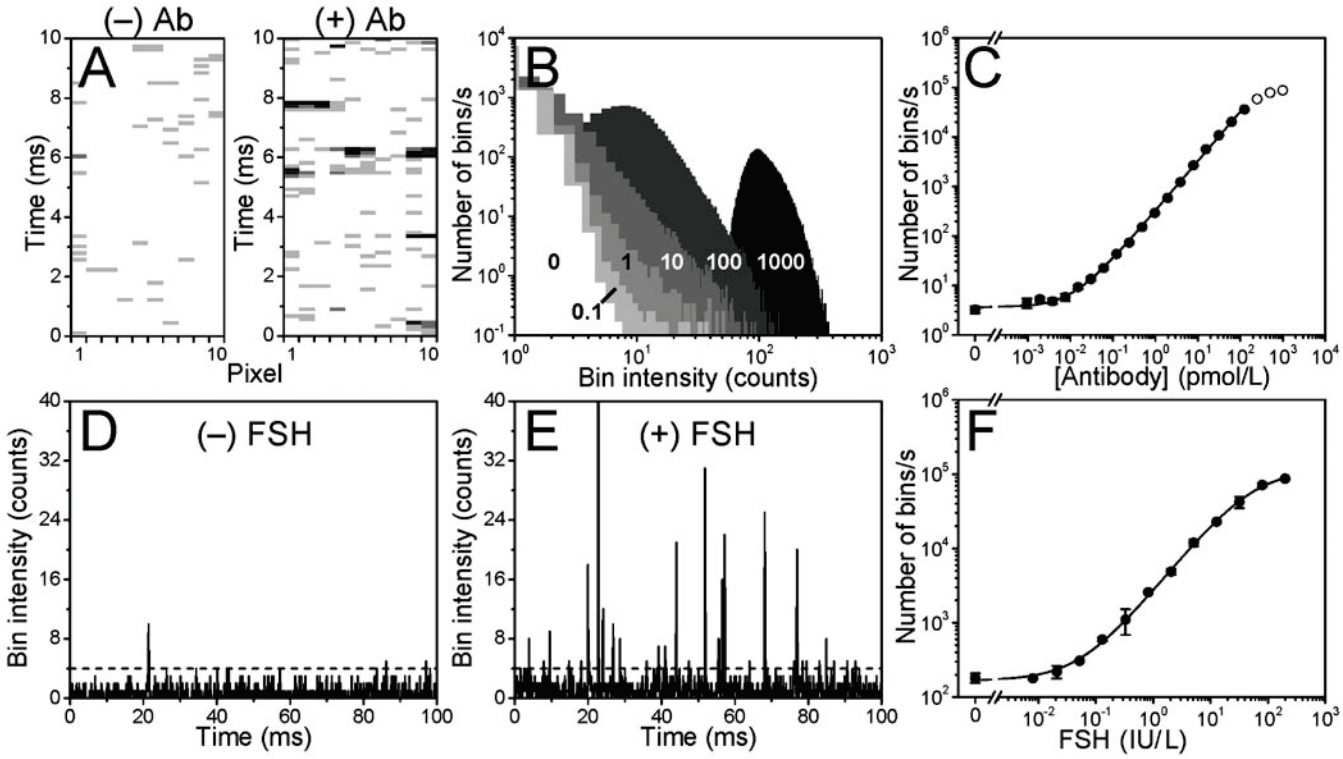



Fig. 1. Single molecule detection.

*(A)*, digitized data recorded in 10 adjacent pixels, represented on the *x*-axis, of the Red channel over 10 ms, represented on the *y*-axis, from control buffer *(left)* or a 4 pmol/L solution of Cy5-labeled antibody *(right)*. Bin intensities recorded on the CCD were scaled downward 20-fold and then gray-scaled equivalently in both panels from low intensity *(white)*, to intermediate *(grays)*, and to high intensity *(black)* for this representation. *(B)*, histograms of bin intensities for data collected in single pixels of the Red channel over 12 s from increasing concentrations of Cy5-labeled antibody (0–1000 pmol/L), illustrating the increase in mean bin intensity. The number of bins was normalized to time. *(C)*, dose dependence of the number of bins observed to exceed the dynamic fluorescence threshold, normalized to time, on the concentration of Cy5-labeled antibody. Symbols represent the mean of multiple replicates for no antibody (n = 20) or the indicated concentrations of antibody (n = 3). Standard deviations of replicates are indicated by *bars*, which are in most cases smaller than *symbols*. The *solid line* represents linear fitting of the data over 125 pmol/L; *open symbols* represent data deviating from linearity. LLOD is calculated here as 15 fmol/L. *(D–E)*. Raw trace files collected in the Red channel over 100 ms in single pixels on eluents from immunoreactions containing no FSH *(D)* or 1 IU/L FSH *(E)*. The dynamic threshold value of 4 counts used to detect antibody molecules is indicated by the dashed horizontal line. *(F)*, FSH immunoassay dose–response curve, illustrating the dependence of observed numbers of bins that exceed dynamically applied thresholds, normalized to time, on the amount of FSH in the reaction. *Symbols* represent mean values for multiple replicates of no FSH (n = 11) or 12 different FSH dilutions (n = 3). Standard deviations of replicates are indicated by *bars*, which are smaller than *symbols* in most cases. The *solid line* represents fitting of data with a 4-parameter logistic equation. LLOD is calculated here at 20 mIU/L.

are readily distinguishable from background. Counting molecular events, in turn, provides a very sensitive and precise way to quantify biomolecules of interest. Analysis times of only a few seconds are required to detect as little as zeptomoles of protein analytes, leading to low femtomolar LODs.

In addition to several advantages offered by heterogeneous formats *(9)*, analyte enrichment during the capture step provides a unique opportunity to capitalize on the exquisite sensitivity provided by single-molecule analysis. Because the interrogation zone is on the order of femtoliters, the inner diameter of the sample delivery microcapillary is on the order of tens of micrometers, suitable counting statistics are achieved in seconds, and only small volumes of captured and released reporter antibodies are required for analysis. For instance, at 10 $\mu$m/ms, the typical linear flow velocity, only a few microliters are consumed in 12 s, a small fraction of the tens of microliters of reporter antibodies eluted from immune reactions conducted on 100 $\mu$L of sample, as reported here. Liquid handling procedures designed to deal with smaller volumes would further decrease the required sample size. This feature would be very useful in pediatric tests, for which only small sample volumes are dedicated per test. An added advantage of the single molecule approach is the requirement for only small quantities of probe reagents: for the FSH assay described here, only 30–50 ng of capture and reporter antibodies are consumed per sample per well, and even less would be needed with further miniaturization.

We used FSH as an example to demonstrate the principles and features of single-molecule, heterogeneous-immunoassays. The platform should be equally suitable for the analysis of other fluorescently labeled reporter antibodies and antigens. Although interference, antibody cross-reactivity, and matrix effects that potentially limit other immunoassays must be considered, they pose no particular challenge for the single-molecule approach. The present study used a capture approach involving biotinylated antibodies immobilized to streptavidin-con-

Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000330

jugated beads, but the method is not limited to this approach; we have successfully quantified antigens with capture strategies involving antibodies covalently attached or nonspecifically adsorbed to beads and membranes (data not shown). Furthermore, with inclusion of additional sets of capture reagents and reporter antibodies matching the other fluorescent channels offered by the Trilogy instrument, the platform can simultaneously detect multiple analytes (data not shown). Finally, the platform can be used for precise and sensitive detection of fluorescently labeled probe molecules used in other assays, including those specific for particular nucleic acids *(5)*.

## References


1. Parsons G. An introduction to clinical laboratory immunodiagnostics. In: Lewandrowski K, ed. Clinical Chemistry: Management, Analysis and Clinical Correlation. Philadelphia, PA: Lippincott, Williams and Wilkins, 2002:413–28.
2. O'Sullivan MJ, Capper S, Horton JK, Whateley J, Baxendale P. Immunoassay applications in life-science research. In: Wild D, ed. The Immunoassay Handbook, 2nd ed. London: Nature Publishing Group, 2001:817–45.
3. Anderson NL, Anderson NG. The human plasma proteome: history, character, and diagnostic prospects. Mol Cell Proteomics 2002;1:845–67.
4. Li H, Ying L, Ren X, Balasubramanian S, Klenerman D. Fluorescence studies of single biomolecules. Biochem Soc Trans 2004;32:753–6.
5. Neely LA, Patel S, Garver J, Gallo M, Hackett M, McLaughlin S, et al. A single-molecule method for the quantitation of microRNA gene expression. Nature Methods 2006;3:41–6.
6. D'Antoni CM, Fuchs M, Harris JL, Ko H-P, Meyer RE, Nadel ME, et al. Rapid quantitative analysis using a single molecule counting method. Anal Biochem 2006;352:97–109.
7. Rose MP, Gaines Das RE, Balen AH. Definition and measurement of follicle stimulating hormone. Endocr Rev 2000;21:5–22.
8. Taylor AE, Khoury RH, Crowley WF Jr. A comparison of 13 different immunometric assay kits for gonadotropins: implications for clinical investigation. J Clin Endocrinol Metab 1994;79:240–7.
9. Wild D. Separation systems. In: Wild D, ed. The Immunoassay Handbook, 2nd ed. London: Nature Publishing Group, 2001:149–58.


DOI: 10.1373/clinchem.2006.072850

Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000331

**EX-1035H** Citation records to *Nalefski*, obtained from Google Scholar.

**EX1035H**
Citations to Nalefski

**Source Document**

Nalefski, E. A., D'Antoni, C. M., Ferrell, E. P., Lloyd, J. A., Qiu, H., Harris, J. L., & Whitney, D. H. (2006, November). Single-molecule detection for femtomolar quantification of proteins in heterogeneous immunoassays. *Clinical chemistry*, *52*(11), 2172-2175.

**Citations: 2008 – 2009** (in chronological order)

Bhartia, R., Hug, W. F., Salas, E. C., Reid, R. D., Sijapati, K. K., Tsapin, A., ... & Conrad, P. G. (2008, October). Classification of organic and biological materials with deep ultraviolet excitation. *Applied spectroscopy*, *62*(10), 1070-1077.

Luchowski, R., Matveeva, E. G., Gryczynski, I., Terpetschnig, E. A., Patsenker, L., Laczko, G., ... & Gryczynski, Z. (2008, October). Single molecule studies of multiple-fluorophore labeled antibodies. Effect of homo-FRET on the number of photons available before photobleaching. *Current pharmaceutical biotechnology*, *9*(5), 411-420.

Barletta, J., Bartolome, A., & Constantine, N. T. (2009, May). Immunomagnetic quantitative immuno-PCR for detection of less than one HIV-1 virion. *Journal of virological methods*, *157*(2), 122-132.

Li, J., Xie, W., Fang, N., & Yeung, E. S. (2009, May). Single-molecule immunosorbent assay as a tool for human immunodeficiency virus-1 antigen detection. *Analytical and bioanalytical chemistry*, *394*(2), 489-497.

**EX-1036A** Webpage for *Aβ-42* from Singulex, archived by Internet Archive on September 12, 2009, available at https://web.archive.org/web/20090912044340/http://www.singulex.com:80/assay_details.html?id=2.

https://web.archive.org/web/20090912044340/http://www.singulex.com:80/assay_deta 120%
http://www.singulex.com/assay_details.html?id=2 Go JUL SEP AUG
3 captures 12
27 Jul 2007 - 17 Aug 2010 2007 2009 2010 About this capture



For Drug Development

Assay Menu

Erenna® Immunoassay System

Back to Assays

# Aβ-42 (Amyloid beta protein 42)

The Singulex Aβ-40 and Aβ-42 assays allow the quantification of amyloid beta proteins from human plasma with exceptional sensitivity, enabling use of Aβ-40/Aβ-42 as a velocity biomarker in Alzheimer's disease studies and to evaluate therapeutic interventions.

## Biology and Diseases

Amyloid beta proteins (40 and 42 amino acids) are the main constituent of amyloid plaques in the brains of Alzheimer's disease (AD) patients. In healthy and disease states Aβ-40 is the more common form (10–20X higher than Aβ-42) of the two in both cerebrospinal fluid (CSF) and plasma. In patients with AD, Aβ-42 primarily aggregates and deposits in the brain forming plaques. Thus the concentration of Aβ-42 is decreased in the CSF of many AD patients. Recent studies suggest that a decrease in Aβ-42 concentrations (with a paralleled change in the ratio of Aβ-40/Aβ-42) in CSF and plasma are predictive of the onset of AD.

Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000335

The Wayback Machine - https://web.archive.org/web/20090912044340/http://www.singulex.com:80/assay_details.html?id=2



# Aβ-42 (Amyloid beta protein 42)

The Singulex Aβ-40 and Aβ-42 assays allow the quantification of amyloid beta proteins from human plasma with exceptional sensitivity, enabling use of Aβ-40/Aβ-42 as a velocity biomarker in Alzheimer's disease studies and to evaluate therapeutic interventions.

## Biology and Diseases

Amyloid beta proteins (40 and 42 amino acids) are the main constituent of amyloid plaques in the brains of Alzheimer's

**EX-1011A** Copy of Bourzac available at https://www.technologyreview.com/2008/05/13/220548/next-generation-diagnostics/ from MIT Technology Review.

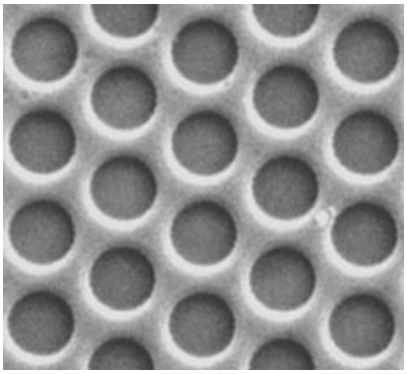
# Next-Generation Diagnostics

A startup can detect tiny traces of cancer markers in blood samples.

## By Katherine Bourzac

May 13, 2008

**One of the loftier dreams of personalized medicine is to detect and eliminate tumors before they become life** threatening–before they are even visible on medical images. Now a Cambridge, MA, startup called Quanterix is developing an extremely sensitive protein-detection technology that can count single molecules–and could potentially detect the trace amounts of characteristic proteins that tiny tumors release into the blood.



**Lab on a tip:** Wells carved into the tip of an optical fiber allow researchers to detect single proteins in blood samples. Each well in this image is about 2.5 micrometers in diameter and sits at the tip of an individual thread of an optical fiber.

"The premise is to get diagnostics to the most sensitive level possible," says David Walt, a chemist and Howard Hughes Medical Institute professor at Tufts University, who developed the Quanterix technology. Trace proteins in the blood could also reveal early signs of heart disease, Alzheimer's, and other ailments, and enable noninvasive fetal diagnostics.

"If we could understand the baseline levels of proteins in the serum, it could be used to track the integrated health of a person over the course of life," says Christopher Love, a chemical-engineering professor at MIT who is not involved with Quanterix.

With current clinical technologies, hospital labs can detect only the most abundant proteins–only a quarter of



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000338

all those known to be present in the blood. Because proteins are present in the blood at a range of different concentrations spanning about 16 orders of magnitude, abundant proteins mask the rare ones. "It's like trying to look for a slightly different piece of hay in the haystack," says Forest White, a biological engineer at MIT.

**Multimedia**

**Watch proteins light up inside an optical fiber.**

The current detection limit is 10 picograms of protein per milliliter of blood. But Walt has developed a detection technique that allows him to count individual protein molecules present in the blood using specially treated optical fibers. A single optical fiber is a bundle made up of thousands of individual glass threads, each of which carries a distinct stream of light. By dipping optical fibers in acid, Walt etches them with tens of thousands of microwells, one at the tip of each thread. That effectively makes each fiber into a large array of nanoscale test tubes, each of which is then coated with thousands of protein-capturing antibodies.

The tip of the fiber is dipped into a droplet containing a blood sample and a protein-targeting enzyme. If the protein is present in the blood trapped inside an individual well, it will be captured between the antibody and the enzyme like the meat inside a sandwich. When Walt sends light down the optical fiber, the sandwiched antibody and enzyme undergo a reaction that produces red or yellow fluorescent light. The light travels back up the optical fiber.

By counting how many microwells light up, Walt can determine the concentration of a protein in a blood sample. In an unpublished proof-of-principle experiment, Walt says that his optical-fiber method was able to detect a human cancer biomarker in cow's blood at concentrations 250 times lower than that possible using clinical techniques.

So little is known about the 800 or more remaining blood proteins that fall under current detection limits that scientists can only speculate on their clinical relevance. "We're talking to clinicians to figure out what makes sense to test for," says Walt. Once the company picks target proteins, they'll draw on blood samples archived at hospitals and try to correlate protein levels with clinical outcomes. "Every time a more sensitive technology has become available, it has opened up new diagnostics and led to advances in treatment," says Walt.

Early detection can have a downside. "We don't want to scare people by telling them, 'You have an early tumor,'" says Walt. "It may be that the immune system takes care of small tumors." So any potential biomarkers will have to be carefully validated. But even if the new method only leads to a test for a single cancer biomarker, Walt hopes that it will improve survival rates for a large number of people.

"We believe this has the potential for transforming diagnostics," Walt says.

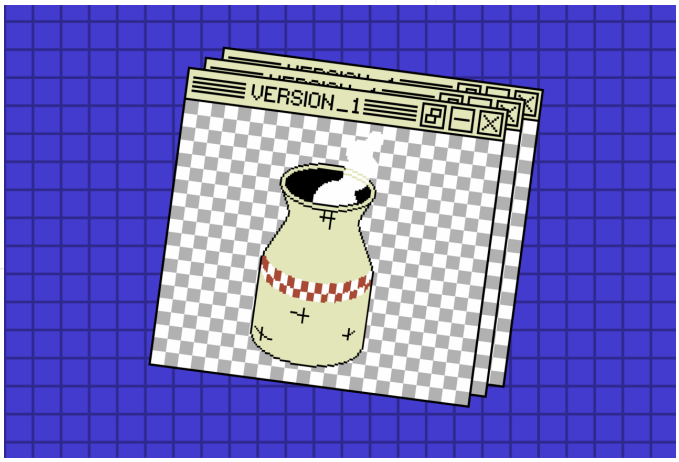
**by Katherine Bourzac**

KEEP READING



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000339

# MOST POPULAR




## We did the math on AI's energy footprint. Here's the story you haven't heard.

The emissions from individual AI text, image, and video queries seem small—until you add up what the industry isn't tracking and consider where it's heading next.

**By James O'Donnell & Casey Crownhart**



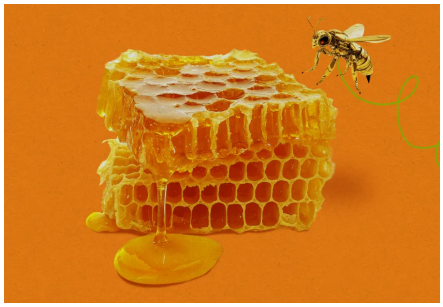
## The US has approved CRISPR pigs for food

Pigs whose DNA makes them resistant to a virus could be the first big consumer product using gene editing.

**By Antonio Regalado**



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000340



## Cyberattacks by AI agents are coming

Agents could make it easier and cheaper for criminals to hack systems at scale. We need to be ready.

**By Rhiannon Williams**



## How the federal government is tracking changes in the supply of street drugs

The National Institute of Standards and Technology's new harm reduction initiative is helping prevent needless deaths.

**By Adam Bluestein**



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000341

STAY CONNECTED

Illustration by Rose Wong

## Get the latest updates from MIT Technology Review

Discover special offers, top stories, upcoming events, and more.

Enter your email

Privacy Policy

### The latest iteration of a legacy

Founded at the Massachusetts Institute of Technology in 1899, MIT Technology Review is a world-renowned, independent media company whose insight, analysis, reviews, interviews and live events explain the newest technologies and their commercial, social and political impact.

READ ABOUT OUR HISTORY

### Advertise with MIT Technology Review

Elevate your brand to the forefront of conversation around emerging technologies that are radically transforming business. From event sponsorships to custom content to visually arresting video storytelling, advertising with MIT Technology Review creates opportunities for your brand to resonate with an unmatched audience of technology and business elite.

ADVERTISE WITH US



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000342

About us

Careers

Custom content

Advertise with us

International Editions

Republishing

MIT Alumni News

Help & FAQ

My subscription

Editorial guidelines

Privacy policy

Terms of Service

Write for us

Contact us



© 2025 MIT Technology Review



Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000343

Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000344

**EX-1011B** Bourzac, K. (May 13, 2008). Next-Generation Diagnostics: A startup can detect tiny traces of cancer markers in blood samples, MIT Technology Review. ("*Bourzac*").

https://web.archive.org/web/20080513175840/http://www.technologyreview.com/Biztech/2
120%
http://www.technologyreview.com/Biztech/20760/
Go
16 capture
13 May 2008
APR MAY JUN
13
2007 2008 2009
About this capture



Advertisement

[1] 2 Next »

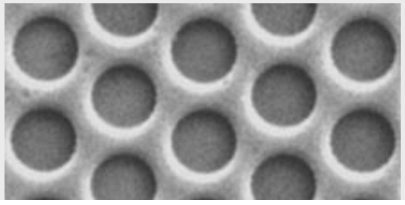
Tuesday, May 13, 2008

# Next-Generation Diagnostics

## A startup can detect tiny traces of cancer markers in blood samples.

By Katherine Bourzac

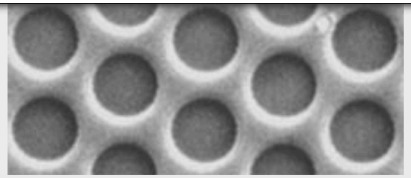
Audio » Share » Favorite Print E-mail



One of the loftier dreams of personalized medicine is to detect and eliminate tumors before they become life threatening--before they are even visible on medical images. Now a Cambridge, MA, startup called Quanterix is developing an extremely sensitive protein-detection technology that can count single molecules--and could potentially detect the trace amounts of characteristic proteins that tiny tumors release into the blood.

Advertisement
Advertisement
Circle of Innovation
PitneyBowes
THE VIDEO YOU ARE TRYING TO WATCH IS CURRENTLY UNAVAILABLE. PLEASE CHECK BACK SOON.
Click here for additional information on Pitney Bowes customer centered innovation process

Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000346



**Lab on a tip:** Wells carved into the tip of an optical fiber allow researchers to detect single proteins in blood samples. Each well in this image is about 2.5 micrometers in diameter and sits at the tip of an individual thread of an optical fiber.
Credit: Quanterix

**MULTIMEDIA**

Watch proteins light up inside an optical fiber.

"The premise is to get diagnostics to the most sensitive level possible," says David Walt, a chemist and Howard Hughes Medical Institute professor at Tufts University, who developed the Quanterix technology. Trace proteins in the blood could also reveal early signs of heart disease, Alzheimer's, and other ailments, and enable noninvasive fetal diagnostics.

"If we could understand the baseline levels of proteins in the serum, it could be used to track the integrated health of a person over the course of life," says Christopher Love, a chemical-engineering professor at MIT who is not involved with Quanterix.

With current clinical technologies, hospital labs can detect only the most abundant proteins--only a quarter of all those known to be present in the blood. Because proteins are present in the blood at a range of different concentrations spanning about 16 orders of magnitude, abundant proteins mask the rare ones. "It's like trying to look for a slightly different piece of hay in the haystack," says Forest White, a biological engineer at MIT.

The current detection limit is 10 picograms of protein per milliliter of blood. But Walt has developed a detection technique that allows him to count individual protein molecules present in the blood using specially treated optical fibers. A single optical fiber is a bundle made up of thousands of individual glass threads, each of which carries a distinct stream of light. By dipping optical fibers in acid, Walt etches them with tens of thousands of microwells, one at the tip of each thread. That effectively makes each fiber into a large array of nanoscale test tubes, each of which is then coated with thousands of protein-capturing antibodies.

The tip of the fiber is dipped into a droplet containing a blood sample and a protein-targeting enzyme. If the protein is present in the blood trapped inside an individual well, it will be captured between the antibody and the enzyme like the meat inside a sandwich. When Walt sends light down the optical fiber, the sandwiched antibody and enzyme undergo a reaction that produces red or yellow fluorescent light. The light


**Current Issue**




**An Electrifying Startup**
A new lithium-ion battery from A123 Systems could help electric cars and hybrids come to dominate the roads.
- Subscribe
  Save 41%
- Table of Contents
- MIT News

**Magazine Services**
- Gift Subscription
- Digital Subscription
- Reprints, Back Issues, Customer Service

**Career Resources**
Visit the Job Board and Resource Center to move your career to the next level.

**MIT Technology Insider**
Stories and breaking news from inside MIT about the latest research, innovations, and startups--in a convenient monthly e-newsletter. Subscribe today

Advertisement

**More Technology News from Forbes**
What Your Cellphone Says About You
Ten Gadgets For Your Geeky Mom
Top 10 Digital Cameras For Travelers


Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000347

sandwiched antibody and enzyme undergo a reaction that produces red or yellow fluorescent light. The light travels back up the optical fiber.

[1] 2 Next »

## Comments

Add New Thread

## Related Articles

- Biologists Enlist Online Gamers 05/08/2008
- Biology's Next Breakthroughs 05/02/2008
- Lab-on-a-Tip 07/01/1998

Top 10 Digital Cameras For Travelers
Maker's Faire Inventing Delights
Eight Grand Theft Auto IV Shockers

## Wire Stories

Stung by cyber warfare, Estonia, NATO allies to sign deal on cyber defense center
British IT watchdog complains to EU about Microsoft's OOXML format
Disney to create laboratory to test high-tech advertising for ABC, ESPN
Joint Sprint, Clearwire network could boost consumer power
Apple says iPhone sold out online in US and UK, likely signaling next-generation is on the way

Advertisement

Advertisement

## Local Business Directory

401K Plans
Accounting
Advertising & Marketing
Air Charter
Air Travel
Annuities
Answering Services
Antivirus / Antispam Solutions
Apartment Loans

Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000348

https://web.archive.org/web/20080517045755/http://www.technologyreview.com/Biztech/2
120%
http://www.technologyreview.com/Biztech/20760/page2/
Go
APR MAY JAN
17
3 captures
17 May 2008
2007 2008 2009
About this capture



Advertisement

« Back 1 [2]

Tuesday, May 13, 2008

# Next-Generation Diagnostics

## Continued from page 1

By Katherine Bourzac

Audio » Share » Favorite Print E-mail

By counting how many microwells light up, Walt can determine the concentration of a protein in a blood sample. In an unpublished proof-of-principle experiment, Walt says that his optical-fiber method was able to detect a human cancer biomarker in cow's blood at concentrations 250 times lower than that possible using clinical techniques.

Advertisement

Current Issue




An Electrifying Startup
A new lithium-ion battery from A123 Systems could help electric cars and hybrids come to dominate the roads.
• Subscribe
Save 41%
• Table of Contents
• MIT News

Magazine Services | Career Resources

Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000349

So little is known about the 800 or more remaining blood proteins that fall under current detection limits that scientists can only speculate on their clinical relevance. "We're talking to clinicians to figure out what makes sense to test for," says Walt. Once the company picks target proteins, they'll draw on blood samples archived at hospitals and try to correlate protein levels with clinical outcomes. "Every time a more sensitive technology has become available, it has opened up new diagnostics and led to advances in treatment," says Walt.

Early detection can have a downside. "We don't want to scare people by telling them, 'You have an early tumor,'" says Walt. "It may be that the immune system takes care of small tumors." So any potential biomarkers will have to be carefully validated. But even if the new method only leads to a test for a single cancer biomarker, Walt hopes that it will improve survival rates for a large number of people.

"We believe this has the potential for transforming diagnostics," Walt says.

« Back 1 [2]


- Gift Subscription
- Digital Subscription
- Reprints, Back Issues, Customer Service

Visit the Job Board and Resource Center to move your career to the next level.

**MIT Technology Insider**

Stories and breaking news from inside MIT about the latest research, innovations, and startups--in a convenient monthly e-newsletter. Subscribe today

Advertisement

**More Technology News from Forbes**

Gadgets For Stopping Identity Theft

Companies That Profit From Your Data

10 Cool Wii Games

Eight Ways To Hack The Web

Cyber Attack Hot Spots

**Wire Stories**

High-tech workers meet haute cuisine in cafeterias

Group agrees on liability for GMO damage

South Korea's LG Display says it plans to spend nearly US$1 billion to raise LCD output

EU warns Google over photos on Street View

Microsoft in deal on European environment data


Fujirebio Diagnostics, Inc. v. Quanterix Corp.
EX-1043
000350