

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

10X GENOMICS, INC,

Petitioner,

v.

PARSE BIOSCIENCES, INC.

Patent Owner

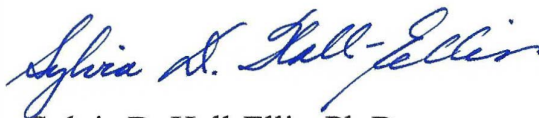
IPR2023-XXXXX

U.S. PATENT NO. 10,155,981

DECLARATION OF SYLVIA D. HALL-ELLIS, Ph.D.

Dated: April 17, 2023

By:



Sylvia D. Hall-Ellis, Ph.D.

I, Sylvia D. Hall-Ellis, declare as follows:

I. INTRODUCTION

1. My name is Sylvia D. Hall-Ellis. I have been retained as an expert by Parse Biosciences, Inc., the Petitioner, in the above-captioned *inter parte* review.

2. I have written this Declaration at the request of the Petitioner to provide my expert opinion regarding the authenticity and public availability of a publication (“McCloskey”). My Declaration sets forth my opinions in detail and provides the basis for my opinions regarding the authenticity and public availability of McCloskey. If called to testify in the above-captioned proceeding, I will testify regarding the opinions and bases set forth below.

3. I reserve the right to supplement or amend my opinions, and bases for them, in response to any additional evidence, testimony, discovery, argument, and/or other additional information that may be provided to me after the date of this Declaration.

4. I am being compensated for my time spent working on this matter at my normal consulting rate of \$350 per hour, plus reimbursement for any additional reasonable expenses. My compensation is not in any way tied to the content of this Declaration, the substance of my opinions, or the outcome of this proceeding. I have no other interests in this proceeding or with any of the parties.

5. All the materials that I considered and relied upon are discussed explicitly in this Declaration.

II. QUALIFICATIONS

6. I am currently an Adjunct Professor in the School of Information at San José State University in San José, California. I obtained a Master of Library Science from the University of North Texas in 1972 and a Ph.D. in Library and Information Science from the University of Pittsburgh in 1985. Over the last fifty years, I have held various positions in the field of library and information resources. I was first employed as a librarian in 1966 and have been involved in the field of library sciences since, holding numerous positions.

7. I am a member of the American Library Association (ALA) and its Association for Library Collections & Technical Services (ALCTS) Division, and I served on the Committee on Cataloging: Resource and Description (which wrote the new cataloging rules) and as the chair of the Committee for Education and Training of Catalogers and the Competencies and Education for a Career in Cataloging Interest Group. I also served as the founding Chair of the ALCTS Division's Task Force on Competencies and Education for a Career in Cataloging. Additionally, I have served as the Chair for the ALA Office of Diversity's Committee on Diversity, as a member of the REFORMA National Board of Directors, as a member of the Editorial Board for the ALCTS premier cataloging

journal, *Library Resources and Technical Services*, and as a Co-Chair of the Membership Committee for the Library Research Round Table (LRRT) of the American Library Association. Currently I serve as a member of the LRRT Nominating Committee.

8. I have also given over one hundred presentations in the field, including several on library cataloging systems and Machine-Readable Cataloging (“MARC”) standards. My current research interests include library cataloging systems, metadata, and organization of electronic resources.

9. I have been deposed twenty-seven times: (1) *Symantec Corp. v. Finjan, Inc.*, Petition for *Inter Partes Review* of U.S. Patent No. 7,613,926, May 26, 2016, on behalf of Symantec Corp.; (2) *Symantec Corp. v. Finjan, Inc.*, 14-cv-299-HSG (N.D. Cal.), on behalf of Symantec Corp., September 14, 2017; (3) one deposition for ten matters: *Intellectual Ventures I LLC v. AT&T Mobility LLC*; AT&T Mobility II LLC, New Cingular Wireless Services, Inc., SBC Internet Services, Inc., Wayport, Inc., and Cricket Wireless LLC, C.A. No. 12-193 (LPS); *Intellectual Ventures II LLC v. AT&T Mobility LLC*; AT&T Mobility II LLC, New Cingular Wireless Services, Inc., SBC Internet Services, Inc., Wayport, Inc., and Cricket Wireless LLC, C.A. No. 13-1631 (LPS); *Intellectual Ventures I LLC v. T-Mobile USA, Inc. and T-Mobile US, Inc.*, C.A. No. 13-1632 (LPS); *Intellectual Ventures II LLC v. T-Mobile USA, Inc. and T-Mobile US, Inc.*, C.A.

No. 13-1633 (LPS); *Intellectual Ventures I LLC, v. Nextel Operations, Inc., Sprint Spectrum L.P., Boost Mobile, LLC and Virgin Mobile USA, L.P.*, C.A. No. 13-1634 (LPS); *Intellectual Ventures II LLC v. Nextel Operations, Inc., Sprint Spectrum L.P., Boost Mobile, LLC and Virgin Mobile USA, L.P.*, C.A. No. 13-1635 (LPS); *Intellectual Ventures I LLC, v. United States Cellular Corporation*, C.A. No. 13-1636 (LPS); *Intellectual Ventures I LLC v. United States Cellular Corporation*, C.A. No. 13-1637 (LPS); *Intellectual Ventures II LLC v. AT&T Mobility LLC, AT&T Mobility II LLC, New Cingular Wireless Services, Inc.*, C.A. No. 15-799 (LPS); *Intellectual Ventures I LLC v. T-Mobile USA, Inc. and T-Mobile US, Inc.*, C.A. No. 15-800 (LPS), on behalf of AT&T Mobility LLC; AT&T Mobility II LLC, Boost Mobile, LLC Cricket Wireless LLC, Nextel Operations, Inc., New Cingular Wireless Services, Inc., SBC Internet Services, Inc., Sprint Spectrum L.P., T-Mobile USA, Inc., T-Mobile US, Inc., United States Cellular Corporation Virgin Mobile USA, L.P., and Wayport, Inc., November 15, 2016; (4) *Hitachi Maxell, LTD., v. Top Victory Electronics (Taiwan) Co. Ltd., et al.*, 2:14-cv-1121 JRG-RSP (E.D. Texas), on behalf of Top Victory Electronics (Taiwan) Co. LTD, *et. al.*, January 20, 2016; (5) *Sprint Spectrum, L.P. v. General Access Solutions, Ltd.*, Petition for *Inter Partes Review* of U.S. Patent No. 7,173,916, on behalf of Sprint Spectrum L.P., July 13, 2018; (6) *Nichia Corporation v. Vizio, Inc.*, 8:16-cv-00545; on behalf of Vizio, Inc., October 12, 2018; (7) *Intellectual Ventures I*

LLC, v. T-Mobile USA, Inc., T-Mobile US, Inc., Ericsson Inc., and Telefonaktiebolaget LM Ericsson, 2:17-cv-00557 (JRG), on behalf of T-Mobile USA, Inc., T-Mobile US, Inc., Ericsson Inc., and Telefonaktiebolaget LM Ericsson, October 19, 2018; (8) *Pfizer, Inc. v. Biogen, Inc.*, Petition for *Inter Partes Review* of U.S. Patent No. 8,821,873, on behalf of Pfizer, November 3, 2018; (9) *Finjan, Inc. v. ESET, LLC and ESET SPOL. S.R.O.*, 3:17-cv-00183-CAB-BGS, on behalf of ESET, January 15, 2019; (10) *Finjan, Inc. v. Cisco Systems, Inc.*, 5:17-cv-00072-BLF-SVK, on behalf of Cisco Systems, Inc., September 6, 2019; (11) *Facebook, Inc., Instagram, LLC and Whatsapp Inc. v. Blackberry Limited*, Petition for *Inter Partes Review* of U.S. Patent No. 9,349,120 B2, on behalf of Facebook, Inc., Instagram, LLC and Whatsapp Inc. December 20, 2019; (12) *3Shape A/S and 3Shape Inc. v. Align Technology, Inc.*, Petition for *Inter Partes Review* of U.S. Patent No. 7,156,661, IPR 2020-00222 and IPR 2020-00223, August 10, 2020, on behalf of 3Shape A/S and 3Shape Inc.; (13) *Finjan Inc. v. Rapid7, Inc. and Rapid7 LLC*, Northern District of Delaware; 1:18-cv-01519-MN, September 15, 2020; (14) *VLSI Technology LLC v. Intel Corporation*, Western District of Texas, 6:19-cv-00254, 6:19-cv-00255, 6:19-cv-00256, on behalf of Intel Corporation, September 23, 2020; (15) *Finjan Inc. v. Sonicwall, Inc.*, Northern District of California, 5:17-cv-04467-BLF-HRL, on behalf of Sonicwall, Inc., October 27, 2020; (16) *VLSI Technology, LLC v. Intel*

Corporation, District of Delaware, 1:18-cv-00966-CFC-CJB, February 5, 2021, on behalf of the Intel Corporation; (17) *Unified Patents, LLC v. Good Kaisha IP Bridge 1*, Petition for *Inter Partes Review* of U. S. Patent 7,817,868, February 11, 2021, on behalf of Unified Patents; (18) *Finjan, Inc. v. Qualsys, Inc.*, Northern District of California, 4:18-cv-07229-YGR, March 1, 2021, on behalf of Qualsys, Inc.; (19) *Qualcomm, Inc. v. Monterey Research LLC*, Petition for *Inter Partes Review* of U. S. Patent 6,534,805, May 6, 2021, on behalf of Qualcomm, Inc.; (20) *Hulu, LLC v. Sound View Innovations, LLC*, Petition for *Inter Partes Review* of U. S. Patent 5,806,062, May 14, 2021, on behalf of Hulu, LLC; (21) *VLSI Technology LLC v. Intel Corporation*, Western District of Texas, 6:19-cv-00254, 6:19-cv-00255 and 6:19-cv-00256, August 3, 2021, on behalf of Intel Corporation; (22) *Liquidia Technologies, Inc. v. United Therapeutics Corporation*, Petition for *Inter Partes Review* of U. S. Patent 10,716,793 B2, October 20, 2021, on behalf of Liquidia Technologies, Inc.; (23) *EcoFactor, Inc. v. Google, Inc.*, Western District of Texas, 6:20-cv-00075 (ADA), 6:20-0078-ADA, and 6:20-cv-00080 ADA, October 27, 2021, on behalf of Google, Inc.; (24) *Liquidia Technologies, Inc. v. United Therapeutics Corporation*, Petition for *Inter Partes Review* of U. S. Patent 10,716,793 B2, March 11, 2022, on behalf of Liquidia Technologies, Inc.; (25) *Juniper Networks, Inc. v. Swarm Technology LLC*, Petition for *Inter*

Partes Review of U. S. Patent 9,852,004, May 5, 2022, on behalf of Juniper Networks, Inc.; (26) *ParkerVision, Inc. v. Intel Corporation*, Western District of Texas, 6:20-cv-108 (ADA), October 26, 2022, on behalf of the Intel Corporation; and, (27) *CommScope v. TQ Delta*, Petition for *Inter Parties Review* of U. S. Patents 9,094,348 and 10,833,809, February 16, 2023, on behalf of CommScope.

10. My full curriculum vitae is attached as Appendix 1.

III. PRELIMINARIES

A. Scope of Declaration and Legal Standards

11. I am not an attorney and will not offer opinions on the law. I am, however, rendering my expert opinion on the authenticity of the documents referenced herein and on when and how each of these documents was disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art, exercising ordinary diligence, could have located the documents on or after August 20, 2009.

12. I am informed by counsel that a printed publication qualifies as publicly accessible as of the date it was disseminated or otherwise made available such that a person interested in and ordinarily skilled in the relevant subject matter could locate it through the exercise of ordinary diligence.

13. While I understand that the determination of public accessibility under

the foregoing standard rests on a case-by-case analysis of the facts particular to an individual publication, I also understand that a printed publication is rendered “publicly accessible” if it is cataloged and indexed by a library such that a person interested in the relevant subject matter could locate it (*i.e.*, I understand that cataloging and indexing by a library is sufficient, though there are other ways that a printed publication may qualify as publicly accessible). One manner of sufficient indexing is indexing according to subject matter category. I understand that the cataloging and indexing by a single library of a single instance of a particular printed publication is sufficient, even if the single library is in a foreign country. I understand that, even if access to a library is restricted, a printed publication that has been cataloged and indexed therein is publicly accessible so long as a presumption is raised that the portion of the public concerned with the relevant subject matter would know of the printed publication. I also understand that the cataloging and indexing of information that would guide a person interested in the relevant subject matter to the printed publication, such as the cataloging and indexing of an abstract for the printed publication, is sufficient to render the printed publication publicly accessible.

14. I understand that routine business practices, such as general library cataloging and indexing practices, can be used to establish an approximate date on which a printed publication became publicly accessible.

B. Persons of Ordinary Skill in the Art.

15. I am told by counsel that the subject matter of this proceeding relates to methods of analyzing nucleic acid sequences.

16. I have been informed by counsel that a “person of ordinary skill in the art at the time of the invention” (“POSITA”) is a hypothetical person who is presumed to be familiar with the relevant field and its literature at the time of the inventions. This hypothetical person is also a person of ordinary creativity, capable of understanding the scientific principles applicable to the pertinent field.

17. I am told by counsel a POSITA would have had a Masters degree and/or Ph.D. in molecular biology, genetics, chemistry, engineering, or a related discipline and at least two years of post-Masters, postdoctoral, or industry experience or (2) a Bachelor of Science in such disciplines and at least five years of academic or industry experience (including any experimental work toward a graduate degree), relating to DNA sequencing technologies, amplification methods, and gene expression analysis.. I understand that a POSITA would have familiarity with associated tools, methods, and techniques including: (1) polynucleotide tagging, (2) amplification, (3) use of tags to overcome amplification bias, (4) single cell analysis, (5) ligation and primer extension, and (6) DNA sequencing. I have been further informed by counsel that a person of ordinary skill in the art would have been familiar with and able to understand the

information known in the art relating to these fields, including the information disclosed in the publication discussed in this Declaration.

18. It is my opinion that such a person would have been engaged in research, learning, study, and practice in the field, and formal instruction so that bibliographic resources relevant to his or her research would be familiar. After August 20, 2009, such a person would have had access to a vast array of long-established print resources in the field as well as to a rich set of online resources providing indexing information, abstracts, and full text services.

IV. LIBRARY PROFESSIONAL PRACTICES

19. In preparing this Declaration, I used authoritative databases, such as the OCLC bibliographic database, the Library of Congress Online Catalog, and the Library of Congress Subject Authorities, to confirm citation details of the various publications discussed. Unless I note otherwise below in reference to a specific serial publication, it is my expert opinion that this standard protocol was followed for the serial publication discussed below.

20. *Indexing.* A researcher may discover material relevant to his or her topic in a variety of ways. One common means of discovery is to search for relevant information in an index of periodicals and other publications. Having found relevant material, the researcher will then normally obtain it online, look for it in libraries, or purchase it from the publisher, a bookstore, a document delivery

service, or other provider. Sometimes, the date of a document's public accessibility will involve both indexing and library date information. However, date information for indexing entries is often unavailable. This is especially true for online indices.

21. Indexing services use a wide variety of controlled vocabularies to provide subject access and other means of discovering the content of documents. The Library of Congress Subject Authorities includes standard forms of terms and cross references that are included in bibliographic records. Subject headings are terms that an individual seeking a document regardless of format can enter in the search bar of the online catalog. Subjects also connect an authenticated term (one included in the Library of Congress subject headings list) with related, broader, and narrower terms. The formats in which these access terms are presented vary from service to service.

22. Online indexing services commonly provide bibliographic information, abstracts, and full-text copies of the indexed publications, along with a list of the documents cited in the indexed publication. These services also often provide lists of publications that cite a given document. A citation of a document is evidence that the document was publicly available and in use by researchers no later than the publication date of the citing document. Prominent indexing services include *Scopus*, the *IEEE Xplore* database, the *ACM Digital Library*, *Google Scholar*, and the *Internet Archive*.

V. ONLINE LIBRARY CATALOGS

23. Learning to use an online library catalog begins in elementary school and continues through high school and post-secondary studies. Undergraduate students further develop their skills to use the online catalog at the academic institution where they are studying through information literacy instruction which is provided by professional reference and user experience librarians. The skills required to search, identify, and obtain the resources identified in this declaration are fundamental to using the online catalogs in libraries and information centers. Therefore, a POSITA who has attained the undergraduate and/or graduate educational levels described above (see paragraphs 17-18) possesses the searching and retrieval skills needed to search library catalogs.

24. Professional catalog and metadata librarians prepare and enhance MARC records to provide points of access for each item in the library collection. Using a set of internationally adopted guidelines, rules for the assignment of classification numbers, and the assignment of subject headings from standardized lists, taxonomies, folksonomies, locally developed lists. An information seeker (including POSITAs) can search the online library catalog in a number of ways to identify a specific item or resources on a defined topic.

25. The continued development of the software that supports integrated online library catalogs resulted in the potential to search by an individual creator or

author, title proper or variant title, a series that contains the desired item, subjects, corporate bodies responsible in part for the creation of an item, or standard identification numbers associated with the item (e.g., International Standard Book Numbers (ISBN), International Standard Serial Numbers (ISSN), and Publisher's Numbers). Each of these data elements appears in a prescribed location within the MARC framework so that the software can parse, index, and display data elements resulting from a user-initiated search.

VI. LIBRARY CATALOGING PRACTICES AND MARC RECORDS

26. I am fully familiar with the library cataloging standard known as the MARC standard, which is an industry-wide standard method of storing and organizing library catalog information.¹ MARC was first developed in the 1960s by the Library of Congress. A MARC-compatible library is one that has a catalog consisting of individual MARC records for each of its items. Today, MARC is the primary communications protocol for the transfer and storage of bibliographic metadata in libraries.²

¹ The full text of the standard is available from the Library of Congress at <http://www.loc.gov/marc/bibliographic/> (last visited March 2, 2023).

² Almost every major library in the world is MARC-compatible. *See, e.g., MARC Frequently Asked Questions (FAQ)*, Library of Congress, <https://www.loc.gov/marc/faq.html> (last visited March 2, 2023) (“MARC is the

27. MARC is a framework into which descriptive bibliographic data are transcribed to interact with the software in online library catalogs to provide access to books, journals, and other resources in the collection. The bibliographic data provide points of access and can be searched by a POSITA to identify and obtain resources in the library collection. An information seeker (or POSITA) can search a local online library catalog or the holdings of a group of libraries in a state or region or in the global catalog WorldCat.

28. MARC records are not designed for public viewing. Although a significant number of libraries provide access to the MARC version of a bibliographic record, the public display is designed to show information in a succinct manner that is quickly understood and useful to the information seeker. Libraries determine the default search for the online catalog to make the entry of search terms efficient and result in a successful search. Information seekers can enter a keyword, title, author, or standard number for the item. Libraries may also

acronym for Machine-Readable Cataloging. It defines a data format that emerged from a Library of Congress-led initiative that began nearly fifty years ago. It provides the mechanism by which computers exchange, use, and interpret bibliographic information, and its data elements make up the foundation of most library catalogs used today.”). MARC is the ANSI/NISO Z39.2-1994 (reaffirmed 2016) standard for Information Interchange Format.

provide a search capability called “Summon” that allows the information seeker to enter known information about the item to conduct a search.

29. Since at least the early 1970s and continuing to the present day, MARC has been the primary communications protocol for the transfer and storage of bibliographic metadata in libraries.³ As explained by the Library of Congress:

You could devise your own method of organizing the bibliographic information, but you would be isolating your library, limiting its options, and creating much more work for yourself. Using the MARC standard prevents duplication of work and allows libraries to better share bibliographic resources. Choosing to use MARC enables libraries to acquire cataloging data that is predictable and reliable. If a library were to develop a “home-grown” system that did not use MARC records, it would not be taking advantage of an industry-wide standard whose primary purpose is to foster communication of information.

Using the MARC standard also enables libraries to make

³ A complete history of the development of MARC can be found in *MARC: Its History and Implications* by Henrietta D. Avram (Washington, DC: Library of Congress, 1975) and available online from the Hathi Trust (<https://babel.hathitrust.org/cgi/pt?id=mdp.39015034388556;view=1up;seq=1>; last visited March 2, 2023).

use of commercially available library automation systems to manage library operations. Many systems are available for libraries of all sizes and are designed to work with the MARC format. Systems are maintained and improved by the vendor so that libraries can benefit from the latest advances in computer technology. The MARC standard also allows libraries to replace one system with another with the assurance that their data will still be compatible.

Why Is a MARC Record Necessary? LIBRARY OF CONGRESS.⁴

30. Thus, almost every major library in the world is MARC-compatible. See, e.g., *MARC Frequently Asked Questions (FAQ)*, LIBRARY OF CONGRESS.⁵ (“MARC is the acronym for MACHine-Readable Cataloging. It defines a data format that emerged from a Library of Congress-led initiative that began fifty years ago. It provides the mechanism by which computers exchange, use, and interpret bibliographic information, and its data elements make up the foundation of most library catalogs used today.”). MARC is the ANSI/NISO Z39.2-1994 standard (reaffirmed in 2016) for Information Interchange Format. The full text of the standard is available from the Library of Congress.⁶

31. Examining the MARC records for a specific item reveals the

⁴ <http://www.loc.gov/marc/umb/um01to06.html#part2>

⁵ <https://www.loc.gov/marc/faq.html>

⁶ <http://www.loc.gov/marc/bibliographic/>

comprehensive data transcribed about a particular item at the time that cataloging and classification occurred. In addition to the creator, title, subjects, and standard numbers, additional information may provide additional and relevant data depending on the type of resource. Understanding the full extent of bibliographic data for an item and the points of access associated with it provide essential information that can be used to determine the indexing and public availability for documents described in this declaration.

32. A MARC record comprises several fields, each of which contains specific data about the work. Each field is identified by a standardized, unique, three-digit code corresponding to the type of data that follow. For example, a work's title is recorded in Field 245; the primary author of the work is transcribed in Field 100; an item's International Standard Book Number ("ISBN") consisting of ten or thirteen digits is transcribed in Field 020; an item's International Standard Serial Number ("ISSN") is transcribed in Field 022; the Library of Congress classification notation is recorded in Field 050; and the publication date is recorded in Field 260 under the subfield "c." If a work is a periodical, then its publication frequency is recorded in Field 310, and the publication dates (e.g., the first and last publication) are recorded in Field 362, which is also referred to as the enumeration/chronology field.⁷

⁷ <http://www.loc.gov/marc/bibliographic/bd3xx.html>

33. The library that created the record is recorded in Field 040 in subfield “a” with a unique library code. When viewing the MARC record online via Online Computer Library Center’s (“OCLC”) bibliographic database, hovering over this code with the mouse reveals the full name of the library. I used this method of “mousing over” the library codes in the OCLC database to identify the originating library for the MARC records discussed in this Declaration. Where this “mouse over” option was not available, I consulted the Directory of OCLC Libraries to identify the institution that created the MARC record.⁸

34. MARC records also include several fields that include subject matter classification information. An overview of MARC record fields is available through the Library of Congress.⁹ For example, 6XX fields are termed “Subject Access Fields.”¹⁰ Among these, for example, is the 650 field; this is the “Subject Added Entry – Topical Term” field.¹¹ The 650 field is a “[s]ubject added entry in which the entry element is a topical term.” These entries “are assigned to a bibliographic record to provide access according to generally accepted thesaurus-building rules (e.g., *Library of Congress Subject Headings* (LCSH), *Medical*

⁸ <https://www.oclc.org/en/contacts/libraries.html>

⁹ <http://www.loc.gov/marc/bibliographic/>

¹⁰ <http://www.loc.gov/marc/bibliographic/bd6xx.html>

¹¹ <http://www.loc.gov/marc/bibliographic/bd650.html>

Subject Headings (MeSH)).” *Id.* Further, MARC records include call numbers, which themselves include a classification number. For example, the 050 field is the “Library of Congress Call Number.”¹² A defined portion of the Library of Congress Call (LCC) Number is the classification number, and “source of the classification number is *Library of Congress Classification* and the *LC Classification-Additions and Changes*.” Thus, included in the 050 field is a subject matter classification. Further, the 082 field is the “Dewey Decimal Call Number.”¹³ A defined portion of the Dewey Decimal Call (DDC) Number is the classification number, and “source of the classification number is the *Dewey Decimal Classification and Relative Index*.” Thus, included in the 082 field is a subject matter classification. Each item in a library has a single classification number. A library selects a classification scheme (*e.g.*, the Library of Congress classification scheme just described or a similar scheme such as the Dewey Decimal classification scheme) and uses it consistently. When the Library of Congress assigns the LCC classification number, it appears as part of the 050 field. When the Library of Congress assigns the DDC classification number, it appears as part of the 082 field. If a local library assigns the classification number, it appears in a 090 field. In either scenario, the MARC record includes a classification number that

¹² <http://www.loc.gov/marc/bibliographic/bd050.html>

¹³ <http://www.loc.gov/marc/bibliographic/bd082.html>

represents a subject matter classification.

35. The OCLC was created “to establish, maintain and operate a computerized library network and to promote the evolution of library use, of libraries themselves, and of librarianship, and to provide processes and products for the benefit of library users and libraries, including such objectives as increasing availability of library resources to individual library patrons and reducing the rate of rise of library per-unit costs, all for the fundamental public purpose of furthering ease of access to and use of the ever-expanding body of worldwide scientific, literary and educational knowledge and information.”¹⁴ Among other services, OCLC and its members are responsible for maintaining the WorldCat database (<http://www.worldcat.org/>), used by independent and institutional libraries throughout the world.

36. OCLC also provides its members online access to MARC records through its OCLC bibliographic database. When an OCLC member institution acquires a work, it creates a MARC record for this work in its computer catalog system in the ordinary course of its business. MARC records created at the Library of Congress are tape-loaded into the OCLC database through a subscription to

¹⁴ Third Article, Amended Articles of Incorporation of OCLC Online Computer Library Center, Incorporated (available at <https://www.oclc.org/content/dam/oclc/membership/articles-of-incorporation.pdf>).

MARC Distribution Services daily or weekly. Once the MARC record is created by a cataloger at an OCLC member institution or is tape-loaded from the Library of Congress, the MARC record is then made available to any other OCLC members online, and therefore made available to the public. Accordingly, once the MARC record is created by a cataloger at an OCLC member institution or is tape-loaded from the Library of Congress or another library anywhere in the world, any publication corresponding to the MARC record has been cataloged and indexed according to its subject matter such that a person interested in that subject matter could, with reasonable diligence, locate and access the publication through any library with access to the OCLC bibliographic database or through the Library of Congress.

37. When an OCLC member institution creates a new MARC record, OCLC automatically supplies the date of creation for that record. The date of creation for the MARC record appears in the fixed Field (008), characters 00 through 05. The MARC record creation date reflects the date on which, or shortly after which, the item was first acquired or cataloged. Initially, Field 005 of the MARC record is automatically populated with the date the MARC record was created in year, month, day format (YYYYMMDD) (some of the newer library catalog systems also include hour, minute, second (HHMMSS)). Thereafter, the library's computer system may automatically update the date in Field 005 every

time the library updates the MARC record (*e.g.*, to reflect that an item has been moved to a different shelving location within the library). Field 005 is visible when viewing a MARC record via an appropriate computerized interface, but when a MARC record is printed to hardcopy, no “005” label appears. The initial Field 005 date (*i.e.*, the date the MARC record was created) does appear, however, next to the label “Entered.”¹⁵ The date upon which the most recent update to Field 005 occurred also appears, next to the label “Replaced.” Thus, when an item’s MARC record has been printed to hardcopy—as is the case with the exhibit to this Declaration—the date reflected next to the label “Entered” is necessarily on or after the date the library first cataloged and indexed the underlying item.

38. Once one library has cataloged and indexed a publication by creating a MARC record for that publication, other libraries that receive the publication do not create additional MARC records—the other libraries instead rely on the original MARC record. They may update or revise the MARC record to ensure accuracy, but they do not replace or duplicate it. This practice does more than save libraries from duplicating labor. It also enhances the accuracy of MARC records.

¹⁵ Field 005 is visible when viewing a MARC record via an appropriate computerized interface. But when a MARC record is printed directly to hardcopy from the OCLC database, the “005” label is not shown. The date in the 005 field instead appears next to the label “Replaced.”

Further, it allows librarians around the world to know that a particular MARC record is authoritative (in contrast, a hypothetical system wherein duplicative records were created would result in confusion as to which record is authoritative).

39. Catalogers can create MARC records for all types of print, online, and digital resources. The date of creation of the MARC record by a cataloger at an OCLC member institution reflects when the underlying item is accessible to the public. Upwards of two-thirds to three-quarters of book sales to libraries come from a jobber or wholesaler for online and print resources. These resellers make it their business to provide books to their customers as fast as possible, often providing turnaround times of only a single day after publication. Libraries purchase a significant portion of the balance of their books directly from publishers themselves, which provide delivery on a similarly expedited schedule. In general, libraries make these purchases throughout the year as the books are published and shelve the books as soon thereafter as possible to make the books available to their patrons. Thus, books are generally available at libraries across the country within just a few days of publication.

40. *Journals.* MARC records that cover serial publications include both serially-published monographs and journals. OCLC hosts MARC records for more than 320 million serial publications. Serial publications are those publications that have the same collective title but are intended to be continued indefinitely with

enumeration such as a volume or issue number (*e.g.*, magazines, journals, etc.). In the OCLC bibliographic database, the first issue of the serial publication is typically cataloged (*i.e.*, a corresponding MARC record is created), but the date is left open-ended with the use of a punctuation mark such as a dash. OCLC serial publication MARC records represent the entire run of the serial title. With knowledge of the first issue published, future issues can be predicted based on the information provided in the MARC record, for example in field 362. In my extensive professional experience, is it highly unusual for a library to stop collecting and shelving a serial publication prior to the end of its publication run. If a subscription to a serial publication ends its run or is cancelled before the end of its run, the library will denote that it has stopped receiving new volumes by filling in the end date in the MARC record.

41. The handling of printed journal subscriptions is shown on the cover or the first few pages of individual issues. As was the best practice among libraries, issues arrived at a central facility and were immediately received, verified as part of a subscription, checked in, and stamped or labeled with the institution's name and date. Determining that the issue was part of the library subscription ensured that the entire set of publications for the year had been received so that they could be professionally bound and retained. This process also verified that all of the published issues arrived so that the library staff did not have to request or claim an

issue that did not arrive as expected. In large public libraries with branches and multi-campus libraries within academic institutions, the journals were sorted and delivered to the subscribing unit. The new issue was placed in the public area; the older issue was stored so that it remained available.

42. The foregoing process has been standard library practice longer than I have been working in the profession. I first learned the steps in the process in the late 1970s and later supervised it. Although the checking in process has become automated and now links electronically to holdings records for the MARC record for each serial title, the manual placement of a stamp or label and placing the issue in a public area has not changed for 50 years. Unless I note otherwise below in reference to a specific serial publication, it is my expert opinion that this standard protocol was followed for the serial publication discussed below.

VII. “*Encoding PCR Products with Batch-stamps and Barcodes*” by Megan L. McCloskey, Reinhard Stöger, R. Scott Hansen, and Charles D. Laird. EXHIBIT A (“McCloskey”)

43. Attached hereto as Exhibit A is a copy of the journal article “Encoding PCR Products with Batch-stamps and Barcodes” by Megan L. McCloskey, Reinhard Stöger, R. Scott Hansen, and Charles D. Laird (hereafter “McCloskey”). The McCloskey article was published in Volume 45, Number 11/12 of the journal *Biochemical Genetics* and was found in the Linda Hall Library of Science, Engineering & Technology (Kansas City, Missouri). The McCloskey

article appears beginning on page 761 of this issue dated December 2007. Exhibit A is a true and correct copy of the McCloskey article (pages 761-767). Specifically, the text of the article is complete; no pages are missing, and the text on each page appears to flow seamlessly from one page to the next; further, there are no visible alterations to the document. The McCloskey article is also available from the publisher, Springer,¹⁶ through the National Library of Medicine,¹⁷ and through the digital repository *ResearchGate*.¹⁸ The publisher indicates that the McCloskey article was published online on October 23, 2007. Exhibit A was found within the custody of a library – a place where an authentic copy of this journal would likely be. Exhibit A is a true and correct copy in a condition that creates no suspicion about its authenticity.

44. Attached hereto as Attachment 1A is a true and correct copy of the MARC record for the journal *Biochemical Genetics* in the online catalog at the Linda Hall Library of Science, Engineering & Technology. The library ownership is indicated by the presence of the library's code (LHL) in field 049. The library

¹⁶ <https://link.springer.com/article/10.1007/s10528-007-9114-x>

¹⁷ <https://pubmed.ncbi.nlm.nih.gov/17955361/>

¹⁸

https://www.researchgate.net/publication/5891130_Encoding_PCR_Products_with_Batch-stamps_and_Barcodes

continues to update this MARC record and enhanced the MARC record to meet current cataloging rules. The most recent enhancement to Attachment 1A occurred on October 29, 2019, as shown in field 005 (“20191029”). I personally identified and retrieved the MARC record that is Attachment 1A.

45. Based on finding a print copy of Exhibit A in the Linda Hall Library of Science, Engineering & Technology and MARC record in its online library catalog attached as Attachment 1A, it is my opinion that the McCloskey article published in the journal *Biochemical Genetics* was publicly available on or shortly after January 3, 2008, as shown on the cover. Attachment 1A also shows that Exhibit A was catalogued with a descriptor term reading “Biochemical genetics \$v Periodicals” (see Attachment 1B, Library of Congress subject heading sh85014121 and Attachment 1C, Library of Congress subject heading sh85099890) in the 650 field.

46. As noted in the holdings information (362 field), the Linda Hall Library of Science, Engineering & Technology has received the journal *Biochemical Genetics* since June 1967 and continues to receive the publication. In view of the MARC record for Exhibit A, the McCloskey article was publicly available on or shortly after January 3, 2008, because the serial title had been received, cataloged, and indexed in the Linda Hall Library of Science, Engineering & Technology and made part of its online catalog database.

47. Attached hereto as Attachment 1D is a true and correct copy of the MARC record for the journal *Biochemical Genetics* obtained from the OCLC bibliographic database. As previously noted, the library that created the record is recorded in field 040 with a unique library code. For Attachment 1D, that library code is “MUL,” which means that the MARC record for this serial was cataloged as part of the Minnesota Union List of Serials project at the University of Minnesota Libraries (Minneapolis, Minnesota). A cataloger in the University of Minnesota Libraries created OCLC record number 1532961 on August 10, 1975, as shown in the “Entered” field in the MARC record for this exhibit (“19750810”). The library continues to update this MARC record and enhanced the MARC record to meet current cataloging rules. The most recent enhancement to Attachment 1D occurred on November 27, 2022, as shown in the “Replaced” field (“20221127”). I personally identified and retrieved the MARC record that is Attachment 1D. The “BLvl” entry in Attachment 1D is “s,” which indicates that the journal *Biochemical Genetics* is a serial publication. Accordingly, the MARC record for Exhibit A corresponds to the journal *Biochemical Genetics* from the time the serial title began publication and includes the date of the McCloskey article.

48. Attachment 1D includes an entry in field 050 (“QH431 \$b .B54”) (as described above, a subject matter classification number consistent with the Library of Congress classification system (analogous to the Dewey Decimal classification

system)), an entry in field 060 (“W1 \$b BI621”) (a subject matter classification number consistent with the National Library of Medicine classification system (analogous to the Dewey Decimal classification system)), and an entry in field 082 (“575.2/1”) (a subject matter consistent with the Dewey Decimal classification system). Attachment 1D further includes a descriptor term reading “Biochemical genetics \$v Periodicals” (see Attachment 1B, Library of Congress subject heading sh85014121, and Attachment 1C, Library of Congress subject heading sh85099890) in the 650 field. Thus, as of its cataloging, the publication corresponding to the MARC record attached hereto as Attachment 1D was indexed according to its subject matter by virtue of at least four independently sufficient classifications: the field 050 entry, the field 060 entry, the field 082 entry, and the field 650 entry. As of August 10, 1975, the MARC record attached hereto as Attachment 1D was accessible through any library with access to the OCLC bibliographic database or the online catalog at a library that subscribed to the serial, which means that the corresponding publication was publicly available on or before that same date through any library with access to the OCLC bibliographic database or through an individual library.

49. Attachment 1D indicates that the journal *Biochemical Genetics* as cataloged at the University of Minnesota Libraries is currently available from 441 libraries. In view of the above, this issue of the journal *Biochemical Genetics* was

publicly available on or shortly after January 3, 2008, because by that date it had been cataloged and indexed in the University of Minnesota Libraries, made part of the OCLC bibliographic database, and received in the Linda Hall Library of Science, Engineering & Technology. For these reasons, it is my opinion that Exhibit A was published and accessible to the public on or shortly after January 3, 2008.

VIII. SUMMARY OF OPINIONS

50. In view of the foregoing, it is my opinion that the publication described above was publicly available no later than the corresponding date listed in the table below:

Publication	Publicly Available No Later Than
McCloskey, Megan L., Reinhard Stöger, R. Scott Hansen, and Charles D. Laird. "Encoding PCR Products with Batch-stamps and Barcodes." <i>Biochemical Genetics</i> , vol 45, no. 11/12 (December 2007): 761-767.	January 3, 2008

51. I declare that all statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Exhibit A

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Development of a Species-diagnostic SCAR Marker of the Blue Swimming Crab (*Portunus pelagicus*)

Sirawut Klinbunga · Kannika Khetpu ·
Bavornlak Khamnamtong · Piamsak Menasveta



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Introduction

The blue swimming crab, *Portunus pelagicus*, is distributed from the intertidal zone to approximately 50 m depth along the coastlines (Kangas 2000). Commercial fishing of *P. pelagicus* has rapidly expanded in the last few years, resulting in overexploitation of natural *P. pelagicus* in Thailand.

Species-specific markers play important roles in quality control of products of economically important species (Klinbunga et al. 2000). They can be used to verify species origins of various forms of the blue swimming crab products from Thailand to prevent intentional use of the wrong species in canning.

Amplified fragment length polymorphism (AFLP) is a relatively simple method for the identification of genetic markers at different taxonomic levels without the need for knowledge of sequences of the genome under investigation (Vos et al. 1995; Lui and Cordes 2004). Recently, Zhang et al. (2004) applied AFLP to identify and characterize 11 *Lutjanus* species captured in Nansha coral reefs. The similarity

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Encoding PCR Products with Batch-stamps and Barcodes

Megan L. McCloskey · Reinhard Stöger ·
R. Scott Hansen · Charles D. Laird

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Abstract Polymerase chain reaction (PCR) has become the mainstay of DNA sequence analysis. Yet there is always uncertainty concerning the source of the template DNA that gave rise to a particular PCR product. The risks of contamination, biased amplification, and product redundancy are especially high when limited amounts of template DNA are used. We have developed and applied molecular encoding principles to solve this source-uncertainty problem for DNA sequences generated by standard PCR. Batch-stamps specify the date and sample identity, and barcodes detect template redundancy. Our approach thus enables classification of each PCR-derived sequence as valid, contaminant, or redundant, and provides a measure of sequence diversity. We recommend that batch-stamps and barcodes be used when amplifying irreplaceable DNAs and cDNAs available for forensic, clinical, single cell, and ancient DNA analyses.

Keywords PCR · Contamination · Redundancy · Batch-stamp · Barcode · Source DNA · Populations of molecules

Introduction

One essential condition of DNA-based technologies is that sequence information be reliable (Lewontin 1994). Sequence information obtained by PCR, however, always

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carries an element of uncertainty because of risks posed by contamination, biased amplification, and product redundancy. The potential clinical impact of this uncertainty was recently illustrated when “thousands [of people] were given antibiotics and a vaccine ... [and] hospital beds were taken out of commission” after a PCR-based assay incorrectly indicated that 142 individuals were infected with the bacterium that causes whooping cough (Kolata 2007). It is thus apparent that the reliability of PCR-derived assays would be significantly improved if methods were available to distinguish valid from data-corrupting sequences.

We recently addressed this problem by applying molecular encoding principles to hairpin-bisulfite PCR (Miner et al. 2004). This approach is highly successful in identifying valid, double-stranded sequences and their methylation patterns, but requires bisulfite conversion and more template material than is usually available from irreplaceable or single-cell samples (Miner et al. 2004; Laird et al. 2004; Li et al. 1988). We now report a method by which molecular codes are added to single-stranded DNA or cDNA templates, thus providing a solution to the source-uncertainty problem for the standard form of PCR.

Materials and Methods

General Design of the Encoding Oligonucleotide

Our method utilizes an encoding oligonucleotide with five distinct informational regions (Fig. 1): (1) the batch-stamp, unique to each experiment, specifies the DNA source such as the patient or sample identification, and the date of reaction; (2) the random barcode distinguishes among sequences arising from different cell or allele copies; (3) the primer-binding site facilitates specific PCR amplification; (4) the genomic target-binding site targets the locus to be encoded prior to amplification; and (5) the extra 5' bases serve as an internal sentinel of recoding. This encoding oligonucleotide is annealed to denatured DNA and extended by Sequenase (USB) (Fig. 1). Sequenase-extension products are column-filtered to remove any unincorporated, encoding oligonucleotides and amplified using standard PCR protocols (Fig. 1).

Each encoding oligonucleotide is unique because of distinct batch-stamp and random barcode regions. There are several features, however, that are common to all encoding oligonucleotides. Each encoding oligonucleotide is designed to have only the genomic target-binding site available for annealing at 37°C, while the remaining bases are unavailable due to secondary structure. At higher temperatures ($\geq 55^\circ\text{C}$), following Sequenase extension and column purification (see below), this secondary structure melts and makes available a primer-binding site for PCR amplification. Encoding oligonucleotides are between 65 and 75 bases in length and were ordered with PAGE purification from Invitrogen. Upon receipt, encoding oligonucleotides were diluted to 50 μM and stored at -20°C .

Encoding oligonucleotides were usually designed with the batch-stamp located adjacent to the 3' genomic target-binding site (Fig. 1); this is the current standard in the lab. We have also designed and used oligonucleotides for which the positions of the barcode and batch-stamp were reversed. An encoding oligonucleotide of this form was

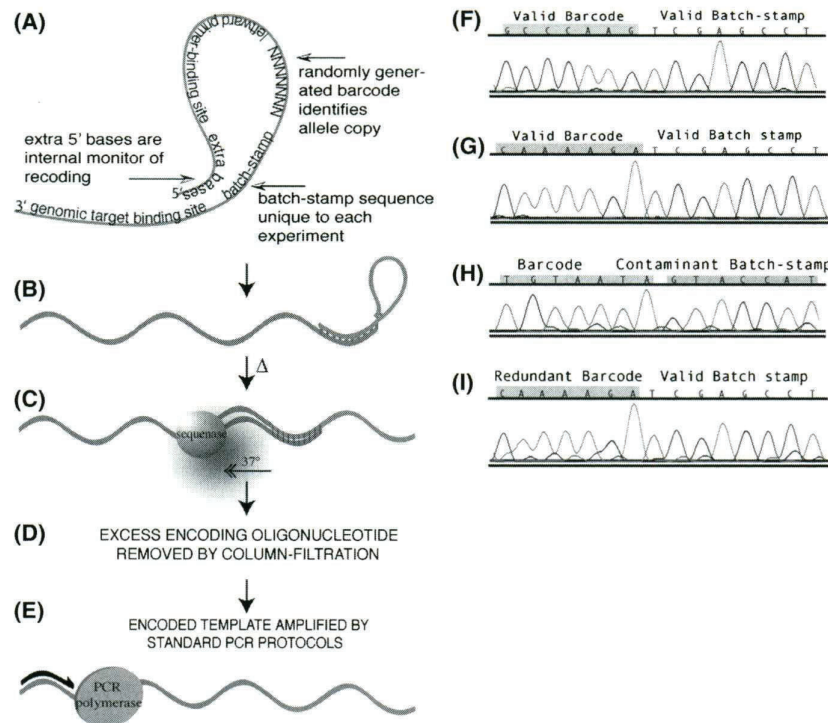


Fig. 1 Encoding oligonucleotide (a) has five distinct regions: a genomic target-binding site, a batch-stamp, a barcode, a primer-binding site for PCR, and extra bases that serve as internal sentinels of recoding as well as tethering the oligonucleotide to itself, thus minimizing nonspecific annealing. Encoding oligonucleotides are annealed to denatured genomic DNA for 15 min at 37°C (b) and extended at 37°C by Sequenase (c). The resulting encoded DNA strands are column-purified with Qiagen QIAquick columns (d) to remove unincorporated encoding oligonucleotides prior to PCR amplification (e). PCR products were sequenced and their encoded information was evaluated. Three classes of encoded sequences recovered from a single PCR amplification are illustrated here. Of 320 sequences analyzed, 299 were valid, each having the correct batch-stamp and a distinct barcode (f and g); 13 were contaminants, having batch-stamps that were used in previous reactions (h); and 8 were redundant, having barcodes and the batch-stamp identical to sequences previously analyzed from the same PCR (i)

used to encode the sequences presented here. This encoding oligonucleotide was ordered as: 5'-TCGAGCACATGCATGTCTTCAAAGTGGAGGCTCGANNNNNN NTCTCTTCAAAGTGGCCTGGGAGC-3'. Note that Fig. 1 illustrates sequences that are the reverse-complement of the ordered, encoding oligonucleotide.

Genomic Target-Binding Site

The genomic target-binding site is designed to be available for annealing at 37°C, as indicated by a $\Delta G \geq 0$ for this region (<http://www.bioinfo.rpi.edu/applications/>

mfold/dna/form1.cgi). For our assays on the *FMRI* locus, the sequence of the genomic target-binding site was (5'-TCTCTTCAAGTGGCCTGGGAGC-3').

Batch-stamp

We have used batch-stamps of different lengths in different experiments. We typically use between six and eight base pairs to encode sample identity and date of reaction. The valid batch-stamp shown in Fig. 1 is (5'-AGGCTCGA-3'). Each different nucleotide sequence yields a unique batch-stamp. The assigned batch-stamp is registered for a specific sample run on a specific date and is used only once.

Barcode

The barcode is a random sequence of the four deoxyribonucleotides. The number of distinguishable barcodes in a population of oligonucleotides used in a reaction is determined by the number of random bases, n . This enables one to distinguish among 4^n allele copies per reaction. We currently use seven nucleotides for the barcode, giving 16,384 possible barcodes for each encoding oligonucleotide.

Primer-binding Site

The primer-binding site of the encoding oligonucleotide is the target of one of the primers used for PCR amplification. It is designed to have no complementarity with competing genomic fragments. The primer-binding site for the oligonucleotide shown in Fig. 1 is 5'-ACATGCATGTCTTCAAAGTGG-3'. The other primer-binding site for PCR amplification is contained in genomic DNA that is copied during the initial Sequenase extension.

Internal Sentinel of Recoding

Extra bases 5' to the primer-binding site serve two functions: (1) these bases would be present in sequences if the oligonucleotide were used inappropriately as a primer during the final round of PCR amplification and thus serve as a sentinel for recoding; (2) these bases contribute to the secondary structure of the oligonucleotide at 37°C. The sentinel bases are chosen to tether the 5' end of the oligonucleotide to a complementary portion of the batch-stamp, thus forming a hairpin loop that exposes only the genomic target-binding site for annealing to template molecules. This design is intended to protect against preferential annealing of encoding oligonucleotides whose random barcodes have some complementarity to, and thus higher stability of hybridization with, the target locus. Nonrandom use of barcodes has been observed when hairpin-loop structures are used to encode double-stranded DNA molecules (Miner et al. 2004). At temperatures appropriate for PCR ($\geq 55^\circ\text{C}$), the secondary structure of the oligonucleotide will melt and expose the primer-binding site. Each oligonucleotide is designed to have a slightly negative ΔG of

folding at 37°C and a positive ΔG at higher temperatures. For the valid oligonucleotide shown in Fig. 1, the extra sentinel bases are (5'-TCGAGC-3').

Sequenase v2.0 (USB) Extension

To reduce the occurrence of secondary structure in the *FMRI* target region, the 5' CGG repeat was removed by restriction enzyme digestion. Human genomic DNA (2.71 μg) was cleaved with *HinfI* (Boehringer Mannheim GmbH) and *AluI* (New England Biolabs), 2 μl each (10,000 units/ml), at 37°C for 1 h, followed by enzyme inactivation at 80°C for 30 min. Digested genomic DNA (0.27 μg) was mixed with 5 $\times$ Sequenase buffer (1.65 μl) and diluted with water to a total volume of 13 μl , denatured at 95°C for 2 min, cooled on ice, and centrifuged for 10 s to avoid condensation. Encoding oligonucleotide, stored at 50 μM at -20°C, was diluted in 1 $\times$ Sequenase buffer to 450 nM, heated to 95°C for 2–5 min, and allowed to self-anneal by gradual cooling to room temperature. Self-annealed oligonucleotides may be prepared prior to use and stored at -20°C. Self-annealed encoding oligonucleotide (2 μl) was added to the digested, denatured genomic DNA and annealed at 37°C for 15 min. During the annealing period, a fresh dNTP mixture was prepared as follows: 3.7 μl each 1 M MgCl_2 and 100 mM DTT, 4.6 μl 100 mM dNTPs, and 4.0 μl each 5 $\times$ Sequenase buffer and water were mixed by pipetting and kept on ice. After the 15 min annealing period, the oligonucleotide-annealed DNA was placed on ice and then microfuged for 10 s. The fresh dNTP mixture (2 μl) was added to the oligonucleotide-annealed DNA. Sequenase v2.0 polymerase (1.5 μl 13 units/ μl , diluted 1:5 in cold 1 $\times$ TE, pH 8, to 2.6 units/ μl) was then added, resulting in a total volume of 18.5 μl . Sequenase extension was carried out at 37°C for at least 30 min, followed by inactivation at 67°C for 30 min.

Contamination of virgin DNA or RNA prior to addition of barcodes and batch-stamps will not be detected with our methods. To minimize the possibility of such contamination, we recommend that the steps of extension and heat inactivation of Sequenase be carried out in heat blocks without lids, rather than in closed PCR machines, coupled with standard pre-PCR precautions such as using separate rooms and dedicated filter-tip pipets and solutions.

Column Purification

Sequenase extension products were purified to remove any unincorporated encoding oligonucleotides using the Qiagen QIAquick PCR purification kit. Columns were used per manufacturer's instructions.

PCR Conditions

Amplification

In an effort to reduce contamination with PCR products from previous experiments, the underside of the heated lid of the PCR thermal-cycler was cleaned with DNAZap

(Ambion) prior to each thermal-cycler use. This treatment of our thermal-cyclers reduced, but did not always prevent, contamination from previous runs.

HotStarTaq Master Mix was used per manufacturer's instructions (Qiagen) with activation at 95°C for 15 min, followed by 35 cycles of denaturation at 95°C for 35 s, annealing at 63°C for 35 s, and extension at 72°C for 40 s; final extension at 72°C was for 4 min. Primers used were 5'-ACATGCATGTCTTCAAAGTGG-3' and 5'-GGATGCATTTGATTTCACGCC-3'.

Sequence Recovery

All PCR products were visualized with ethidium bromide using 1.8% agarose gel electrophoresis; PCR products of the expected size were subcloned and analyzed with TOPO-TA Cloning Kits (Invitrogen). Sequencing reactions were carried out with fluorescent dideoxynucleotides (BigDye Terminator v3.1 Applied Biosystems) in the Comparative Genomics Center, Department of Biology, University of Washington. Each base-call was verified using the electropherogram trace.

Results and Discussion

We applied molecular encoding and standard PCR amplification to the human locus *FMRI*. Valid sequences were identified by their date- and sample-specific batch-stamp and their unique cell or allele copy-specific barcodes (Fig. 1). Contaminant sequences were identified by batch-stamps assigned to separate reactions (Fig. 1). The appearance of sequences bearing inappropriate batch-stamps enabled us to trace contaminating sequences to PCR reactions run either in parallel or previously in our laboratory, even though standard precautions were used to limit contamination. With this sensitive method, contaminant sequences were detected even when control PCR reactions lacking template DNAs appeared negative on agarose gels. This result confirms our previous observations with batch-stamps and barcode sequences amplified by hairpin-bisulfite PCR (Miner et al. 2004).

In addition to distinguishing valid from contaminant sequences, our methods detect redundant sequences arising from the same cellular DNA template (Fig. 1). Redundancy is frequent when template quantities are limited, or when large numbers of product sequences are analyzed. Redundant sequences recovered from the same PCR reaction are readily identified because they are identical in both barcode and batch-stamp. Identifying redundant sequences and removing them from data sets is especially important when analyzing mosaic samples, which occur in both genetic and epigenetic diseases (Cohn et al. 1990; Stöger et al. 1997; Wong et al. 1997). An additional benefit of our method for mosaic samples is that counting sequences with nonredundant barcodes provides a quantitative measure of template diversity.

The accurate validation of sequences requires efficient removal of unincorporated, encoding oligonucleotides, which we ensure by column purification prior to PCR. Without column purification, recoding of PCR products was readily detected.

In our method, incorporation of a free oligonucleotide during PCR could replace an original barcode, producing erroneous and misleading results. We have designed two assays to test for efficient removal of unincorporated oligonucleotides. The first assay is intrinsic to each experiment. Extra bases 5' to the primer-binding site on the encoding oligonucleotide (Fig. 1) mark any product that resulted from use of an unincorporated, encoding oligonucleotide in lieu of the bona fide PCR primer, during the last round of PCR.

Our second assay can detect and quantify recoding in any round of PCR. In control experiments, a “spiking” oligonucleotide with a distinct batch-stamp was added after Sequenase extension and before column purification. After column purification, recoding was significantly less than 1% ($P < 0.05$): among 320 analyzed sequences, none was observed to have the extra 5' bases or to have the batch-stamp of the spiking oligonucleotide. In a control experiment, we verified that the spiking oligonucleotide is efficiently incorporated as a primer in PCR amplification when not removed by column purification.

The encoding concepts described here for standard PCR can markedly increase the reliability of PCR-based sequence information. Although our method adds extra costs to PCR amplification, these costs are modest when compared with those that arise from incorrect diagnoses and decisions such as those reported by Kolata (2007). We recommend that batch-stamps and barcodes be used when amplifying irreplaceable DNAs and cDNAs for forensic, clinical, single cell, and ancient DNA analyses.

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