Exhibit A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re *Ex Parte* Reexamination:	)	Group Art Unit: 3991
U.S. Patent Nos. 6,440,706; 7,824,889; and 7,915,015	)	Docket No. 001107.00989 001107.00990 001107.00988
Control No. 90/012,894, 90/012,895, 90/012,896	)	Confirmation No: 8361
Reexam Filing Date: June 17, 2013	)	Examiner: Bruce R. Campell

For: DIGITAL AMPLIFICATION

DECLARATION OF IE-MING SHIH

1. My name is Ie-Ming Shih. I make this declaration based on my personal knowledge. I am over 21 and otherwise competent to make this declaration.
2. I am currently the Richard W. TeLinde Distinguished Professor in the Department of Gynecology and Obstetrics at the Johns Hopkins University Medical School in Baltimore, MD. I have secondary appointments in the departments of Oncology and Pathology. A copy of my Curriculum vitae is attached as Exhibit 1 that details my training background and research experience.
3. As my *Curriculum vitae* indicates, I obtained my M.D. from Taipei Medical University in Taiwan, obtained my Ph.D. in pathology from University of Pennsylvania. Thereafter I finished my residency training in anatomic pathology and did further clinical and research fellowships at the Johns Hopkins Medical Institutions until I became a member of the faculty.
4. As can be gleaned from my *Curriculum vitae*, I have been engaged in medical

research since about 1989. My current research is focused on cancer genes and markers of gynecological cancers. Throughout my career I have followed new developments in the field by reading of the scientific literature, active research, and interactions with colleagues. Because of my training and experience, I consider myself knowledgeable in various aspects of nucleic acid amplification. This includes technologies that are used to analyze DNA sequences and variations in DNA sequences.

5. In 2004 I co-authored a review article on digital PCR that appeared in Expert Reviews in Molecular Diagnostics, appended as Exhibit 3. I draw from that review as well, as applications of digital PCR more current than at that time with which I am familiar.

6. I have also been informed that Johns Hopkins University (JHU) owns U.S. patents 7,915,015 ("'015 patent") 7,824,889 ("'889 patent") and 6,440,706 ("'706 patent") and has licensed them to LabCorp (Esoterix), and Exact Sciences.

7. I have reviewed the '015 patent, the '889 patent, and the '706 patent, including the original claims and the amendments filed July 9, 2014, (attached as Exhibit 2).

8. I have been asked to review and summarize the state of the digital PCR field. The statements that I make include my reading and interpretation of the statements as represented in the exhibits. The readings and interpretations are my own, and I have no stake in the outcome of the re-examination proceedings.

9. I understand that the "digital PCR" methods described in the claims of the three subject patents involve (1) analysis of two different analytes and (2) comparing

the number of assay samples containing one of the analytes to the number of assay samples containing the other analyte. While I understand that the inventors coined and applied the term "digital PCR" to their methods, I understand that many in this field subsequently adopted the term "digital PCR" and use it more broadly. I have attempted in this declaration to refer only to examples of digital PCR that share the two features stated above, rather than the broader usage.

10. As an illustration of the different ways that the term is often used in the field, Day *et al., Methods 59:*101-107, 2013, describes two types of digital PCR as those which (1) calculate absolute abundance of a target sequence and those which (2) obtain a relative abundance by comparing to an internal reference sequence. Exhibit 12, paragraph spanning pages 101-102. Day refers to the latter type as the more common use. *Ibid.* The latter type is what I understand is described in the claims of the three subject patents.

11. The study of DNA sequence variation is important for many areas of research. Prior to digital PCR, conventional PCR did not allow the identification and quantification of rare molecular genetic changes because conventional PCR amplifies a pool of DNA templates from the starting material. Digital PCR is useful for amplifying a single DNA template from limiting dilution samples, therefore transforming the exponential, analog signals from conventional PCR to linear, digital signals, allowing statistical analysis of the PCR products. Digital PCR has been applied in the quantification of muant alleles and detection of allelic imbalance in clinical specimens, providing a useful molecular diagnostic tool for cancer detection. Exhibit 3, page 46, col. 2, text box. Digital PCR has also been applied in the

quantification of muant alleles and detection of allelic imbalance in fetal abnormalities.

12. In 2004, in our review article, we noted twelve different examples in twelve different scientific publications in the scientific literature in which digital PCR had been used for molecular analysis of clinical samples. These involved detection of cancer mutations, detection of allelic imbalance, detection of loss of heterozygosity, quantitative detection of tumor suppressor gene expression. Exhibit 3, Table 1.

13. The digital PCR technique is especially powerful in experiments requiring quantitative investigation of individual alleles in DNA samples isolated from a mixed cell population. Exhibit 3, page 46, col. 1, last full paragraph.

14. Vogelstein and Kinzler published their original scientific paper on digital PCR in *Proc. Natl. Acad.* Sciences *USA 96*: 9236-9241 (1999). Exhibit 19. I understand that the paper served as the basis for the application underlying the three subject patents, as its text and figures appear to have been incorporated entirely in the application. Exhibit 18.

Recognition in the Art

15. According to Google Scholar™, the original digital PCR publication of inventors Vogelstein and Kinzler, *Proc. Natl. Acad. Sciences USA 96*: 9236-9241 (1999), has been cited in 532 scholarly publications in its archive from 2009-2014. Exhibit 4. That is an indication of its unusually high impact in the scientific community. According to the Altmetric™ score, this article was in the 88th

percentile of a sample of the 1888361 tracked articles of a similar age published within six weeks on either side in al journals. Exhibit 4, page 2.

16. I am aware of a number of scientific conferences on digital PCR that have been organized in the US and in Europe. One, put on by Cambridge Health Tech Institute, October 6-8, 2014, the third annual such conference, describes digital PCR as "**creating waves** across the diagnostic landscape" in its conference announcement. Exhibit 5, emphasis added. One of the featured presentations at last year's conference was titled "Use of digital PCR in Oncology: **Changing the paradigm** for systemic therapy." Exhibit 6, emphasis added. The organizers of the 2013 digital PCR conference in San Diego, CA, stated that digital PCR "has already shown potential to be a **disruptive technology** in many areas of diagnostics." Exhibit 7, emphasis added. The existence of these conferences as well as the descriptions they use are indications of the high importance of digital PCR in the scientific community.

17. Another conference, put on by an organization called Global Engage, will hold its second annual event in Europe on "qPCR and digital PCR." Exhibit 8. The first such congress in 2013 reportedly had 150 attendees, and over 200 attendees are expected in 2014. Global Engage indicates that "increasing numbers of real-time PCR users [are] purchasing digital PCR [machines] due to its reduction in cost, absolute quantification, improved sensitivity, precision and greater robustness." Exhibit 8. This reflects the growing adoption of digital PCR (broadly used) in the scientific and diagnostic communities.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.