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February 25, 2015

Dr. Kellie Kelm
Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostics and Radiological
Health (OIR) Food and Drug Administration
10903 New Hampshire Avenue W066, Room
5648 Silver Spring, MD 20993-0002

Re: IDE Pre-Submission Supplement for Submission Number Q140229

Dear Dr. Kelm:

The following package of documents is an IDE pre-submission supplement regarding an NIH U19 Research Grant entitled, "Sequencing of Newborn Blood Spot DNA to Improve and Expand Newborn Screening." This is a supplement to submission number Q140229. Our project was asked to supplement our original submission with information on Genelex, the company that will be orthogonally confirming the pharmacogenetic test results we will be returning to parents who have consented to have their primary immunodeficient child's newborn blood spot sequenced. This sequencing is being done to learn if a primary immunodeficiency previously undiscoverable through current newborn screening practices can be discovered through DNA sequencing. As you know, we will additionally return secondary pharmacogenetic findings to parents who consent to receive this information. The following submission addresses questions FDA posed to us about Genelex and their pharmacogenetic testing panels. Please feel free to contact us regarding any additional information you may need.

Sincerely,

Robert L. Nussbaum, MD, FACP, FACMGG
Holly Smith Professor of Medicine

Note: The ecopy is an exact duplicate of the paper copy.

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Requested Information

UCSF will be returning the following pharmacogenetic results to parents who have consented to receive these secondary findings from their child's sequenced newborn blood spot:

CYP2D6
CYP2C19
CYP2C9
CYP3A4
CYP2B6

Genelex has a CLIA approved YouScript Panel that includes CYP2D6, CYP2C19, CYP2C9+VKORC1, and CYP3A4. They have a separate CLIA approved test for CYP2B6.
Genelex performs PCR based assay using Sequenom Mass Array 4. This detects listed alleles including all common and most rare variants with known clinical significance at analytical sensitivity and specificity >99%. The variants tested include:

CYP2C19: active *1; inactive *2, *3, *4, *5, *6, *7, *8, *12; partially active *9, *10; rapid *17

CYP2D6: active *1, *2; *2A, *35; inactive *3, *4, *5, *6, *7, *8, *10, 11, *12, *14, *15, *19, *20, *36; partially active *9, *17, *29, *41; gene duplications *1, *2, *4, *10,*41

CYP2C9: active *1; inactive *2, *3, *4, *5, *6, *8, *11, *13, *15
VKORC1: high sensitivity 1639G>A

CYP3A4: active *1; partially active *22.

Genelex has offered pharmacogenetic testing since 2000. Their high-complexity laboratory facilities feature test validation across multiple platforms and dedicated customer support. The Genelex laboratory is fully accredited: College of American Pathologists (CAP) accreditation; 100% pass rate on CAP efficiency tests; Clinical Laboratory Improvement Amendments (CLIA) certification-licensed to perform testing in all U.S. states; State of New York Department of Health-accredited clinical laboratory for molecular genetic testing; Secure Laboratory Information Systems (LIS); Code of Federal Regulations (CFR) 21 compliant; and Health Insurance Portability and Accountability Act (HIPAA) compliant.

Genelex also holds laboratory permits in the following states as required:

California
Florida
Maryland
Rhode Island
Pennsylvania
Washington

Changes in Protocol

There have been no methodological changes in the original research protocol since our initial submission. We have, however, changed the company that will be performing the orthogonal validation of our Next Generation Sequencing Results. This company as noted above is:

Genelex (http://genelex.com/)
Genelex Corporation
3101 Western Ave., Suite 100,
Seattle, WA 98121
Direct (206) 826-1951 or (800) 523-3080 x2851

Specific Questions for FDA and Form of Feedback

Specific Questions:

1. Does Genelex meet FDA orthogonal confirmation standards for this study?
2. Will UCSF need to submit an IDE?

Form of Feedback from FDA:
We would like a teleconference