Understanding the Intent and Public Health Benefits of Exploratory Biomarker and Pharmacogenomic Research

What is Biomarker and Pharmacogenomic (PGx) research?

Biomarker Research	PGx Research
A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic response to a therapeutic intervention.	A type of biomarker that can be used to better understand associations between genetic/genomic information and disease and why people respond differently to drugs.
This research may help scientists understand patient response to the study drug or other medications they are taking, or the patient's disease or medical condition. This research may be influential across all phases of drug development.	PGx research focuses on genetic differences that affect the way drugs exert their effects, including adverse events and variable efficacy, or understanding genetic differences of a disease that help us understand variability in response.

How is Biomarker and PGx research conducted?

PROTOCOL AND INFORMED CONSENT: The protocol and consent define parameters such as the research scope, retention period, risks/benefits, and disclosure plan. For clinical trials, information about the research may be found in the main consent document for the trial or in a separate consent form.

SAMPLE COLLECTION: Biologic samples are collected from trial participants. Samples are for laboratory research and/or stored for additional analysis if that becomes necessary.

LABORATORY RESEARCH: In some circumstances samples are used immediately for planned research. Other times, samples are stored and used at a later date, as the science evolves, in accordance with the consent and protocol.

DATA ANALYSIS AND DRUG DEVELOPMENT: Results are analyzed using various bioinformatic and statistical tools. Findings may be confirmed using samples from subsequent trials. This exploratory research may lead to the development of better drugs and treatment regimens.

LONG-TERM STORAGE AND RESEARCH: With appropriate consent, biological samples are stored for future research as specified in the protocol and consent documents.

Why is Biomarker and PGx research important?

It is unlikely that the patients who contribute samples for biomarker/ PGx research will see an immediate benefit. However, this research has the potential to improve our understanding of how individuals respond to drugs in a population (see examples below) and improve our ability to predict, detect, and monitor diseases. This may ultimately result in clinical decision-making about therapies that are safer and more efficacious.

- Biomarker/PGx research may lessen the incidence and healthcare burden of adverse drug reactions
- Drug development can be streamlined by using biomarkers as "surrogate" safety/efficacy endpoints
- Regulatory agencies have recognized the potential public health benefits of this research and have communicated sample collection and research expectations.

Sample sizes that are large enough to represent the study population are needed in order to conduct meaningful research that has a global impact. Regardless, identifying associations between genetic and other biomarkers with disease and drug response can be extremely complex which is why not all research will be successful, but we hope to increases successes as our knowledge and technological capabilities expand.

What are some examples of biomarker research in drug discovery and development?

Drug/Disease	Example
Cetuximab	***Oncology*:** Studies in metastatic colorectal cancer (mCRC) demonstrated that in patients treated with cetuximab, only those whose tumor expressed EGFR and were *K-Ras* mutation negative (wild-type) had a benefit. Cetuximab is indicated only for patients with EGFR-expressing *K-Ras* mutation-negative mCRC.
Carbamazepine (CBZ)	***Neurology:*** Individuals positive for the *HLA-B*1502* allele have increased risk for CBZ induced Stevens Johnson syndrome or toxic epidermal necrolysis, which are potentially fatal. While *HLA-B*1502* is found almost exclusively in patients with ancestry across broad areas of Asia, other studies in patients of European, Korean, and Japanese ancestry have found a moderate association between CBZ-induced hypersensitivity reactions and *HLA-A*3101*. Screening is recommended in patients with ancestry in genetically at-risk populations.
Clopidogrel	***Cardiology:*** Poor metabolizers for *CYP2C19* treated with clopidogrel at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome or percutaneous coronary intervention. Tests are available to identify *CYP2C19* genotype and can be used as an aid to determine therapeutic strategy.
Alzheimer's Disease	***Neurology:*** Genetic analyses using specimens from a variety of sources, including clinical trial subjects, have identified associations between multiple variants at the *BIN1* locus and susceptibility to late-onset Alzheimer's Disease (LOAD). These new findings potentially nominate or support additional mechanisms and pathways for the pharmacologic treatment of sporadic LOAD.

What results may be returned from this research?

In general, much of the biomarker and PGx research performed by pharmaceutical companies is exploratory in nature. For patients this means results are often of limited immediate clinical value and are generated in laboratories that meet research needs, but do not meet the quality and capability standards needed for use in medical decision making. In addition, due to the length of time that samples are stored and used it is often difficult to re-contact patients.

Due to these factors, the majority of biomarker research results are not returned to patients. However, where required by local regulations, or where results are medically relevant and generated in a way that they can be used for medical decision making, these results may be returned to those who are interested.

What privacy, confidentiality, and patient rights concerns may pertain to this type of research?

Given the risk associated with the inadvertent or intentional disclosure and misuse of genetic information, there is a responsibility to safeguard the privacy of a study participant in accordance with pertinent laws, regulations, standards, and policies. The I-PWG considers single coding as an adequate measure to protect privacy.

Genome wide approaches (e.g. whole genome sequencing (WGS), whole exome sequencing (WES), and Genome wide association studies (GWAS)) allow researchers to generate significant amounts of genetic data that are unique to an individual. Single coding provides protection for patient privacy especially when combined with additional safeguards (e.g. storage in a secure location with limited access). Researchers often limit access to the full dataset unless the patient specifically authorizes sharing of this information and understands the risks involved with doing so. Likewise these data should only be studied to answer the specific research scope defined in the consent and protocol without the obligation to "hunt" for additional significant findings that may be contained in the dataset.

**For information regarding the resources used to generate this document please refer to the "Pharmacogenomics Resource" document.*

Pharmacogenomics Resources

The information available in the Industry Pharmacogenomics Working Group (I-PWG) resource "Understanding the Intent and Public Health Benefits of Exploratory Biomarker and Pharmacogenomic Research" was obtained from information in the following resources. We hope you find these references helpful at better understanding this topic. If you are interested in learning more about genetics or PGx specifically, you may consult the following resources on the web for more information. As these are web resources please keep in mind that URL's may change over time.

For information on Genetics and PGx:

Industry Pharmacogenomics Working Group (I-PWG) (www.i-pwg.org)	The I-PWG has a number of educational resources including web-based courses, audiovisual resources, podcasts and textbook recommendations
PharmGKB (www.pharmgkb.org)	A comprehensive resource that curates knowledge about the impact of genetic variation on drug response for clinicians and researchers and is managed at Stanford University
Genetics Home Reference (ghr.nlm.nih.gov)	This site provides consumer-friendly information about the effects of genetic variations on human health
American Medical Association (http://www.ama-assn.org/ama/pub/physician-resources/medical-science/genetics-molecular-medicine/education-research.page)	The AMA offers a number of free education and research references that pertain to genetics and molecular medicine.
Human Genome Project Information (http://web.ornl.gov/sci/techresources/Human_Genome/education/index.shtml)	This site provides a wealth of genetics information in various formats (publications, teaching aids, videos, webcasts, etc.). This includes a quick "Genetics 101" lesson that takes you from the genome to the proteome.
Genetics and Social Science: Expanding Transdisciplinary Research (www.nchpeg.org/bssr/)	This free, web-based course is aimed at giving scientists the skills necessary to assess genetics research for validity and utility as well as providing users with the ability to conceive of progressive but feasible studies.
National Coalition for Health Professional Education in Genetics (http://www.nchpeg.org)	NCHPEG is committed to a national effort to a national effort to promote health professional education and access to information about advances in human genetics.

The following resources contain information provided in the document entitled "Understanding the Intent and Public Health Benefits of Exploratory Biomarker and Pharmacogenomic Research":

1. ICH E15 - Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Finalized in November 2007 and adopted by FDA in April 2008. (Accessed at: http://www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0199-gdl.pdf and at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E15/Step4/E15_Guideline.pdf)
2. Iyer L, King CD, Green MD, et al. Genetic predisposition to the metabolism of irinotecan (CPT-11). Role of uridine diphosphate glucuronosyltravsferase isoform 1A1 in the glucuronidation of its active metabolite (SN-38) in human liver microsomes. *J Clin Invest* 1998; 101(4): 847-54.
3. Mette L, Mitropoulos K, Vozikis A, Patrinos GP. Pharmacogenomics and public health: implementing 'populationalized' medicine. Pharmacogenomics 2012; 13(7): 803-13.
4. Morimoto T, Sakuma M, Matsui K et al. Incidence of Adverse Drug Events and Medication Errors in Japan: the JADE Study. Journal of General Internal Medicine 2011; 26(2): 148-53.
5. Maliepaard M, Nofziger C, Papaluca M et al. Pharmacogenetics in the evaluation of new drugs: a multiregional regulatory perspective. Nature Reviews. Drug Discovery 2013; 12(2): 103-15.
6. Yasuda SU, Zhang L, Huang SM. The role of ethnicity in variability in response to drugs: focus on clinical pharmacology studies. Clinical Pharmacology and Therapeutics 2008; 84(3): 417-23.
7. Ozeki T, Mushiroda T, Yowang A, et al. Genome-wide association study identifies HLA-A*3101 allele as a genetic risk factor for carbamazepine-induced cutaneous drug reactions in Japanese population. Human Molecular Genetics 2011; 20(5): 1034-41.

8. Otsubo Y, Ashahina Y, Noguchi A, et al. Similarities and differences between US and Japan as to pharmacogenomics biomarker information in drug labels. Drug Metabolism and Pharmacokinetics 2012: 27(1): 142-9.
9. Franc MA, Warner AW, Cohen N et al. Current Practices for DNA Sample Collection and Storage in the Pharmaceutical Industry, and Potential Areas for Harmonization: perspective of the I-PWG. Clinical Pharmacology and Therapeutics 2011: 89(4): 546-53.
10. FDA. Draft Guidance-Clinical Pharmacogenomics: Premarketing Evaluation in Early Phase Clinical Studies. February 2011. (Accessed at: https://www.federalregister.gov/articles/2011/02/18/2011-3679/draft-guidance-for-industry-on-clinical-pharmacogenomics-premarketing-evaluation-in-early-phase)
11. Anderson DC, Gomez-Mancilla B, Spear BB, et al. Elements of Informed Consent for Pharmacogenetic Research; perspective of the pharmacogenetics working group. Pharmacogenomics Journal 2002; 2(5):284-92.
12. ICH E6 (R1) - Guideline for Good Clinical Practice. June 1996. (Accessed at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf)
13. Prucka SK, Arnold LJ, Brandt JE, Gilardi S, Harty LC, Hong F, Malia JS, Pulford DJ. An Update to Returning Genetic Research Results to Individuals: Perspectives of the Industry Pharmacogenomics Working Group. Bioethics 2014: in press.
14. JAPAN. JPMA: Pharmaceutical Administration and Regulations in Japan, March 2012. (Accessed at http://www.jpma.or.jp/english/parj/pdf/2012.pdf)
15. JAPAN. JPMA: Issues regarding Clinical Implementation of Pharmacogenetics, March 2008 (Japanese). (Accessed at http://www.jpma.or.jp/) (Also accessed at: http://www.jpma.or.jp/about/basis/guide/pdf/phamageno.pdf)
15. JAPAN. Ethical Guidelines for Genetic Analysis in Clinical Trials. Three ministries (Ministry of Education, Culture, Sports, Science and Technology; Ministry of Economy, Trade and Industry; and Ministry of Health, Labour and Welfare), Feb. 2013. (Access at: http://www.meti.go.jp/english/press/2013/0208_02.html)
17. Renegar G, Webster CJ, Stuerzebecher S, et al. Returning genetic research results to individuals: points-to-consider. Bioethics 2006;20(1):24-36. (Accessed at: http://onlinelibrary.wiley.com/doi/10.1111/j.1467-8519.2006.00473.x/pdf)
18. Franc MA, Cohen N, Warner AW, et al. Coding of DNA Samples and Data in the Pharmaceutical Industry: Current Practices and Future Directions-Perspective of the I-PWG. Clinical Pharmacology & Therapeutics 2011; 90(4): 537-545. (Accessed at: http://www.nature.com/clpt/journal/v89/n4/pdf/clpt2010306a.pdf)
19. Genetic Information Nondiscrimination Act (GINA): 2007-2008. (Accessed at: http://www.genome.gov/24519851)
20. Hudson KL, Holohan MK, Collins FS. Keeping pace with the times—the Genetic Information Nondiscrimination Act of 2008. New England Journal of Medicine 2008;358(25):2661-3.
21. Ricci DS, Broderick ED, Tchelet A, et al. Global Requirements for DNA Sample Collections: Results of a Survey of 204 Ethics Committees in 40 Countries. Clinical Pharmacology & Therapeutics 2011; 89 (4); 554-561. (Accessed at: http://www.nature.com/clpt/journal/v89/n4/pdf/clpt2010319a.pdf)
22. Warner AW, Bhathena A, Gilardi S, et al. Challenges in Obtaining Adequate Genetic Sample Sets in Clinical Trials: The Perspective of the Industry Pharmacogenomics Working Group. Clinical Pharmacology & Therapeutics 2011; 89(4): 529-536. (Accessed at: http://www.nature.com/clpt/journal/v89/n4/pdf/clpt2010305a.pdf)
23. OHRP. International Compilation of Human Research Protections, ed. 2014. (Accessed at: http://www.hhs.gov/ohrp/international)
24. PMDA Notice 0930007 on Clinical Trials Using Pharmacogenomics (Accessed at: http://www.pmda.go.jp/operations/shonin/outline/shinrai/file/tuchi/1_0930007.pdf)
25. EMA CHMP. Reflection Paper on Pharmacogenomics in Oncology - Draft. 2008. (Accessed at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003866.pdf)
26. EMA CHMP. Position Paper on Terminology in Pharmacogenetics. June 2003. (Accessed at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003889.pdf)
27. EMA CHMP. Reflection Paper on the Use of Pharmacogenetics in the Pharmacokinetic Evaluation of Medicinal Products. May 2007. (Accessed at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003890.pdf)
28. EMA CHMP. Guideline on Pharmacogenetic Briefing Meetings. November 2006. (Accessed at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003886.pdf)
29. EMA CHMP. Reflection Paper on Pharmacogenomic Samples, Testing, and Data Handling. November 2007. (Accessed at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003864.pdf)
30. EMA CHMP. Reflection Paper on the Use of Genomics in Cardiovascular Clinical Intervention Trials. November 2007. (Accessed at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003865.pdf)
31. EMA CHMP. Qualification of Novel Methodologies for Drug Development: Guidance to Applicants. January 2014. (Accessed at: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004201.pdf)
32. EMA. Understanding the Terminology Used in Pharmacogenetics June 2003. (Accessed at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003889.pdf)
33. FDA. Companion Guidance - Pharmacogenomic Data Submissions - draft. August 2007. (Accessed at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079855.pdf)
34. FDA. Guidance - Pharmacogenetic Tests and Genetic Tests for Heritable Markers. June 2007. (Accessed at: www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm077862.htm)
35. FDA. Guidance - Pharmacogenomic Data Submissions. March 2005. (Accessed at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126957.pdf)
36. EMA FDA. – Guiding principles Processing Joint FDA EMEA Voluntary Genomic Data Submissions (VGDSs) within the framework of the Confidentiality Arrangement May 2006. (Accessed at : http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/12/WC500017982.pdf)
37. EMA CHMP. Draft Guideline on the Use of Pharmacogenetic Methodologies in the Pharmacokinetic Evaluation of Medical Products. April 2010. (Accessed at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/05/WC500090323.pdf)
38. EMA CHMP. Draft Reflection Paper on Co-Development of Pharmacogenomic Biomarkers and Assays in the Context of Drug Development. June 2010 (Accessed at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/07/WC500094445.pdf)
39. EMA CHMP. Draft Reflection Paper on Methodological Issues Associated with Pharmacogenomic Biomarkers in Relation to Clinical Development and Patient Selection. June 2011(Accessed at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/07/WC500108672.pdf)
40. Rittenhouse P. Framing DNA collection in the clinic. Biocentury, The Bernstein Report on BioBusiness March 2008:A13-5.
41. Hetherington S, McGuirk S, Powell G, Cutrell A, Naderer O, Spreen B. Hypersensitivity reactions during therapy with the nucleoside reverse transcriptase inhibitor abacavir. Clin Ther. Oct 2001;23(10):1603-14
42. Hu X, Pickering E, Liu YC et al. Meta-Analysis for Genome-Wide Association Study Identifies Multiple Variants at the BIN1 Locus Associated with Late-Onset Alzheimer's Disease. PloS One 2011; 6(2): 1-9