



# AN UPDATE TO RETURNING GENETIC RESEARCH RESULTS TO INDIVIDUALS: PERSPECTIVES OF THE INDUSTRY PHARMACOGENOMICS WORKING GROUP

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## ABSTRACT

The ease with which genotyping technologies generate tremendous amounts of data on research participants has been well chronicled, a feat that continues to become both faster and cheaper to perform. In parallel to these advances come additional ethical considerations and debates, one of which centers on providing individual research results and incidental findings back to research participants taking part in genetic research efforts. In 2006 the Industry Pharmacogenomics Working Group (I-PWG) offered some 'Points-to-Consider' on this topic within the context of the drug development process from those who are affiliated to pharmaceutical companies. Today many of these points remain applicable to the discussion but will be expanded upon in this updated viewpoint from the I-PWG. The exploratory nature of pharmacogenomic work in the pharmaceutical industry is discussed to provide context for why these results typically are not best suited for return. Operational challenges unique to this industry which cause barriers to returning this information are also explained.

## INTRODUCTION

There is much literature on individual research results (IRRs) and incidental findings (IF) from genetic research, and the April 2012 issue of the journal *Genetics in Medicine* was devoted to this topic. It includes a consensus statement from a United States (US) National Institutes of Health-funded working group, which provided recommendations from a two year project culminating in '10 concrete recommendations, addressing new biobanks as well as those already in existence'.<sup>1</sup> This and similar publications provide limited perspectives from the pharmaceutical industry regarding the risks and benefits to the research participant or the limitations and operational

challenges of providing individual research results to these participants.

Pharmaceutical companies are increasingly including pharmacogenomics (PGx) in their drug development programs. As discussed in the 2006 I-PWG publication, this effort is directed at both improving the understanding of the conditions targeted by the pharmaceutical industry, and developing medicines with enhanced risk/benefit profiles that target specific patient populations.<sup>2</sup> Samples for PGx research are often contributed from individuals around the globe, bringing unique challenges to the IRR/IF discussion. Much of this research is exploratory in nature and does not produce results suitable for providing to research participants. The goal of this publication is to provide updated thoughts from the I-PWG on

<sup>1</sup> S.M. Wolf et al. Managing Incidental Findings and Research Results in Genomic Research Involving Biobanks and Archived Data Sets. *Genet Med* 2012; 14: 361–384: 361. (introduction)

<sup>2</sup> Renegar et al. Returning Genetic Research Results to Individuals: Points-to-consider. *Bioethics* 2006; 20: 24–36.

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how this industry could address providing results to research participants and increase awareness of the operational considerations faced by the industry. The focus will be on samples that are coded and can thus be linked back to the research participant with involvement of the investigator. Genetic research data from anonymized samples which cannot be linked back to the research participant will not be discussed.

## 1. GENETICS AND THE PHARMACEUTICAL INDUSTRY

While advances in genetic science and our understanding of the role of genetics in health, disease and response to medicines have become more familiar to both the scientific and lay communities, the application of genetics in the pharmaceutical industry is commonly misunderstood. It is important to distinguish PGx research typically performed by the pharmaceutical industry from genetic and genomic biobank research, and clinical genetic testing, since the expectation for providing results and content of information may differ.

Traditionally, researchers collected health information and relevant biological samples to enable focused research projects. These relatively small collections had limited use; however by the late 1990s researchers began to establish large biobanks to enable statistically powered research.<sup>3</sup> Samples collected from many thousands of donors are stored, and access may be granted to numerous research scientists to explore a wide range of medical research questions, with an emphasis on epidemiological studies. For example, the UK Biobank aims to use samples and data to study the prevention, diagnosis, and treatment of illness and for the promotion of health throughout society.<sup>4</sup> Likewise, DNA biobanks facilitate the analysis of research participants' genomes and correlate the output to phenotypic data so researchers can better understand the genetics of traits and diseases.

By contrast, pharmaceutical drug development often involves international multi-center clinical trials in which the objectives are typically to understand the pharmacokinetics, pharmacodynamics, safety and/or efficacy of the medicines in development. DNA samples collected from the intent to treat (ITT) population for industry-sponsored trials by investigators at numerous clinical sites are often stored for future use in these PGx research efforts, so that efficacy and safety variability can be addressed in the study population. Additionally, know-

ledge of the genetic etiology of disease may help define subtypes that respond differently to interventional drugs.<sup>5</sup> A review of the FDA Table of Pharmacogenomic Biomarkers in Drug Labels reveals the extent to which this research has contributed to personalized medicine.<sup>6</sup> Since clinical trials recruit a relatively small number of patients, pharmaceutical genetic research tends to have a correspondingly limited sample size. Unlike many commercial and academic biobanks, pharmaceutical companies often limit access of coded genetic samples to scientists directly involved in the drug development process. Furthermore, the original clinical protocol, informed consent and ethical approvals for genetic research, generally limit the scope to specific study objectives, such as understanding disease status and response to the investigational product under development. Genetic samples will not include personal identifiers and industry researchers will not have direct contact with research participants.

The goals of clinical genetics differ from pharmaceutical PGx research as well. Clinical genetics aims to assess genetic and non-genetic risk factors, often utilizing validated and approved genetic tests to explain or predict susceptibility for disease.<sup>7</sup> In contrast, pharmaceutical PGx research studies are not designed to supplement or guide clinical care and often utilize exploratory test methods or hypotheses which produce results that must be validated in additional studies before utilized in clinical practice.

Elucidation of the differences among various types of genetic research helps set realistic expectations for what results of industry-sponsored PGx research lend themselves to being provided back to research participants.

## 2. RESULTS CATEGORIZATION

Given the described scope of pharmaceutical PGx research, we examined the systems presented in several prominent publications to determine what, if any, results from such research are suitable to provide to research participants. Our reasoning was that, while there has been some debate on the ethical duty to return IRRs, a more defined consensus seems to be developing that identifies criteria for what genetic research results should and should not be provided to research participants. Three

<sup>3</sup> H.T. Creely. The Uneasy Ethical and Legal Underpinnings of Large-scale Genomic Biobanks. *Ann Rev Genomics Hum Genet* 2007; 8: 343–364.

<sup>4</sup> UK Biobank. 2012. Available at: <http://www.ukbiobank.ac.uk/about-biobank-uk/> [Accessed 24 June 2013].

<sup>5</sup> R. Murphy et al. Clinical Implications of a Molecular Genetic Classification of Monogenetic b-cell Diabetes. *Nat Clin Pract Endocrinol Metab* 2008; 4: 200–213.

<sup>6</sup> U.S. Food and Drug Administration (FDA). 2012. Table of Pharmacogenomic Biomarkers in Drug Labels. Available at: <http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm> [Accessed 24 June 2013].

<sup>7</sup> C.J. Epstein. Medical Genetics in the Genomic Medicine of the 21<sup>st</sup> Century. *Am J Hum Genet* 2006; 79: 434–438.

publications are described below that were particularly informative.

## Background

We examined the results of the National Heart Lung and Blood Institute (NHLBI) 2004 and 2009 working groups, which addressed the issue of how, when and what IRRs should be returned to research participants.<sup>8</sup> The updated criteria Fabsitz et al. present in their 2010 publication share many similarities with the criteria presented by Wolf et al. in 2012.<sup>9</sup> These similarities are summarized in Table 1 and provide a framework for considering how to handle the results generated in pharmaceutical PGx research. In Table 1, data are classified under three different headings: data that *should* be offered to research participants;<sup>10</sup> data that *may* be offered to research participants;<sup>11</sup> and data that *should not* be offered to research participants.<sup>12</sup>

The term clinical validity in this table refers to an established association between genotype and a particular clinical outcome. This association may begin with a single publication but is strengthened by the quality and quantity of empirical evidence.<sup>13</sup> Clinical utility, however, is a result that is 'analytically valid and can be used to improve a participant's well-being'.<sup>14</sup>

## Application to the pharmaceutical industry

Using the criteria defined in Table 1 for results that *should* or *may be offered* to research participants, as discussed below, we conclude that the results of industry PGx research generally do not meet the threshold defined as being ideal for providing to research participants.

When looking closer at the work done by the pharmaceutical industry and how it could fit into the proposed system, it is important to understand how PGx research progresses as part of the drug development process and at what point it is appropriate to provide results to investigators, who in turn share these with research participants.

During a drug candidate's development, PGx samples may be collected at any point from early Phase 1 safety studies through post-marketing commitments, a period typically spanning ten to fifteen years or more. If a testable hypothesis is identified, PGx research is often

<sup>8</sup> E.B. Bookman et al. Reporting Genetic Results in Research Studies: Summary and Recommendations of an NHLBI Working Group. *Am J Med Genet A* 2006; 140: 1033–1040; R. Fabsitz et al. Ethical and Practical Guidelines for Reporting Genetic Research Results to Study Participants: Updated Guidelines from a National Heart, Lung and Blood Institute Working Group. *Circ Cardiovasc Genet* 2010; 574–580.

<sup>9</sup> Wolf et al., *op. cit.* note 1, pp. 361–384.

<sup>10</sup> Fabsitz et al., *op. cit.* note 8; Wolf et al., *op. cit.* note 1.

<sup>11</sup> Fabsitz et al., *ibid.*; Wolf et al., *ibid.*

<sup>12</sup> Wolf et al., *ibid.*

<sup>13</sup> V. Ravitsky & B.S. Wilfond. Disclosing Individual Genetic Results to Research Participants. *Am J Bioeth* 2006; 6: 8–17.

<sup>14</sup> *Ibid.*: 10.

Table 1. Criteria to be considered and recommendations on the return of individual genetic research results.

Recommendation	Elements
Classification of data that <i>should be offered</i> to research participants (all criteria must be met)	<ul style="list-style-type: none"> <li>• The findings are analytically valid and are disclosed in a manner that complies with applicable local laws (e.g. CLIA-certified labs within the United States).</li> <li>• The findings are clinically valid, meaning the association between IRR and health risk has been established. The result also poses a substantial risk for a serious health conditions.</li> <li>• The findings have established clinical utility, where the intervention(s) have significant potential to change the course of the condition or alter its treatment.</li> <li>• The research participant has been given the option to receive results and has elected to do so.</li> </ul>
Classification of data that <i>may be offered</i> to research participants (all criteria must be met).	<ul style="list-style-type: none"> <li>• The findings are analytically valid and are disclosed in a manner that complies with applicable local laws (e.g. CLIA-certified labs within the US).</li> <li>• The research participant has been given the option to receive results and has elected to do so.</li> <li>• Fabsitz et al. then defined results that <i>may be</i> disclosed as those where the benefit to the research participant outweighs the risks from the research participant's perspective. Wolf et al. defined this as a finding where there is established and substantial risk of likely health or reproductive importance or personal utility to the research participant and return is likely to provide net benefit from the research participant's perspective.</li> </ul>
Classification of data that <i>should not be offered</i> to research participants	<ul style="list-style-type: none"> <li>• Results with uncertain health, reproductive, or personal utility that provide unlikely net benefit to the contributor</li> </ul>

conducted in parallel with the development of the therapeutic. The data generated are derived initially from relatively small sample sizes as hypotheses are developed, tested and confirmed. Until a hypothesis has been replicated and an association between the marker(s) and outcome has been validated, at which point the association may be reflected in the drug label, the PGx data often have uncertain clinical utility and validity. Throughout this process there is a risk that hypothesized associations will fail to replicate. Disclosing a non-validated association could therefore mislead research participants about anticipated response or disease risk. In addition, the data generated during this process often consists of a list of multiple genetic markers, such as single nucleotide polymorphisms, which is refined and condensed throughout the research process. Providing preliminary results would mean the research participant is given a potentially long list of markers whose association to drug response,

or the condition being studied, is still uncertain. PGx research often utilizes emerging technologies, so there is also a greater likelihood that the genetic assay may not be available in a CLIA certified laboratory. While it is debatable whether or not it is proper for research participants to receive results from a non-CLIA certified lab in situations where a CLIA certified lab is not available,<sup>15</sup> the absence of established analytical validity is seen as another barrier to providing a preliminary research result to participants. In fact some jurisdictions require by law that results must be generated in a certified lab, such as CLIA for the United States, in order to be provided to research participants.

One could argue that the potential harm from disclosing preliminary results might be minimized if the research participant is properly educated about the limitations of these results during the consent process.<sup>16</sup> However, research has shown that research participants may overestimate the accuracy of research results, or may misjudge the significance of the result even when the clinical significance is uncertain.<sup>17</sup> One consequence of this action is a potential for research participants to misunderstand the impact of their result and make ill-informed treatment decisions that could negatively impact their medical management. On a larger scale, this could increase the burden on the medical system with potentially unnecessary and invasive follow-up evaluations.<sup>18</sup>

## International perspectives

There are many regions or countries, such as Austria, Canada and Japan that have ethics guidelines recognizing exploratory genetic results as having questionable utility and lacking the qualities useful for meaningful medical decision making.<sup>19</sup> Australian regulations recognize that

<sup>15</sup> R. Fabsitz et al., *op. cit.* note 8, p. 577.

<sup>16</sup> E.W. Clayton & L.F. Ross. Implications of Disclosing Individual Results of Clinical Research. *JAMA* 2006; 295: 37.

<sup>17</sup> E.B. Bookman et al., *op. cit.* note 8, pp. 1033–1040; M.J. Mehlman. Predictive Genetic Testing in Urology: Ethical and Social Issues. *World J Urol* 2004; 21: 433–437.

<sup>18</sup> A.L. McGuire, T. Caulfield & M.K. Cho. Research Ethics and the Challenge of Whole-genome Sequencing. *Nat Rev Genet* 2008; 9: 152–156; 153; M.J. Bledsoe. Practical Implementation Issues and Challenges for Biobanks in the Return of Individual Research Results. *Genet Med* 2012; 14: 478–483; 482.

<sup>19</sup> C. Mannhalter, C. Druml & E. Singer. Practice Guidelines for Formulation of Patient or Subject Information and for the Declaration of Consent in Genetic Studies (inclusive of pharmaceutical genetics). *Wien Klin Wochenschr* 2001; 133: 867–869; Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada 2010, Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans. Available at [www.pre.ethics.gc.ca](http://www.pre.ethics.gc.ca) (Accessed 24 June 2013); Japan Pharmaceutical Manufacturers Association Drug Evaluation Committee, 2008: Issues to be Taken into Account when Applying Pharmacogenomics to Clinical Trials of

harm can result from providing exploratory results and now require investigators to submit a plan to the EC to defend their reasoning if they intend to provide research results.<sup>20</sup>

There are instances however, where laws or regulations provide research participants with the right to access their genetic research result regardless of how preliminary in nature. For example, Spanish Law 14/2007 on Biomedical Research and Brazil's CONEP Resolution 340/2004 provides research participants with the right to request access to genetic data generated from their sample.<sup>21</sup> Additionally, both 14/2007 and 340/2004 define the responsibility of the researcher not only to return genetic results when requested, but also to provide adequate counseling regarding the meaning and potential impact to the research participant. Thus working in a global research environment may give rise to situations where researchers are legally obligated to provide results in some countries that would not otherwise meet the threshold for return.

## Results that 'should be offered' to research participants

While the majority of the research performed by our industry generates results that are not ideal to provide research participants, there will be times when results are produced that meet the criteria defined in Table 1 as 'should be offered', or 'may be offered'. While results may be provided to interested research participants in these situations, certain operational challenges unique to our industry would dictate the need to tailor the plan for each situation instead of following generalized recommendations.

Since samples may be collected years in advance of PGx research efforts, one such challenge is the often temporary relationship between the investigator and research participants, making it difficult to reconnect with research participants. Many research participants choose not to participate in the follow-up phase of the clinical

Medicinal Products. Available at (Japanese) [www.jpma.or.jp/about/basis/guide/pdf/phamageno.pdf](http://www.jpma.or.jp/about/basis/guide/pdf/phamageno.pdf) (Accessed 24 June 2013); M.H. Zawati & B.M. Knoppers. International Normative Perspectives on the Return of Individual Research Results and Incidental Findings in Genomic Biobanks. *Genet Med* 2012; 14: 484–489.

<sup>20</sup> Australian Government National Health and Medical Research Council. 2009. National Statement on Ethical Conduct in Human Research. Available at: <http://www.nhmrc.gov.au/guidelines/publications/e72> (Accessed 24 June 2013).

<sup>21</sup> Brazil Ministry of Health. CNS Resolution 340/04. Guidelines for Conduct and Ethical Analysis of Research projects of the Special Thematic Area of Human Genetics. Available at: <http://conselho.saude.gov.br/resolucoes/2004/Reso340.doc> (Accessed 24 June 2013); Juan Carlos I. Law 14/2007, of 3 July, on Biomedical Research. Inter-University Chair in Law and Humane Genome. Available at: <http://www.catedraderechoygenomahumano.es/images/novedades/SpanishLawonBiomedicalResearchEnglish.pdf> (Accessed 24 June 2013).

trial or not to continue receiving monitoring after completion of the trial. Such research participants also may not update investigators with their current contact information, and may not receive subsequent medical care at the same facility at which the trial was conducted. In addition, samples may be collected years in advance of PGx research efforts rendering it very difficult to re-contact research participants if records retention requirements for investigative sites, which can differ within and between countries, have expired. Clinical investigators may also lack sufficient knowledge of the genetic research carried out by the sponsor or collaborating researchers, and may not adequately interpret genetic data to effectively communicate information and minimize the risk for misinterpretation by the patient. In these situations, it may be necessary to refer research participants to a medical professional trained in genetics.

Additional complexities arise when considering how long PGx researchers in the pharmaceutical industry would be obligated to provide updates to the scientific relevance of reported findings, since a finding with no known medical consequences or PGx significance today may well be interpretable in the future. There are logistical limitations to fulfilling this commitment as well. While pharmaceutical company personnel are actively engaging investigators during the course of the trial, once planned analyses are completed and the final result reported, these resources often disperse to support different internal efforts. From the industry perspective, while not insurmountable, many operational challenges exist with trying to pull together these resources years after trial completion and re-engaging investigators to deliver PGx results. These factors need to be considered in developing a plan for providing results back to research participants, recognizing that there are limitations to providing updated scientific interpretations for PGx data in a field that is ever evolving. If large scale genome-wide analysis was to be performed during the trial, genetic data may be available earlier. Although many of the limitations described would still remain, if such an approach became more commonplace in the future some of these operational challenges may not be as significant a barrier.

In summary, the majority of PGx research done by the pharmaceutical industry is exploratory in nature and not suited for return. When results that should be offered to research participants arise, operational challenges and timing considerations are essential factors to consider in identifying when such results can be effectively returned.

### 3. AGGREGATE RESULTS

The pharmaceutical industry frequently reports aggregate PGx research findings, whether positive or negative, through peer reviewed journal articles or on clinical-

trials.gov. PGx researchers in the pharmaceutical industry however don't often provide aggregate results directly to individual research participants, due to same operational issues defined above for IRR return.

There has been an increased advocacy in the literature however to consider this option where IRR return is not appropriate. This approach acknowledges the importance of the research participant's contribution and may increase their understanding of how they have contributed to the overall drug development program.<sup>22</sup>

While operationally challenging, if PGx researchers in this industry were to return aggregate results, one potential model could be to provide investigators with a report that briefly describes the purpose of the research, summarizes the result(s), the potential utility of the data, the limitations of interpreting exploratory results, and how findings contributed to the overall PGx research goals. As with IRR return, the research participant would need to consent to receiving this information, and the IRB and/or Independent Ethics Committee (IEC) would need to approve this approach.

For some research participants however, learning the aggregate result may prompt a stronger desire to know their IRR.<sup>23</sup> This desire may be lessened for research participants participating in clinical trials since PGx results are often not available until after trial completion at which time participants may already have an understanding of whether or not they responded to treatment and what adverse events they may have experienced.

There are also cultural, educational and operational challenges to providing aggregate research results in a way that is understandable by globally diverse populations of research participants. While challenges of health literacy are not unique to the genetics community, the wide range in variability of genetic knowledge, even among medical professionals, and the diversity in regional acceptance of genomic medicine, can make this especially challenging. For this reason it is essential that the research participant clearly understands what information will be provided back, why, and whether he/she is interested in receiving the results under these conditions. This means engaging the research participant in understanding the overall research aims and how their sample may specifically contribute to that process. Having an open dialog with the ethics committee is also essential to ensure effective communication in a manner that acknowledges global views and expectations for providing genetic research results.

<sup>22</sup> L.M. Beskow et al. Offering Aggregate Results to Participants in Genomic Research: Opportunities and Challenges. *Gen Med* 2012; 14: 490–496: 491.

<sup>23</sup> Ibid: 492.

#### 4. INCIDENTAL FINDINGS

While the focus thus far has been on IRRs, it is important to consider some of the unique challenges incidental findings (IF) may pose for our industry. By definition an IF has potential health or reproductive importance.<sup>24</sup> The concerns over analytic validity and legality (e.g. CLIA certified lab for data return in the US) pose the same challenges for returning an IF as they do an IRR, and may undermine the ability to determine if an IF has true health or reproductive significance from a clinical perspective.

Current US law and federal regulations do not provide direct guidance on how to deal with IFs in research, and such advice is generally limited globally. Perhaps one of the more explicit national mandates for IF return is found in Canada's *Tri-Council Policy Statement of 2010*, which stipulates that the researcher should have a protocol-level plan for the management of genetic IFs and their implications for the research participant as well as his/her family members and relatives.<sup>25</sup> While not generally mandated, there is increasing support for IF return in the literature. Wolf et al. (2012) argue that an 'intermediate' duty of care should apply for IFs discovered during research, meaning a plan for delivering IFs should be both outlined in the protocol and supported by the informed consent process so that relevant IFs can be returned to research participants.<sup>26</sup> The area of clinical genetics has seen increasing support for IF return as well, as evidenced in the June 2013 statement by the American College of Medical Genetics and Genomics (ACMG) on reporting incidental findings of clinical exome and genome sequencing, in which they call for laboratories to report constitutional mutations found in a minimum list of genes that will be updated at least annually.<sup>27</sup> Although a minimum list of genes was not designed to apply to genomic research it is possible these recommendations may contribute to the effort 'to design thresholds and lists for the return of genomic findings to research participants'.<sup>28</sup> However, the elements discussed in Table 1 and operational challenges presented here would still apply, keeping in mind that whole genome/exome sequencing is not always employed for pharmaceutical genomic research.

<sup>24</sup> S.M. Wolf et al., *op. cit.* note 1, p. 364.

<sup>25</sup> Canadian Institutes of Health Research, *op. cit.* note 18.

<sup>26</sup> S.M. Wolf et al., *op. cit.* note 1, p. 379.

<sup>27</sup> R.C. Green et al. ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing. *Gen Med* 2013 (Epub ahead of print) Available at: [http://www.acmg.net/docs/ACMG\\_Releases\\_Highly-Anticipated\\_Recommendations\\_on\\_Incidental\\_Findings\\_in\\_Clinical\\_Exome\\_and\\_Genome\\_Sequencing.pdf](http://www.acmg.net/docs/ACMG_Releases_Highly-Anticipated_Recommendations_on_Incidental_Findings_in_Clinical_Exome_and_Genome_Sequencing.pdf) (Accessed 28 Jun 2013).

<sup>28</sup> *Ibid*: 13.

The authors support the responsibility for transparency in the protocol and informed consent process regarding the research plan for IFs but also support the view expressed by Wolf et al. that there should not be an obligation to hunt for IFs or to collect more or different information than the research protocol requires.<sup>29</sup> As with IRRs, there are operational complexities to providing these results to research participants however, we recognize the need to provide IFs meeting the criteria for return outlined in Table 1, when practical and possible.

#### 5. INFORMED CONSENT

Informed consent within this context poses its own unique challenges. A research participant's consent to participate in pharmaceutical PGx research is often either captured as part of the main consent form used for enrollment in the clinical trial, or is provided as a supplementary consent at the same time as the main consent. Regardless, the description of genomic research is in proportion to the primary focus of the consent (i.e. drug evaluation), meaning it may occupy anywhere from a few paragraphs to just over a page, in a consent that is often over 20 pages. This may differ significantly from some non-pharmaceutical research settings where contributing a DNA sample for research is the focus of the informed consent document and process.

One potential way to address these challenges is a two-step consent process. As stated in the 2006 I-PWG publication, this approach 'takes into account that participants may change their minds during the course of the study' while also acknowledging the possibility that genetic markers would have been identified during this time that have attained clinical relevance.<sup>30</sup> This approach would be helpful in instances where the criteria for IRR/IF return have been met, allowing the research participant to reaffirm their interest through a second, and potentially more detailed consent, at the time results were available. There are operational challenges to this approach that make it very complex to execute on a global scale.

The 2006 I-PWG publication provided a number of elements that could be incorporated into the consent to ensure that the research participant understands if results will be provided.<sup>31</sup> We would add to this that research participants should understand whether this will be an IRR or aggregate result, under what circumstances an IF will be returned, under what circumstances research participants will be given the option to receive or decline this

<sup>29</sup> S.M. Wolf, J. Paradise, & C. Caga-anan. The Law of Incidental Findings in Human Subjects Research: Establishing Researchers' Duties. *J Law Med Ethics* 2008; 36: 361–383: 376.

<sup>30</sup> G. Renegar et al., *op. cit.* note 2, p. 35.

<sup>31</sup> *Ibid*: 35.

information, and whether they understand the importance of keeping their contact information updated with the site to allow for results to be returned. In addition, while it is not advised to incorporate clinical trial results into a patient's medical record due to the potential risks associated, the fact that these results could end up in their medical record should be conveyed to the research participant as part of the informed consent process. Information regarding any genetic discrimination protection for their country or region should also be included. The Office of Human Research Protection in the US for example, provided guidance on incorporating Genetic Information Nondiscrimination Act (GINA) language into the informed consent as it applied to genetic research and/or genetic information being evaluated in the clinical trial.<sup>32</sup>

The consent process should also allow the research participant the opportunity to decline receipt of his or her results either at the time of initial consent or at some future time.<sup>33</sup> However, there are some limitations on what can be stated up front in the consent form. Also, care should be given as to how these results are disclosed to the research participant, and several competencies of persons returning results to research participants are outlined in the I-PWG 2006 publication.<sup>34</sup> The authors agree with the National Cancer Institute (NCI) workshop summary on this topic that pointed out, 'being specific about the process for sharing aggregate research results *a priori* can be problematic for some investigators', as it would be difficult to pre-specify the process by which these results will be provided years in advance of when they are available.<sup>35</sup> This is a difficulty faced by our industry as well, given the many years that often exist between when the sample is collected and when the results are available. This difficulty is not specific to aggregate results but applicable to IRRs and IFs as well.

## 6. OVERSIGHT

Thus far a system has been examined for determining which results are best to offer research participants and

<sup>32</sup> Office for Human Research Protections (OHRP), Department of Health and Human Services (HHS). 2009. Guidance on the Genetic Information Nondiscrimination Act: implications for investigators and institutional review boards. Available at: <http://www.hhs.gov/ohrp/policy/gina.html> [Accessed 24 June 2013].

<sup>33</sup> M.H. Zawati & A. Rioux. Biobanks and the Return of Research Results: Out with the Old and In with the New? *J Law Med Ethics* 2011; 39: 614–620.

<sup>34</sup> G. Renegar et al., *op. cit.* note 2, p. 34.

<sup>35</sup> Office of Biorepositories and Biospecimen Research, National Cancer Institute, National Institutes of Health. 2011. Workshop on release of research results to participants in biospecimen studies: Bethesda, Maryland July 8–9, 2010: 1–57: 43. Available at: [http://biospecimens.cancer.gov/global/pdfs/NCI\\_Return\\_Research\\_Results\\_Summary\\_Final-508.pdf](http://biospecimens.cancer.gov/global/pdfs/NCI_Return_Research_Results_Summary_Final-508.pdf) [Accessed 24 June 2013].

how pharmaceutical industry PGx research fits into this system. While the I-PWG does not advocate the use of an external body to set policies regarding how these results should be provided to research participants, there are some who would support having an oversight or similar body make this determination instead of the researcher.<sup>36</sup> For PGx research within the pharmaceutical industry, internal and external input may be sought as policies are set and revised and in individual cases where results return is considered. Here we review this approach and discuss potential opportunities for additional oversight.

### Setting policy for sample collection and storage

Many pharmaceutical companies already seek both internal and/or external expert input to establish general practices that are applicable across trials to allow genetic samples to be collected and stored, and to determine if results should be returned. In setting up these policies, valuable expert opinion is often sought from disciplines such as ethics, the law, privacy and genetics. Also industry consortia, such as the I-PWG, may discuss elements of a pre-competitive nature and render a consensus statement which can inform individual companies in determining their return of results policies and procedures (as is done here).

### Local Review of Protocol and Informed Consent

The next step in the process involves developing the clinical trial protocol and informed consent document. Since it is common to involve multiple study sites spanning several countries in a clinical trial, these documents may be reviewed by multiple IRBs or IECs.

The oversight provided by the IRBs and IECs is well established and recognized. IRBs and IECs review the risks and benefits of the proposed research to research participants, including the collection of samples to be stored for possible future PGx research. By taking local requirements into account there is a risk of variation in return of results requirements at the country or even study site level. This underscores the fact that there is no IRB or IEC with global jurisdiction, making it impossible to have a broad overview at this stage, since the guidance provided may not be accepted or even implementable on a global scale.

<sup>36</sup> S.M. Fullerton et al. Return of Individual Research Results from Genome-wide Association Studies: Experience of the Electronic Medical Records and Genomics (eMERGE) Network. *Genet Med* 2012; 14: 424–431.

## Research proposals are reviewed

When research project(s) that use the samples collected from one or more clinical trials are proposed, it is common practice for an internal group or committee, independent of the research team, to review the proposal and ensure consistency between what is being proposed and what was communicated in the protocol and informed consent documents. If questions of ethics emerge, additional internal and, at times, external expert opinion, including IRB and IEC review, when applicable, can be sought to determine whether or not to proceed.

## Results are evaluated against criteria for return

If consent has allowed for returning genetic results, there is a need to evaluate research results against the criteria for return. As discussed above, since IRBs and IECs have a patchwork of jurisdictions, it would be difficult for the pharmaceutical industry to involve them in evaluating particular results for return, since these discussions will probably result in inconsistent interpretations and results return practices. It would be preferable to have a system in which results are judged returnable against the criteria of clinical utility, analytical and clinical validity as outlined throughout this manuscript and presented in Table 1.

Fabsitz et al. have advocated for an external Central Advisory Body which acts in an advisory capacity to assemble a roster of genetic research findings which meet generally accepted criteria for return, allowing for greater consistency and efficiency to categorizing results appropriate for return.<sup>37</sup> Indeed, Green et al. observed a high concordance rate among experts for the return of 64 genetic findings discovered incidentally, suggesting it is possible to develop a consensus list.<sup>38</sup> This roster could then be used by a custodian or custodianship committee (such as a Return of Results Oversight Committee<sup>39</sup>) who would act as an interface with the researcher and trigger procedures for returning results if the finding appears on the list.

A system providing a single point of reference (i.e., the consensus list described above) has merit as a model for use by our industry in which actual return practices may vary at a country or site level depending on IRB and/or IEC's review and individual research participant preferences. However, it may be difficult to arrive on a consen-

sus list that is acceptable in all jurisdictions. In addition, operational challenges and intellectual property concerns may arise from use of an external advisory body limit the feasibility of this approach in our industry.

## 7. FUTURE CONSIDERATIONS AND CONCLUSIONS

It is recognized that there are related issues that fall outside the scope of this article. A few of these are shown here:

- a. *Results from pediatric research*  
The tripartite relationship among researchers, parents and minors has to be managed, the best interest of the child has to be pursued, and the respect of the minors and their autonomy have to be ensured.<sup>40</sup>
- b. *Familial communication of results*  
Familial communication of results presents unique challenges, since the pharmaceutical company does not interact directly with patients or their family members. If an inheritance pattern is known, the investigator is responsible for informing the research participant when and if validated results are provided.
- c. *Results from deceased research participants*  
Ormondroyd et al. (2007) studied the communication of genetic research results to families of deceased research participants and noted inefficiencies in communication due to complex family dynamics and lack of authority in the relative who was given the results by the researcher.<sup>41</sup>

As discussed here, there are many unique challenges in the pharmaceutical industry to providing research participants with the results of PGx research. For the most part the PGx research conducted by this industry is exploratory in nature, generating results that do not meet the threshold for returning to research participants. For those results that do meet this threshold, thoughtful consideration must be combined with internal, and often external, input to determine the benefit and operational feasibility of returning these results on a case by case basis. We hope this article actively contributes to the ongoing dialog on this topic in an effort to deliver information to research participants that is most meaningful and relevant to their medical care and decision making.

<sup>37</sup> R. Fabsitz et al., *op. cit.* note 8, p. 577.

<sup>38</sup> R.C. Green et al. Exploring Concordance and Discordance for Return of Incidental Findings from Clinical Sequencing. *Genet Med* 2012; 14: 405–410.

<sup>39</sup> S.M. Fullerton et al., *op. cit.* note 36, pp. 424–431.

<sup>40</sup> D. Avard et al. Pediatric Research and the Return of Individual Research Results. *J Law Med ethics* 2011; 39: 593–604.

<sup>41</sup> E. Ormondroyd et al. Disclosure of Genetics Research Results after the Death of the Patient Participant: a Qualitative Study of the Impact on Relatives. *J Genet Couns* 2007; 16: 527–538.



### Disclosures

All co-authors reported that they have no conflict of interest. All authors are employed by pharmaceutical companies that are actively engaged in pharmacogenomic research; collecting, analyzing and storing DNA samples from research participants in clinical trials. This article does not necessarily reflect the views of the companies that are members of I-PWG.

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