

## **PGRN ESP REPORT**

We greatly appreciate the external scientific panel's advice and guidance on the Pharmacogenetics Research Network's activities. In closed session with the Network members, PGRN Chair, Scott T. Weiss, and the Program Director, Rochelle Long; the External Scientific Panel members: Donna Arnett, Jeffrey Drazen, Joel Hirschhorn, and Howard Jacob raised a number of issues that, as Network Chair, I would like to respond to for the official record on behalf of the PGRN PI's.

**1. Relationship between PharmGKB and the PGRN:** This relationship has evolved over time. Initially, PharmGKB was conceived solely as a data repository for the PGRN. Based on guidance from both within and outside the PGRN, PharmGKB has become a repository for all of the knowledge generated by the Network, in a curated form rather than just as raw data. Both the PGRN and PharmGKB agree that data deposition for large GWAS datasets is best handled by other NIH supported data repositories,(e.g. dbGAP). We recognize however that the smaller datasets that we are depositing in PharmGKB still have substantial value as evidenced by the number of PharmGKB users who have requested these data.

In addition, the database has evolved into the single most comprehensive source of current knowledge of the field of pharmacogenetics. This includes an up-to-date compendium of the literature as well as curated information on VIP genes and relevant pathways. PGRN members continue to work with PharmGKB staff to provide expert support for the annotation of these data base activities

A very important and successful new interaction of PharmGKB and the PGRN has been in the development of consortia, specifically the Warfarin consortium and the emerging Tamoxifen and Irinotecan consortia. If the latter turn out to be as successful as the Warfarin consortium, they will clearly move the science forward in a dramatic way. In this new role, PharmGKB provides a collaborative data model for the field of pharmacogenetics and the infrastructure to sustain it and make it relevant to clinical care.

We are continuing to search for the best methods to further integrate PharmGKB with the PGRN and to communicate scientific results from the PGRN nodes through the PharmGKB to the pharmacogenetics community. PGRN members and PharmGKB staff also collaborate on paper annotation which we continue to work on assiduously to help to make PharmGKB as up to date as possible. We are making every effort to insure that what is in our papers is also on PharmGKB.

All the PGRN investigators agree that it is primarily through our regular webinars, meetings and telephone calls rather than the PharmGKB website that the internal network communication occurs but continues to evolve and to be seen by all of us as the single best repository of our collective knowledge about pharmacogenetics.

**2. Better definition of the objectives of the Program:** We believe that the objectives of the PGRN are to scientifically advance the field of pharmacogenetics, as stated in our mission statement. While this may appear to be overly broad, the Network as a whole feels comfortable with this objective, and at this point we are unwilling to preclude any type of advancement, whether it be in the area of basic discovery or applied pharmacogenetics from our mission.

We also feel, at this still early stage of the application of genetics to clinical medicine, that narrowing the objectives of the PGRN Program prematurely would be a mistake. We strongly agree with the ESP that consideration of technological changes and methodologic issues in the field of pharmacogenetics are critical, and we use our twice-yearly meetings to highlight these issues for the Network. I think that we have been unusually effective in this regard, and are quite up to date with emerging areas and their potential impact on the field. There is systematic review on a monthly basis via our Coordinating committee and all PI calls, of areas where there are substantial changes and where we need to increase communication and education with regard to technological and methodologic advances. We then work to include these areas in our meetings. We have been unusually successful in bringing in leaders of these cutting edge fields to our twice-yearly meetings as well as our annual PGRN Statistical Workshop, to update us on these issues, and we have implemented a number of changes as a result of these meetings. In addition, we have expanded membership of the Network to include Associates from both academia and industry, and they have further enriched our capability to lead the field by using the PGRN as an intellectual focus for expanded activities through these affiliated members.

**3. Establishing the basis of project renewals (discovery or other?):** While we agree that it is important to establish the basis of project renewals, we are hopeful that we will not have to focus on this goal prematurely and have ongoing Network activities slow down in the process. The Network Chair and the Program Director will solicit input from the Coordinating Committee and the All-PIs group with regard to the renewal as we get closer to the renewal date. However, at this point, we would like to hold off on in-depth discussion in order to continue to focus on advancing the science, at least over the bulk of this upcoming next year. At the appropriate time, as determined by the Network Chair and the Program Director, we will bring this topic up for discussion with the PGRN investigators.

**4. Network Management and Decision-Making:** I believe that the Network, as a whole, feels quite confident that our administrative structure and decision-making processes have maximum flexibility and input. The evolution of these systems has been continual over the life of the Network and continues to be refined. At the present time, the Program Director, the Network Chair, and the Working Group leaders believe that all of the Network PIs are comfortable with our management and decision-making structure, feeling that it is both flexible and effective and that our working groups are moving forward with a large number of initiatives that have helped to advance the field. A major issue is determining the relative priority of our many initiatives in light of our mission.

**5. Consideration by the ESP and the Network PIs with regard to actual prediction of drug treatment response.** How soon will it be until we can reliably predict drug treatment response? There are examples in which genetics are used to adjust treatment, and PGRN members are leaders in the adoption of these few clinical examples. However, it is the strong feeling of the Network PIs that more research is needed to make progress in predictive medicine, and a number of barriers and roadblocks still exist that affect widespread prediction of drug treatment response. These were detailed in the Request for Information (RFI) response from the Network to NIH (copy attached). These include sample size, mechanism of action, studies specifically designed to translate pharmacogenetic results, replication populations, and adequate analytic tools to analyze complex interactions in relatively small subsets of people. We believe that the Network

has made many major advances in the field, but that further progress is going to be dependent on a degree to which the NIH will continue to support the evolution of the science and the barriers outlined in our RFI response. It is premature to suggest that we can leap directly to prediction and it is the strong feeling of the Network investigators that we are on a logical track that is moving in the direction of more effective translational science in this important yet complex area. Our RFI response provides a good roadmap of what is needed to advance the field; each of our working groups have as part of their mission setting up research projects and infrastructure that will do the research needed to study prediction of drug treatment response.

The PGRN greatly appreciates the insightful, thoughtful, helpful, and critical support of our outstanding ESP in helping to make this NIH-wide program a success.

Scott T. Weiss, PGRN Chair  
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