



13 September 2004

Food and Drug Administration  
Dockets Management  
5630 Fishers Lane  
Rockville, MD 20852

To Whom It May Concern:

Genomas is submitting the document ***PHYSIOGENOMICS AND THE CRITICAL PATH for posting in the following docket:***

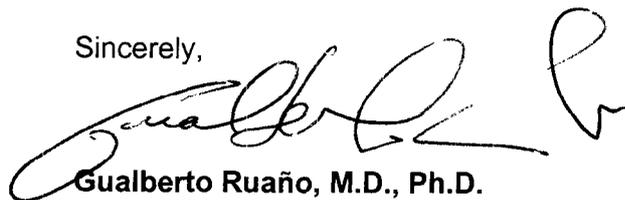
**Docket No. 2004-N-0181  
Critical Path Initiative  
Food and Drug Administration**

As announced in the Federal Register: April 22, 2004 (Volume 69, Number 78, p. 21839-21 840) and posted at: <http://www.fda.gov/OHRMS/DOCKETS/98fr/04-9147.html>.

Should you have any questions, I may be reached at either my office at 860.545.3773, by mobile phone at 203.687.0753 or via email at [g.ruano@genomas.net](mailto:g.ruano@genomas.net).

Thank you,

Sincerely,

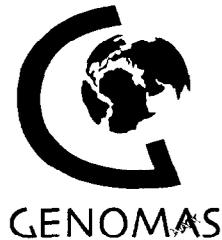


**Gualberto Ruano, M.D., Ph.D.**  
*President & CEO*

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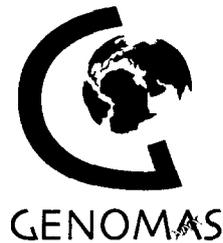
### **PHYSIOGENOMICS AND THE CRITICAL PATH**

Recent advances in physiogenomics allow us to couple human phenotypic information (e.g., drug induced cholesterol and glycemic changes, the metabolic syndrome) with genotypic information from hundreds of genes. Genomas has developed unique capabilities in parallel processing of gene arrays through the Illumina *BeadArray*, which merges the parallel processing capability of fiber optic technology with nanoscale high resolution scanning. Hundreds of genes can be standardized for genotyping and haplotyping and incorporated into physiogenomic models of desired and undesired responses to various drugs. There is a need for modern physiogenomic science to advance this research, particularly for drug safety and deployment into personalized medicine. The scientific innovations we would like to address through our dialogue with the FDA on the Critical Path span the gamut from clinical discovery and systems biology to parallel analytical and statistical processing of several hundred genetic associations with physiogenomics, as follows:

**1. Drug administration as clinical discovery.** No matter how rigorous the clinical development program, one challenge shared by the FDA and the pharmaceutical industry is that new benefits and side effects of drugs are only discovered in the real world of human populations after the drug has been released to market. We should reconsider the balance between preclinical and clinical activities to derive knowledge from both in a synergistic fashion. The current drug "pipeline" concept is linear, and does not incorporate the feedback that physiogenomics allows. The principle for implementation in the Critical Path is that clinical use of approved drugs serves as a new bed of discovery,

**2. Side effects as continuous distributions.** Adverse reactions are rare when severe and life-threatening, but more common when discomforting or even disabling. Relevant safety data can be gathered from the extremes of human response to a drug in terms of the more common side effects. Physiogenomic markers can be discovered to pinpoint individuals at high risk of the more common side effects. Such individuals could then be treated with lower dosages of the drug, or prescription of an alternative agent, and managed with more elaborate scrutiny for drug interactions.

**3. Gene arrays as probes of function.** Single gene effects are the basis of inherited errors of metabolism and other "genetic diseases". Pharmacokinetics and dynamics perforce are multi genetic, as they rely on pathways and networks of genes. Until now, parallel processing of genomic information for these multi-gene pathways was not feasible.



With the advent of gene arrays, parallel processing of gene expression and gene variability is routinely possible at the pathway level, and soon could be feasible on a genome wide basis. Patterns of gene variability or expression can be discerned as a correlate of drug administration and response. It is possible to abstract such patterns from experimental trials in drug development or most relevant to this proposal, from clinical use of an approved drug. These patterns can populate databases and "train" algorithms for near term prospective targeting of the drug to safe responders.

**4. Drug side effects as environmental responses.** It has been surmised that environment-gene interactions are too complex for genetic analysis. Physiogenomic analysis actually benefits from these interactions when the environmental trigger can be identified, which is the case in drug administration. In fact, drug response is probably one of the best applications of physiogenomics, as there is a long research chronicle employing pharmacological challenges to probe function. With physiogenomics, we can incorporate the genetic underpinnings responsible for variability in response to the pharmacological challenge.

**5. Covariate analysis as the pivot for systems biology.** In concert with the *in silico* development of complex models of function through physiological networks, we can begin linear additive physiogenomic models of genetic traits coalescing into development of drug side effects. These traits by themselves are lacking specificity and sensitivity. Covariate analysis has been a field of research in epidemiology, which now can be integrated into physiogenomics for systems analysis. Unintended and poorly understood side effects of pharmacological treatments are multi-gene, drug induced phenotypes suit-able for physio-genomics and systems biology.

A handwritten signature in black ink, appearing to read 'Gualberto Ruaño', is written over a white background.

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